

Archives of Hematology and Blood Transfusion

Original Article

Clinical Impact of Delayed Hemolytic Transfusion Reactions in Sickle Cell Disease Cohorts

Nagy B^{1*}, Matuska K² and Gregor A³

¹Department of Cellular Therapy and Transplantation, Vardar Center for Bleeding Disorders Research, Montenegro

²Department of Laboratory Hematology, Tundzha Institute of Transfusion Epidemiology, Hungary

³Department of Hematology, Maas Institute of Myeloproliferative Disease Research, Latvia

*Address for Correspondence: Blanka Nagy, Department of Cellular Therapy and Transplantation, Vardar Center for Bleeding Disorders Research, Montenegro; E-mail: blanka.nagy@vardar.edu

Received: 24 February 2026; Accepted: 20 May 2026; Published: 26 August 2026.

Citation of this article: Nagy B, Matuska K, Gregor A (2026) Clinical Impact of Delayed Hemolytic Transfusion Reactions in Sickle Cell Disease Cohorts. Arch Hematol Blood Transfus, 8(1): 01-06. DOI: [10.5281/zenodo.22818800](https://doi.org/10.5281/zenodo.22818800)

Copyright: © 2026 Blanka Nagy, et al. This is an open access article distributed under the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Patients with sickle cell disease are alloimmunized against red cell antigens far more often than other transfused populations, underlying delayed hemolytic transfusion reactions (DHTR) that are frequently mistaken for ordinary vaso-occlusive crisis.

Objective: To synthesize the literature on DHTR epidemiology, presentation, hyperhemolysis, and the preventive and management strategies supported by cohort and case-series evidence.

Methods: Narrative synthesis of cohort studies, meta-analyses, and case series on alloimmunization, DHTR, hyperhemolysis, extended/genotype matching, and complement-directed management in sickle cell disease.

Findings: Alloimmunization prevalence has stayed near 29-30% across three decades; DHTR carries 6% mortality in adult cohorts and severe complications in a third of pediatric episodes; extended matching leaves roughly 9% still alloimmunized; and anti-C5 complement blockade produced favorable recovery in most patients with refractory hyperhemolysis in the largest reported series.

Conclusions: DHTR and hyperhemolysis are predictable consequences of persistent alloimmunization, and the largest near-term gains lie in earlier recognition, avoiding reflexive further transfusion, wider genotype-level matching, and expanded complement-directed rescue therapy.

Keywords: sickle cell disease; delayed hemolytic transfusion reaction; hyperhemolysis syndrome; red cell alloimmunization; extended phenotype matching

1. Introduction

Transfusion is one of the few interventions in sickle cell disease (SCD) with an immediate, measurable benefit, and also one of the few that can make a patient acutely worse in a way clinicians are apt to misread as a sickle crisis rather than a consequence of the treatment itself. A delayed hemolytic transfusion reaction (DHTR) typically appears five to fourteen days after an uneventful-looking transfusion, presenting with falling hemoglobin, dark urine, bone and abdominal pain, and laboratory evidence of hemolysis in a patient whose own sickle red cells are now being destroyed alongside the transfused ones. In its most severe form, hyperhemolysis, the post-transfusion hemoglobin drops below the pre-transfusion value, reticulocytopenia appears exactly when more red cell production is needed, and the instinctive response — transfuse more blood — accelerates the process instead of correcting it. In a 12-year retrospective series from the French national reference center, 99 DHTR episodes were identified across 69 adults, with median onset at 9.4 days, hemoglobinuria in 94%, vaso-occlusive pain in 89%, secondary acute chest syndrome in half, and overall mortality of 6% [1]. Those numbers describe a complication that is neither rare nor benign, and one structurally tied to the same alloimmunization biology that makes transfusion support in SCD so much harder than in most other conditions.

