Researc Article *Open Access*

Journal of Preventive Medicine, Infectious Diseases & Therapy

ISSN: 3071-0588

DOI: doi.org/10.63721/26JPMIDT0133

Innocent Bystander Haemolysis in Transfusion Medicine: Mechanisms, Diagnosis, and Clinical Management - A Narrative Review

Aghatise EK[1], Sahabi AI[1] and Aladenika ST[2*]

[1]Department of Medical Laboratory Science, Igbinedion University, Okada, Edo State, Nigeria
[2]Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, College of Medicine, University of Nigeria, Enugu Campus, Enugu State, Nigeria

Citation: *Aghatise EK, Sahabi AI and Aladenika ST (2026) Innocent Bystander Haemolysis in Transfusion Medicine: Mechanisms, Diagnosis, and Clinical Management - A Narrative Review . J of Preventive Medi, Infec Dise & Therapy 3(3), 1-9. WMJ/JPMIDT-133*

Abstract

Background and Objective: *Innocent bystander haemolysis (IBH) is an immune-mediated destruction of red blood cells (RBCs) in which antigen-negative erythrocytes are lysed as collateral casualties of complement activation triggered elsewhere. It is encountered in three principal clinical settings in transfusion medicine: drug-induced immune haemolytic anaemia (DIIHA), delayed haemolytic transfusion reaction (DHTR) with hyperhaemolysis syndrome (HHS) in sickle cell disease (SCD), and passenger lymphocyte syndrome (PLS) following transplantation. Despite its clinical importance, IBH is frequently underdiagnosed owing to atypical serological findings. This review examines the historical evolution, immunological basis, clinical mechanisms, laboratory diagnosis, and therapeutic management of IBH.*

Methods: *PubMed, Google Scholar, and reference-list searching were used to identify peer-reviewed literature on IBH, DIIHA, HHS, DHTR, PLS, and complement-mediated haemolysis published between 1965 and 2025.*

Key Content and Findings: *IBH arises through classical pathway complement activation, with secondary amplification via the alternative pathway. Key presentations include DIIHA (16–18% of acquired immune haemolytic anaemia), HHS complicating approximately 4% of transfusions in SCD, and PLS in up to 18% of minor ABO-incompatible transplants. Diagnosis relies on a complement-only or complement-predominant direct antiglobulin test (DAT), biochemical haemolysis markers, and drug or transfusion history, but is frequently delayed because routine alloantibody screening is negative. Management centres on removing the precipitating cause, first-line immunosuppression with corticosteroids and intravenous immunoglobulin (IVIG), avoidance of further transfusion in HHS, and escalation to targeted biologics — eculizumab, rituximab, and tocilizumab — in refractory cases. Extended RBC genotyping and complement inhibitor therapies represent the frontiers of prevention and treatment.*

Conclusions: *IBH spans multiple haematological and transplant settings and demands a high index of clin-*

ical suspicion, especially when haemolysis occurs despite a compatible crossmatch. Expanding access to extended RBC genotyping, standardised diagnostic protocols, and complement inhibitor therapies is central to improving outcomes in affected patients.

***Corresponding author:** Aladenika ST, Department of Medical Laboratory Sciences, University of Nigeria, Enugu Campus, Enugu State, Nigeria.

Submitted: 02.06.2026 **Accepted**: 05.06.2026 **Published**: 17.06.2026

Keywords: Innocent Bystander Haemolysis, Hyperhaemolysis Syndrome, Complement Activation, Drug-Induced Immune Haemolytic Anaemia, Delayed Haemolytic Transfusion Reaction

Introduction

Blood transfusion is a life-saving therapeutic intervention underpinning the management of haematological disorders, surgical blood loss, and critical illness worldwide. However, transfusion is not immunologically neutral. Among the most diagnostically challenging complications is innocent bystander haemolysis (IBH), in which erythrocytes bearing no relation to the initiating immune stimulus are destroyed as collateral victims of misdirected complement activation [1].