The starting point is the disproportionate rate at which patients with SCD develop red cell alloantibodies. In the founding demonstration of this problem, Vichinsky and colleagues found that roughly 30% of chronically transfused patients with sickle cell anemia became alloimmunized when transfused predominantly with blood from a donor population that did not share their antigen profile [2]. A contemporary systematic review and meta-analysis pooling cohorts worldwide puts overall alloimmunization prevalence in transfused adults with SCD at 28.9% (95% CI 22.4-35.4), essentially unchanged three decades later despite substantial changes in practice

[3]. This review works through why that rate has proven so persistent, how DHTR and hyperhemolysis present and are diagnosed, what extended antigen and genotype matching have and have not achieved, and how clinicians manage a reaction in which the reflex of further transfusion is often the wrong move.

2. Alloimmunization risk specific to sickle cell disease

Most patients with SCD in the United States and Europe are of African ancestry, and most blood donors are not, which creates an antigenic mismatch problem that has nothing to do with ABO or D typing and everything to do with the Rh, Kell, Duffy, Kidd, and MNS systems. The Rh system alone accounts for a disproportionate share of the mismatch: in a genotyping study of 857 patients with SCD and 587 African American blood donors, 29% of RHD alleles and 53% of RHCE alleles carried variant sequence, meaning that serologic Rh typing frequently mislabels a patient's or a donor's true antigen repertoire and that conventional "Rh-matched" units are not always genuinely matched at the molecular level [4]. In that same cohort, 550 transfused patients had produced 175 distinct anti-Rh specificities among 105 individuals, despite most having received blood selected to be C, E, and K negative by standard serology — direct evidence that serologic matching alone leaves a substantial residue of Rh alloimmunization risk in this population [4].

The risk is not evenly distributed. Alloimmunized patients accumulate antibodies against a recurring set of specificities — anti-E, anti-C, anti-Jkb, and anti-K chief among them — and a prior alloimmunization event is one of the strongest predictors of a subsequent one, both because it flags a patient whose immune system responds robustly to foreign red cell antigens and because each new antibody narrows the pool of compatible units. In the pediatric French cohort, 16 of the 37 children who developed DHTR already had a documented alloimmunization history [5], and in the adult cohort, 61%

of the 99 episodes occurred in patients already known to be immunized and 28% were a repeat DHTR [1]. Even under extended antigen-matching protocols, approximately 9% of patients still became alloimmunized, alongside higher lifetime transfusion burden and the sickle beta-zero-thalassemia genotype as persistent risk factors and older age at first transfusion as mildly protective [3]. The rate is not fixed geographically either: SCD patients transfused in the United States were sensitized at meaningfully different rates than cohorts in Africa, the Caribbean, and parts of Europe, a gap plausibly explained by how closely the donor pool's antigen profile tracks the patient population's [6]. Antibody specificity also shifts with cumulative exposure, and a large single-center analysis found the changing pattern of antibodies associated with both chronic pain burden and decreased survival [7]. Autoantibody formation compounds the problem in a meaningful minority of alloimmunized patients, complicating pretransfusion testing [8]. The scale of the problem was documented as early as the Cooperative Study of Sickle Cell Disease [9], and the pathophysiology connecting antigen mismatch, transfusion exposure, and antibody formation has since been synthesized in subsequent reviews [10].

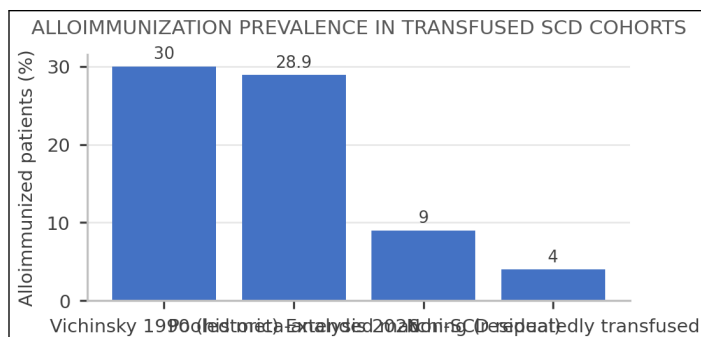


Figure 1: Red cell alloimmunization prevalence in transfused sickle cell disease cohorts has changed little across three decades of practice, from approximately 30% in the founding demonstration of racially mismatched transfusion [2] to a pooled 28.9% across contemporary cohorts [3]; extended antigen-matching protocols lower but do not eliminate the risk, leaving approximately 9% of matched patients still alloimmunized [3], against a background alloimmunization rate of roughly 2-6% in repeatedly transfused patients without sickle cell disease [10].