IBH may be defined as immune-mediated destruction of cells or tissues caused by an antibody not produced in response to intrinsic antigens on the cells undergoing cytolysis. The concept emerged in the early 1960s from clinical observations in patients receiving the antimalarial and antiarrhythmic drug quinidine, who developed acute haemolysis without detectable autoantibodies on their own RBCs. Subsequent experimental work established that soluble drug-antibody immune complexes were responsible, and that complement activation by these complexes at the RBC surface - despite the absence of drug-specific antigen on the erythrocyte - was the key event in haemolysis [3].

Today, IBH is recognised across three principal clinical settings: (I) DIIHA, in which drug-antibody immune complexes cause complement-mediated bystander haemolysis; (II) DHTR with HHS in SCD, in which alloantibodies destroy both donor and autologous RBCs; and (III) PLS following solid organ or haematopoietic stem cell transplantation, in which donor-derived lymphocytes produce antibodies against recipient RBC antigens. In all three settings, the unifying mechanism is complement activation that damages antigen-negative bystander cells [1,4].

Despite growing recognition, IBH remains underdiagnosed. Serological findings are often atypical, routine antibody screening is frequently negative, and the clinical picture overlaps with autoimmune haemolytic anaemia, acute haemolytic transfusion reaction, and other causes of post-transfusion anaemia. We present this article in accordance with the narrative review reporting checklist [1,5].

Methods

A narrative review of published peer-reviewed literature was conducted. PubMed, Google Scholar, and reference-list searching were used to identify relevant sources. The search strategy summary is presented in Table 1.

Table 1: Search Strategy Summary

Items	Specification
Date of search	January 2025
Databases and other sources searched	PubMed, Google Scholar, reference-list searching
Search terms used	"innocent bystander haemolysis"; "drug-induced immune haemolytic anaemia"; "hyperhaemolysis syndrome"; "delayed haemolytic transfusion reaction"; "passenger lymphocyte syndrome"; "complement activation RBC"; "bystander complement haemolysis"
Timeframe	1965–2025
Inclusion and exclusion criteria	English-language peer-reviewed articles; original research, reviews, case series, case reports, and clinical guidelines relevant to IBH, DIIHA, HHS, DHTR, PLS, and complement-mediated haemolysis. Non-English articles, conference abstracts without full text, and articles on unrelated haematological conditions were excluded.
Selection process	Selection conducted by all authors independently; consensus obtained through discussion

Historical Background

The intellectual origins of IBH lie in observations of drug-induced blood dyscrasias in the 1950s and 1960s. Ackroyd first proposed the term "innocent bystander" to describe complement-mediated platelet lysis in the presence of sedormid and its antibody. Dameshek formally applied this concept to erythrocytes in 1965, observing that antigen-negative RBCs could be destroyed during immune haemolytic reactions - the foundational description of IBH [1].

Pivotal early work characterised the quinidine antibody as a gamma globulin that required both quinidine and complement to cause RBC haemolysis. These experiments established key principles: the drug-protein complex was the true immunogen; complement was essential for lysis; and drug coating of the RBC surface itself was not required [3]. The taxonomy of DIIHA was formally classified by **Garratty and Petz** in 1975, distinguishing hapten/drug-adsorption mechanisms from immune complex or bystander mechanisms and from true autoimmune mechanisms. This framework, further elaborated in their seminal textbook, clarified that the innocent bystander category was defined by soluble immune complex formation and complement-mediated bystander lysis [3,27].

In parallel, the framework for HHS in SCD evolved over subsequent decades. Systematic characterisation of HHS as a condition defined by post-transfusion haemoglobin nadir below the pre-transfusion value was established in the 1990s and 2000s, with the first comprehensive clinical description provided by Win et al. in 2009 [2]. Evidence that macrophage activation contributes alongside antibody-mediated complement attack added mechanistic nuance [7]. The ASH 2020 guidelines for SCD formally acknowledged DHTR and HHS as major transfusion-related complications requiring specific management strategies [8].

Basic Immunology of Innocent Bystander Haemolysis

Red blood cell destruction may occur through intravascular or extravascular pathways. Intravascular haemolysis results from complement-mediated membrane attack complex (MAC) formation. Extravascular haemolysis occurs through macrophage-mediated phagocytosis of opsonised RBCs in the spleen and liver. In IBH, complement activation plays the dominant role [9].