3. Clinical presentation and diagnosis of delayed hemolytic reactions

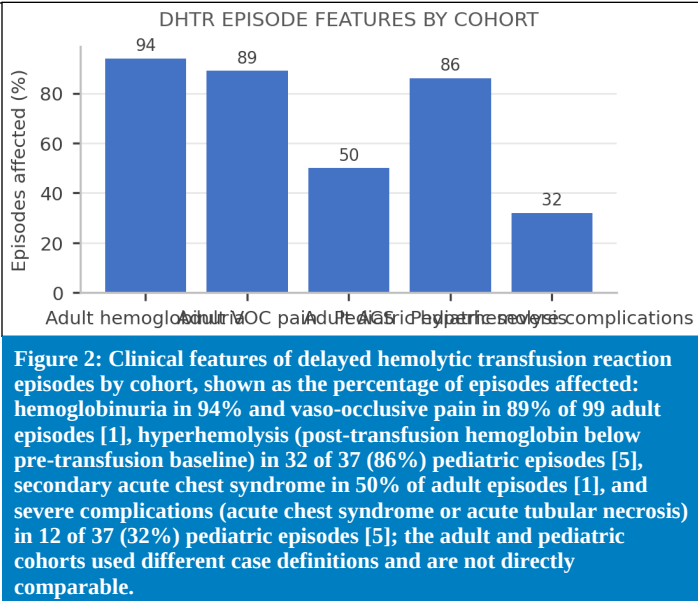
DHTR sits in an uncomfortable diagnostic space because its presenting features overlap almost completely with the vaso-occlusive crisis that brought the patient to transfusion in the first place. Dark urine, fatigue, jaundice, and diffuse pain appearing a week or so later are easy to attribute to "just another crisis," particularly when the direct antiglobulin test is weakly positive or even negative — a recognized feature of DHTR, since the transfused, antigen-positive donor cells being cleared may be eliminated too rapidly for antibody to remain detectable by the time serology is performed. In the adult series, the clues distinguishing DHTR from an uncomplicated crisis were a hemoglobin nadir well below the pre-transfusion baseline (median 5.5 g/dL) and a markedly elevated lactate dehydrogenase (median peak 1,335 IU/L), in the window five to fourteen days after transfusion [1]. The pediatric cohort showed a comparable pattern: of 37 DHTR episodes across 18 French centers over five years, median age at diagnosis was 9 years, 22 children were on hydroxyurea, and severe complications — acute chest syndrome or acute tubular necrosis — occurred in 12 of 37 episodes [5].

The diagnosis is clinically urgent rather than academic because the reflex to a falling hemoglobin — transfuse — is often counterproductive once a DHTR is under way: newly transfused antigen-positive cells are destroyed by the same alloantibody- or, in the hyperhemolytic variant, complement-driven process attacking the first unit. Clinicians increasingly rely on new or reappearing alloantibodies (even when the DAT is unhelpful), an inappropriately low reticulocyte count for the degree of anemia, and the timing window itself to make the diagnosis before a second transfusion is ordered [11]. A predictive scoring approach from the adult French cohort formalized recent transfusion, degree of hemoglobin fall, and reticulocyte response into a bedside tool meant to flag DHTR before it is mistaken for simple crisis pain [12].

Table 1: Delayed hemolytic transfusion reaction cohorts in adult and pediatric sickle cell disease, by episode count, timing, laboratory findings, and outcome [1,5].		
Feature	Adult cohort (99 episodes, 69 patients)	Pediatric cohort (37 episodes, 18 centers)
Median onset after transfusion	9.4 days	not separately reported
Median age	not separately reported	9 years (range 3-15)
Prior alloimmunization	61% of episodes	16 of 37 children
Repeat DHTR	28% of episodes	not separately reported
Hemoglobin nadir / hyperhemolysis	median 5.5 g/dL	32 of 37 (86%) hyperhemolytic
Severe complications	50% secondary acute chest syndrome	12 of 37 (32%)
Mortality	6%	not separately reported

4. Hyperhemolysis as the severe end of the spectrum

Hyperhemolysis describes the subset of DHTR in which destruction extends beyond the transfused donor cells to the patient's own red cells, so that post-transfusion hemoglobin falls below the pre-transfusion value — a paradox that only makes sense once bystander hemolysis and marrow suppression are understood as part of the same complement-mediated process. In the pediatric French cohort, hyperhemolysis was documented in 32 of the 37 DHTR episodes, underscoring that the hyperhemolytic pattern is the rule rather than the exception once DHTR is recognized in children [5]. Mortality attributable to hyperhemolysis and its downstream complications was 6% in the adult series, with deaths concentrated among patients whose diagnosis was delayed or who received further transfusion before the process was recognized [1]. Reticulocytopenia, sometimes profound, is a defining and counterintuitive feature: instead of a compensatory reticulocytosis, bone marrow erythropoiesis appears transiently suppressed, which is part of why hyperhemolysis carries a materially worse prognosis than uncomplicated DHTR.



The underlying immunology is not fully settled, and cases without any detectable new alloantibody are well described, implicating complement activation and macrophage-mediated destruction of the patient's own sickle cells through mechanisms beyond classical antibody-antigen recognition. This matters clinically because a negative antibody screen does not rule out hyperhemolysis, and because it explains why complement-directed therapy has become a rational, and in refractory cases reasonably well-supported, treatment option rather than an empirical last resort [13]. The severity gradient from ordinary DHTR to hyperhemolysis to hyperhemolysis with multi-organ complications also explains the recent emphasis on early recognition scores and structured management algorithms rather than case-by-case improvisation [12,11].

5. Extended phenotype and genotype matching as prevention

If alloimmunization is the upstream driver of DHTR, the most direct preventive lever is matching transfused blood more closely to the patient's extended antigen profile before an antibody ever forms — matching for Rh (C, E), Kell, Duffy, Kidd, and MNS antigens rather than ABO/D alone. The case for doing this prospectively rests on data

such as the RH genotype-matching program described above, where genotyping revealed enough hidden Rh variation in both patients and donors that molecular matching was required to make Rh compatibility real rather than nominal — a program that, once implemented, could meet 95% of patient demand using roughly 85 African American donors per weekday, compared with about 40 needed for serologic matching alone [4].

Table 2: RH genotype-matching program findings and their bearing on prevention of alloimmunization in sickle cell disease, from a cohort of 857 patients and 587 African American blood donors [4], set against the residual alloimmunization risk reported under extended matching in the broader meta-analytic literature [3].

Metric	Finding	Source
RHD alleles carrying variant sequence	29%	[4]
RHCE alleles carrying variant sequence	53%	[4]
Anti-Rh specificities among 550 transfused patients	175 specificities in 105 individuals	[4]
Donors needed to meet 95% of matching demand	85/weekday (genotype) vs 40 (serologic)	[4]
Residual alloimmunization under extended matching	approximately 9% of patients	[3]