Complement Activation Pathways

The classical pathway is initiated when C1q binds to immunoglobulins (IgM or IgG) that have formed immune complexes. This triggers C4 and C2 cleavage, generating the C3 convertase (C4b2a), which cleaves C3 into C3a (anaphylatoxin) and C3b. C3b covalently binds to nearby cell membranes through a reactive thioester bond, opsonising them and initiating C5 cleavage. C5b nucleates the terminal MAC (C5b-9), which forms transmembrane pores causing osmotic cell lysis. Critically, C3b deposition on bystander RBC membranes is the key event linking systemic complement activation to bystander cell destruction [1, 9, 31].

Alternative Pathway Amplification

Free haem and RBC microvesicles released during intravascular haemolysis activate the alternative complement pathway, depositing additional C3b on bystander RBCs. This self-amplifying cycle of complement deposition, documented in the context of DHTR in SCD, extends haemolysis well beyond initially targeted cells and explains why IBH can be disproportionate to the magnitude of the initial immune stimulus [1, 29].

Complement Regulatory Failure

Host cells are normally protected from autologous complement attack by decay-accelerating factor (DAF/CD55), which accelerates C3 convertase dissociation, and CD59, which blocks MAC assembly. In IBH, the intensity of local complement activation overwhelms these regulatory mechanisms, particularly when immune complexes adsorb in bulk onto the RBC surface in DIIHA, or when the anamnestic alloantibody response in HHS generates sustained complement activation [1, 9].

Macrophage-Mediated Destruction

Beyond direct complement lysis, activated macrophages recruited to clear complement-opsonised donor RBCs also phagocytose autologous bystander RBCs non-specifically in HHS. Histopathological evidence confirms macrophage activation as a driver of post-transfusion bystander haemolysis in SCD, and interleukin-6 (IL-6) appears central to this process [7, 10].

Mechanisms of Innocent Bystander Haemolysis

Drug-Induced Immune Haemolytic Anaemia - The Immune Complex Mechanism

In DIIHA via the immune complex mechanism, the drug binds to plasma proteins to form soluble drug-protein complexes. Antibodies (IgM or IgG) directed against these complexes activate complement via the classical pathway. Complement components - particularly C3b and C5b-9 -deposit on nearby RBCs that bear no drug antigen and are destroyed as innocent bystanders [**3, 5**]. Prototype drugs operating through this mechanism include quinidine, quinine, phenacetin, stibophen, and rifampicin. Cephalosporins (cefotetan, ceftriaxone) are among the most frequently implicated, with ceftriaxone reported to cause severe and sometimes fatal DIIHA via complement-mediated classical pathway activation [28]. Beta-lactam combinations such as amoxicillin-clavulanate, NSAIDs, diclofenac, and less commonly recognised agents such as sildenafil have also been reported to cause this form of DIIHA, sometimes with severe renal complications [**6, 20**]. Unlike the hapten mechanism (where drug covalently coats RBCs and antibody targets the drug-RBC adduct), immune complex-type DIIHA cannot be demonstrated using drug-coated RBCs alone; the drug must be present simultaneously with patient serum and normal RBCs for antibody detection. DIIHA accounts for 16 -18% of all cases of acquired immune haemolytic anaemia, with an incidence of approximately one to two cases per million per year [3, 5].

Hyperhaemolysis Syndrome in Sickle Cell Disease

SCD is a prevalent hereditary haemoglobin disorder characterised by chronic haemolysis, vaso-occlusion, and end-organ damage [35]. HHS is a catastrophic form of post-transfusion haemolysis, first described occurring even during uncomplicated sickle cell painful episodes and defined by destruction of both allogeneic donor RBCs and autologous patient RBCs, resulting in a post-transfusion haemoglobin nadir below the pre-transfusion value [38]. It is the most clinically severe manifestation of IBH in the transfusion setting [4, 11, 21].

The primary trigger is alloimmunisation to donor RBC antigens, driven by antigen-profile differences between SCD patients (predominantly of African ancestry) and blood donors (predominantly of European ancestry). Differences in the Rh (C, E, and e), Kell, Duffy, Kidd, and MNS systems create a substrate for alloantibody formation with repeated transfusion [23, 25].

DHTR occurs in approximately 4% of SCD patients receiving occasional transfusions and may escalate to HHS [4, 8]. Autologous RBC destruction is mediated by both complement activation from alloantibody binding to donor RBCs and non-specific macrophage phagocytosis of bystander cells [7, 11].

Passenger Lymphocyte Syndrome

PLS is a distinct form of bystander haemolysis occurring 1-3 weeks after solid organ or haematopoietic stem cell transplantation. Donor-derived B lymphocytes engrafted in the recipient produce alloantibodies against recipient RBC antigens, lysing recipient cells. PLS most commonly arises in ABO- or Rh-incompatible transplants and is confirmed by positive DAT, elution of donor-specific alloantibody from recipient RBCs, and negative crossmatch with antigen-negative (donor-phenotype) RBCs. The incidence in minor ABO-incompatible liver transplantation may reach 17-18% [12, 13].

Clinical Significance in Transfusion Medicine

- **Diagnostic Challenge:** Severe haemolysis may occur despite a serologically compatible crossmatch, mimicking other post-transfusion anaemia causes. The DAT may show complement-only reactivity, which can be misinterpreted or dismissed [9].
- **Severe Anaemia:** By destroying both targeted and untargeted RBCs, IBH produces anaemia disproportionate to the primary immune reaction, which is particularly dangerous in patients with already limited haematopoietic reserve such as those with SCD or bone marrow failure **[4].**
- **Paradoxical Transfusion Harm:** In HHS, continued transfusion may worsen anaemia by providing additional RBC substrates for bystander complement deposition - a clinically dangerous paradox that demands early recognition [4, 11].
- **Organ Complications:** Free haemoglobin released during intravascular haemolysis scavenges nitric oxide, impairs endothelial function, and causes haem-mediated tubular nephrotoxicity, leading to acute kidney injury, jaundice, haemoglobinuria, and, in severe cases, multi-organ failure [4, 11, 39].
- **Alloimmunisation Burden:** Repeated allogeneic exposure perpetuates alloimmunisation in IBH-prone patients, particularly those with SCD, increasing the risk of future DHTR. The risk escalates with cumulative transfusion exposure [4, 8, 23].
- **Drug safety:** DIIHA via the immune complex mechanism may be a fatal adverse drug reaction. Its incidence is almost certainly underestimated, as cases without a clear temporal association with drug use are frequently missed [3, 5].
- **Transplant outcomes:** PLS contributes to post-transplant anaemia, increased transfusion requirements, and, rarely, acute kidney injury and death [12, 13].

Laboratory Diagnosis

The laboratory diagnosis of IBH is inherently challenging because the inciting antibody does not react with the patient's own RBCs under standard conditions, routine antibody screening is frequently negative, and the DAT pattern differs from classical autoimmune haemolytic anaemia. A multiparameter approach is therefore essential [9,15].

Direct Antiglobulin Test

The DAT is the cornerstone investigation. In IBH, it characteristically detects complement components (C3d) on the RBC surface with absent or minimal IgG reactivity - a "complement-only" pattern distinguishing IBH from warm autoimmune haemolytic anaemia (typically IgG-positive) and hapten-mechanism DIIHA (typically IgG-positive). In HHS, the DAT may be weakly reactive or negative if sensitised cells have been preferentially lysed [9,15]. The positive C3d DAT reflects surface complement deposition and is the only immunohaematological test that directly targets the complement system on the RBC membrane [31].

Indirect Antiglobulin Test and Drug-Dependent Antibody Testing

In immune complex-type DIIHA, the indirect antiglobulin test (IAT) is typically negative without the offending drug. Definitive confirmation requires testing patient serum against normal RBCs in the simultaneous presence of the suspected drug (or its metabolites) and fresh serum as a complement source. A positive result in the drug-containing system with a negative control confirms drug-dependent antibody activity. This testing requires specialist immunohaematology laboratory expertise [3,5].