Extended phenotypic matching programs predate genotype-level matching and were shown decades earlier to reduce, though not eliminate, new alloimmunization events, establishing extended matching as the practice standard now recommended by most SCD transfusion guidelines [14]. The persistent ~9% residual alloimmunization rate under extended matching is attributable to several factors together: incomplete concordance between serologic phenotype and true genotype, antigens outside the routinely matched panel, and a subgroup of patients who remain immunologically "responders" regardless of how well the unit is matched [3,4]. Long-running single-center cohorts that adopted extended matching early found that consistent application over many years kept new alloimmunization events well below historical rates, reinforcing that the benefit compounds with sustained use rather than being

realized after any single encounter [15]. Inflammatory state at the time of transfusion is also an independent modifier of risk, with antibody formation more likely during an acute pain crisis or acute chest syndrome than during a steady-state elective transfusion [16]. Genetic variation in immune regulatory genes, including HLA class II alleles, has similarly been proposed as a contributor to why some extensively matched patients still become alloimmunized while others transfused far more heavily do not [17].

6. Management when further transfusion becomes dangerous

Once DHTR or hyperhemolysis is suspected, the first management decision is often what not to do: further transfusion, even with apparently compatible, extended-matched units, can intensify hemolysis, because the process driving destruction in hyperhemolysis is not confined to antigen-positive donor cells. Supportive management — hydration, folate, careful pain control, and close monitoring — is sufficient for a substantial share of episodes; in the adult series, 53% of the 99 episodes were managed with supportive care alone [1]. For episodes that fail to stabilize, several adjunctive strategies have accumulated meaningful, if largely observational, evidence. IVIG and corticosteroids were the first agents used to interrupt hyperhemolysis, blunting macrophage-mediated clearance of red cells, and remain first-line adjuncts in many centers despite an evidence base built mostly from case reports and small series [11]. Rituximab has been used specifically to prevent recurrence in patients with a prior severe DHTR who require further transfusion, blunting the anamnestic antibody response before a subsequent unit is given [18].

Complement blockade is the most substantial recent addition to management of refractory hyperhemolysis. In a series of 18 patients with SCD treated with anti-C5 antibody (eculizumab) for severe, refractory hyperhemolysis, treatment was associated with cessation

or marked reduction of hemolysis and favorable organ recovery in 15 patients (83%), with three deaths attributable to acute liver failure rather than to the therapy itself [13]. That series, described as the largest reported to date, has made eculizumab a recognized option for hyperhemolysis unresponsive to supportive care and IVIG/steroids [13]. Pediatric case-series experience has echoed the adult findings, with recovery after eculizumab reported in children refractory to first-line measures [19], and isolated reports of extreme presentations recovering after complement blockade have reinforced its role as a genuine rescue therapy [20]. Erythropoiesis-stimulating agents are sometimes added to counter the reticulocytopenia of hyperhemolysis, reasoning that stimulating marrow production is safer than transfusing further into an active hemolytic process, though this remains adjunctive [1]. Across these approaches the unifying principle is the same: recognize the syndrome early enough that the reflex to transfuse does not become the intervention that turns a serious reaction into a fatal one.

7. Conclusion

Delayed hemolytic transfusion reaction and its hyperhemolytic extreme are not rare curiosities in sickle cell disease transfusion medicine; they are a predictable consequence of a well-documented alloimmunization rate, close to 29% across contemporary cohorts and essentially unchanged from the 30% reported by Vichinsky and colleagues more than three decades ago [2,3], compounded by the diagnostic difficulty of distinguishing a hemolytic reaction from ordinary sickle pain in the critical first two weeks after transfusion. Extended phenotype and Rh genotype matching programs have demonstrably reduced, without eliminating, the underlying alloimmunization that drives DHTR, in part because standard serology mislabels a meaningful fraction of both patient and donor Rh genotypes [4], and a residual risk of roughly 9% persists even under extended matching [3]. When DHTR does

occur, mortality of 6% in adult series and severe complications in roughly a third of pediatric episodes [1,5] make early recognition — and, critically, avoidance of reflexive further transfusion — the decisive clinical variable. Complement inhibition with agents such as eculizumab has moved from anecdote to a genuinely supported rescue therapy for refractory hyperhemolysis, with recovery in the large majority of a well-documented adult case series [13], and IVIG, corticosteroids, and rituximab retain defined roles in supportive and preventive management. The clinical task going forward is less about discovering new biology than about closing the implementation gap: getting extended or genotype matching to every chronically transfused patient with SCD before the first antibody forms, and getting the diagnosis of DHTR made fast enough, in every emergency department and inpatient ward that sees these patients, that the treatment does not become the harm.