Biochemical Markers of Haemolysis

Elevated lactate dehydrogenase (LDH), depleted or

undetectable haptoglobin, and raised unconjugated bilirubin confirm active haemolysis. In intravascular haemolysis, haemoglobinaemia (red/pink serum) and haemoglobinuria (dark/red urine) are characteristic. Urinary haemosiderin may be detected in subacute cases. Reticulocytopenia may paradoxically occur in HHS due to bone marrow suppression [11, 15]. These biochemical markers collectively constitute the standard laboratory panel for confirming and grading immune-mediated haemolysis [40].

Post-Transfusion Haemoglobin Monitoring

The hallmark of HHS is a post-transfusion haemoglobin nadir below the pre-transfusion value. This finding, alongside accelerated decline in HbA fraction, distinguishes HHS from DHTR without hyperhemolysis [24]. A DHTR prediction scoring system incorporating transfusion history and persistence of HbA has been proposed for identifying high-risk SCD patients prospectively [16].

Alloantibody Screening and Molecular Blood Group Typing

Routine alloantibody screening is negative in many IBH cases. Expanded antibody investigations using enzyme-treated RBCs and adsorption-elution studies may reveal antibodies below standard detection thresholds. Extended RBC genotyping is now recommended for SCD patients to enable comprehensive antigen matching, reducing DHTR risk. The ASH 2020 guidelines recommend genotyping as the preferred approach for alloimmunised SCD patients [8]. Molecular genotyping also identifies RH variants prevalent in patients of African ancestry, which can give rise to antibodies against epitopes they lack [23, 25].

Passenger Lymphocyte Syndrome Serology

PLS diagnosis requires: positive DAT (IgG ± C3d); elution of donor-specific alloantibody from patient RBCs; detectable serum alloantibody of the expected specificity; and negative crossmatch with antigen-negative (donor-phenotype) RBCs. Differential diagnosis must exclude autoimmune haemolytic anaemia and drug-induced haemolysis in the post-transplant setting [12, 13].

Therapeutic Management

The management of IBH is guided by the underlying mechanism and haemolysis severity. No randomised trial evidence exists; treatment recommendations derive from case series, observational data, and expert consensus. The overarching goals are to halt haemolysis, reverse anaemia, prevent organ damage, and remove the precipitating cause [4, 11].

Immediate Measures

In DIIHA, the offending drug must be immediately and permanently discontinued. In HHS, further transfusion must be withheld if haemolysis is ongoing. Supportive care includes intravenous fluid hydration to protect renal function, oxygen supplementation, and haemodynamic monitoring in severe cases [4,15].

Corticosteroids and IVIG

High-dose corticosteroids (prednisolone 1–2 mg/kg/day) suppress antibody production, inhibit macrophage Fc-receptor-mediated phagocytosis, and reduce pro-inflammatory cytokine synthesis. IVIG (1–2 g/kg total) blocks macrophage Fc receptors and neutralises circulating alloantibodies. Both are first-line agents in moderate-to-severe HHS and severe DIIHA [4, 11, 22].

Rituximab

Rituximab, an anti-CD20 monoclonal antibody, depletes alloantibody-producing B cells in refractory HHS. It has been used prophylactically in high-risk SCD patients prior to planned transfusion. Response time is measured in weeks, limiting utility in acute severe haemolysis [4, 11].

Eculizumab

Eculizumab blocks C5 cleavage, preventing MAC formation and providing the most mechanistically targeted interruption of terminal complement-mediated RBC lysis, an approach supported by a growing body of evidence in complement-mediated haemolytic anaemias [32]. reported its successful use in paediatric SCD patients with HHS refractory to standard therapy, a finding consistent with successful outcomes reported in adult SCD patients with HHS managed with complement inhibition as part of a multi-agent approach [37]. The effectiveness of complement inhibition at the C5 level in SCD-related DHTR is further supported by experimental data demonstrating alternative pathway amplification in bystander haemolysis [29]. Cost, availability, and meningococcal infection risk are important considerations.

Tocilizumab

Tocilizumab (anti-IL-6R) targets macrophage activation in HHS. Given histopathological evidence that IL-6 drives macrophage-mediated bystander RBC phagocytosis, tocilizumab addresses the effector arm that eculizumab does not [10, 18].

Transfusion Decisions in HHS

Transfusion in HHS is potentially harmful and should be withheld unless anaemia is life-threatening. When unavoidable, extended antigen-matched RBCs should be used. Exchange transfusion may be preferable to simple transfusion [34]. Haemoglobin-based oxygen carriers have been used as temporising bridges in extreme cases [14]. Therapeutic plasma exchange has also been reported as a rescue strategy in refractory HHS [19].

Passenger Lymphocyte Syndrome Management

First-line treatment for PLS is transfusion with donor-type (antigen-negative) RBCs combined with escalation of immunosuppressive therapy. Refractory cases may require plasmapheresis, rituximab, or IVIG **[12, 13]**.

Prevention

In SCD, extended RBC matching at minimum for Rh (C, c, E, e) and Kell (K) antigens is recommended by the ASH 2020 guidelines. Molecular genotyping offers more comprehensive matching across all clinically relevant antigens [8, 25]. Prevention of DHTR in SCD also requires careful transfusion decision-making: withholding transfusion in stable patients and selecting antigen-matched units where indicated, reserving transfusion for haemoglobin levels or complications that clearly justify the immunological risk [30, 36]. Minimising unnecessary transfusion and post-transplant DAT monitoring further reduce IBH risk [8, 12].

Emerging Therapeutics

Sutimlimab (BIVV009), a selective C1s inhibitor blocking the classical complement pathway, has been shown in the Phase 3 CADENZA randomised controlled trial to rapidly halt haemolysis, improve haemoglobin, and reduce fatigue in patients with cold agglutinin disease [26]. Its mechanism of classical pathway blockade offers particular promise for IBH driven by immune complex activation. In vitro data further support the concept of C1 inhibition as a therapeutic strategy in DIIHA, with PIC1, an early-stage C1 inhibitor, reversing ceftriaxone-induced complement-mediated haemolysis ex vivo [33]. Iptacopan, a factor B inhibitor targeting the alternative pathway amplification loop, represents another potential tool [1].

Strengths and Limitations

This review consolidates the three major clinical manifestations of IBH under a unified pathophysiological framework for the first time, drawing on the most current evidence including the 2024 systematic review on complement in bystander haemolysis and the 2020 ASH guidelines for SCD transfusion [1,8]. By addressing DIIHA, HHS, and PLS within a single narrative, it provides a clinically actionable overview for transfusion medicine practitioners, haematologists, and transplant clinicians.

However, the review is subject to the inherent limitations of the narrative approach. Comprehensive systematic searching of all databases was not performed, and the selection of studies was not independently duplicated in full. Evidence for many IBH management interventions derives from case series and observational data rather than randomised controlled trials, which reflects the rarity of the condition rather than methodological limitations of this review. The management landscape, particularly for complement inhibitors, is evolving rapidly and new evidence may have emerged after the search date of January 2025.

Conclusions

IBH represents a unifying pathophysiological concept spanning multiple haematological and transplant settings. Whether triggered by drug-antibody immune complexes in DIIHA, alloantibody-driven complement activation in DHTR/HHS in SCD, or donor-derived alloimmunity in PLS, the defining feature is the destruction of antigen-negative erythrocytes that are innocent of provoking the immune response that destroys them. A high clinical index of suspicion is essential, particularly when haemolysis occurs despite a compatible crossmatch, in temporal association with drug exposure, or in the post-transplant period. Management is largely empirical, with corticosteroids and IVIG as first-line agents, and mechanistically targeted complement inhibitors and biologic therapies for refractory cases. Expanding access to extended RBC

genotyping, standardised diagnostic algorithms, and prospective trials of complement inhibitor therapies will be central to improving outcomes for this diagnostically elusive and potentially life-threatening condition.