8. References

1. Habibi, A., Mekontso-Dessap, A., Guillaud, C., Michel, M., Razazi, K., Khellaf, M., et al. (2016) Delayed hemolytic transfusion reaction in adult sickle-cell disease: presentations, outcomes, and treatments of 99 referral center episodes. American Journal of Hematology, 91(10): 989-994. DOI: [10.1002/ajh.24460](https://doi.org/10.1002/ajh.24460)
2. Vichinsky, E.P., Earles, A., Johnson, R.A., Hoag, M.S., Williams, A., Lubin, B. (1990) Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. New England Journal of Medicine, 322(23): 1617-1621. DOI: [10.1056/nejm199006073222301](https://doi.org/10.1056/nejm199006073222301)
3. Alsalman, M., Alnajjar, J.S., Alhassan, S.R., Almarzoug, H.A., Alobaid, Q.A., Alhassan, R.R., et al. (2026) Global prevalence of alloimmunization in adults with sickle cell disease receiving red blood cell transfusions: a systematic review and meta-analysis. Journal of Clinical Medicine, 15(10): 3828. DOI: [10.3390/jcm15103828](https://doi.org/10.3390/jcm15103828)
4. Chou, S.T., Evans, P., Vege, S., Coleman, S.L., Friedman, D.F.,

- Keller, M., Westhoff, C.M. (2018) RH genotype matching for transfusion support in sickle cell disease. *Blood*, 132(11): 1198-1207. DOI: [10.1182/blood-2018-05-851360](https://doi.org/10.1182/blood-2018-05-851360)
5. Falguiere, C., Allali, S., Khazem, B., Kamdem, A., Arnaud, C., Belloy, M., et al. (2023) Delayed hemolytic transfusion reaction in children with sickle cell disease: first 5-year retrospective study in mainland France. *Haematologica*, 108(3): 889-894. DOI: [10.3324/haematol.2022.281050](https://doi.org/10.3324/haematol.2022.281050)
6. Zheng, Y., Wang, W., Xu, F., et al. (2016) Alloimmunisation rates of sickle cell disease patients in the United States differ from those in other geographical regions. *Transfusion Medicine*, 26(3): 225-230. DOI: [10.1111/tme.12314](https://doi.org/10.1111/tme.12314)
7. Telen, M.J., Afenyi-Annan, A., Garrett, M.E., Combs, M.R., Orringer, E.P., Ashley-Koch, A.E. (2015) Alloimmunization in sickle cell disease: changing antibody specificities and association with chronic pain and decreased survival. *Transfusion*, 55(6): 1378-1387. DOI: [10.1111/trf.12940](https://doi.org/10.1111/trf.12940)
8. Aygun, B., Padmanabhan, S., Paley, C., Chandrasekaran, V. (2002) Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. *Transfusion*, 42(1): 37-43. DOI: [10.1046/j.1537-2995.2002.00007.x](https://doi.org/10.1046/j.1537-2995.2002.00007.x)
9. Rosse, W.F., Gallagher, D., Kinney, T.R., Castro, O., Dosik, H., Moohr, J., et al. (1990) Transfusion and alloimmunization in sickle cell disease. *Blood*, 76(7): 1431-1437. DOI: [10.1182/blood.v76.7.1431.1431](https://doi.org/10.1182/blood.v76.7.1431.1431)
10. Chou, S.T., Liem, R.I., Thompson, A.A. (2012) Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. *Blood*, 120(3): 528-537. DOI: [10.1182/blood-2011-11-327361](https://doi.org/10.1182/blood-2011-11-327361)
11. Gardner, K., Hoppe, C., Mijovic, A., Thein, S.L. (2015) How we treat delayed haemolytic transfusion reactions in patients with sickle cell disease. *British Journal of Haematology*, 170(6): 745-756. DOI: [10.1111/bjh.13494](https://doi.org/10.1111/bjh.13494)
12. Narbey, D., Habibi, A., Chadebech, P., Mekontso-Dessap, A., Khellaf, M., Lelievre, J.D., et al. (2017) Incidence and predictive score for delayed hemolytic transfusion reaction in adult patients with sickle cell disease. *American Journal of Hematology*, 92(12): 1340-1348. DOI: [10.1002/ajh.24908](https://doi.org/10.1002/ajh.24908)
13. Floch, A., Bierling, P., Bartolucci, P., et al. (2020) Anti-C5 antibody treatment for delayed hemolytic transfusion reactions in sickle cell disease. *Haematologica*, 105(11): 2694-2697. DOI: [10.3324/haematol.2020.253856](https://doi.org/10.3324/haematol.2020.253856)
14. Castro, O., Sandler, S.G., Houston-Yu, P., Rana, S. (2002) Predicting the effect of transfusing only phenotype-matched RBCs to patients with sickle cell disease: theoretical and practical implications. *Transfusion*, 42(6): 684-690. DOI: [10.1046/j.1537-2995.2002.00126.x](https://doi.org/10.1046/j.1537-2995.2002.00126.x)
15. LaSalle-Williams, M., Nuss, R., Le, T., Cole, L., Hassell, K., Murphy, J.R., Ambruso, D.R. (2011) Extended red blood cell antigen matching for transfusions in sickle cell disease: a review of a 14-year experience from a single center. *Transfusion*, 51(8): 1732-1739. DOI: [10.1111/j.1537-2995.2010.03045.x](https://doi.org/10.1111/j.1537-2995.2010.03045.x)
16. Fasano, R.M., Booth, G.S., Miles, M., Du, L., Koyama, T., Meier, E.R., Luban, N.L.C. (2015) Red blood cell alloimmunization is influenced by recipient inflammatory state at time of transfusion in patients with sickle cell disease. *British Journal of Haematology*, 168(2): 291-300. DOI: [10.1111/bjh.13123](https://doi.org/10.1111/bjh.13123)
17. Wong, T.E., Yazdanbakhsh, K., Hsieh, M.M., et al. (2022) HLA class II regulation of immune response in sickle cell disease patients: susceptibility to red blood cell alloimmunization (systematic review and meta-analysis). *Vox Sanguinis*, 117(7): 897-905. DOI: [10.1111/vox.13351](https://doi.org/10.1111/vox.13351)
18. Noizat-Pirenne, F., Habibi, A., Mekontso-Dessap, A., Razazi, K., Chadebech, P., Nzouakou, R., et al. (2015) The use of rituximab to prevent severe delayed haemolytic transfusion reaction in immunized patients with sickle cell disease. *Vox Sanguinis*, 108(3): 262-267. DOI: [10.1111/vox.12217](https://doi.org/10.1111/vox.12217)
19. Lapite, A., Adepoju, T., George, C.M., et al. (2024) Eculizumab

for management of hyperhemolysis syndrome in pediatric patients with sickle cell disease: a single-center case series. Pediatric Blood & Cancer, 71(9): e31061. DOI: [10.1002/pbc.31061](https://doi.org/10.1002/pbc.31061)

20. Wang, Y., Patel, S., Okonkwo, A., et al. (2024) A case report of red blood cell alloimmunization and delayed hemolytic transfusion reaction in a patient with an uncommon phenotype in sickle cell disease: review of diagnosis and management. Case Reports in Hematology, 2024: 9980747. DOI: [10.1155/2024/9980747](https://doi.org/10.1155/2024/9980747)