Acknowledgments

None.

Footnotes

Reporting Checklist: The authors have completed the narrative review reporting checklist. Available at https://aob.amegroups.org/pages/view/guidelines-for-authors

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This narrative review does not involve primary human or animal data.

ORCID: Aladenika ST — 0000-0002-0021-3538

Author Contributions

- **Conception and Design**: Aghatise EK, Sahabi AI, Aladenika ST
- **Administrative Support:** Aghatise EK, Sahabi AI
- **Provision of Study Materials or Patients:** N/A
- **Collection and Assembly of Data:** Aghatise EK, Sahabi AI, Aladenika ST
- **Data Analysis and Interpretation**: Aghatise EK, Sahabi AI, Aladenika ST
- **Manuscript Writing:** All authors
- **Final Approval of Manuscript**: All authors

References

1. Evangelidis P, Evangelidis N, Vlachaki E, Gavriilaki E (2024) What is the role of complement in bystander hemolysis? Old concept, new insights. Expert Rev Hematol 17: 107-116.
2. Win N, Doughty H, Telfer P (2009) Hyperhemolysis syndrome in sickle cell disease. Expert Rev Hematol 2: 111-115.
3. Garratty G, Petz LD (1975) Drug-induced immune hemolytic anemia. Am J Med 58: 398-407.
4. Adkins BD, Carter PW, Dunham AJ (2024) How do we manage hyperhemolysis syndrome. Transfusion doi: 10.1111/trf.17995.
5. Garratty G (2009) Drug-induced immune hemolytic anemia. Hematology Am Soc Hematol Educ Program 2009: 73-79.
6. Koithara B, Sangle S, Barsode S, Gadkari N, Jadhav A (2025) Suspected sildenafil-induced immune hemolytic anemia precipitating acute kidney injury requiring hemodialysis. Cureus doi: 10.7759/cureus.89690.
7. Win N, Lucas S, Hebballi S, McKernan A, Hamilton R, et al. (2019) Histopathological evidence for macrophage activation driving post-transfusion hyperhaemolysis syndrome. Br J Haematol 186: 499-502.
8. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, et al. (2020) American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv 4: 327-355.
9. Daniels G (2013) Human Blood Groups. 3rd ed. Oxford: Wiley-Blackwell.
10. Desai N, Peters J, Davies E, Sharif J (2023) The role of tocilizumab in the treatment of post-transfusion hyperhaemolysis. Transfus Med 4: 1096-1099.
11. Madu AJ, Ugwu AO, Efobi C (2021) Hyperhaemolytic syndrome in sickle cell disease: clearing the cobwebs. Med Princ Pract 30: 236-243.
12. Pan Y, Zhao A, Jiang X, Zhou N, Wang J, et al. (2025) Passenger lymphocyte syndrome - epidemiology, pathogenesis, diagnosis, treatment and future directions: a review. Biomol Biomed 26: 215-226.
13. Lavalleye T, Streel C, Ciccarelli O, de Magnée C, Deneys V (2025) Passenger lymphocyte syndrome: a rare cause of post-transplant hemolysis following minor ABO-incompatible living donor liver transplantation. Transfus Apher Sci doi: 10.1016/j.transci.2025.104264.
14. Epstein SS, Hadley TJ (2019) Successful management of the potentially fatal hyperhaemolysis syndrome of sickle cell anaemia with a regimen including bortezomib and Hemopure. J Clin Pharm Ther 44: 815-818.
15. Harmening DM (2018) Modern Blood Banking and Transfusion Practices. 7th ed. Philadelphia: F.A. Davis.
16. Narbey D, Habibi A, Chadebech P, et al. (2017) Incidence and predictive score for delayed hemolytic transfusion reaction in adult patients with sickle cell disease. Am J Hematol 92: 1340-1348.
17. Lapite A, Bhar S, Fasipe T (2024) Eculizumab for management of hyperhemolysis syndrome in pediatric patients with sickle cell disease: a single-center case series. Pediatr Blood Cancer 71: e31061.

18. Pirenne F, Pondarré C (2023) Alloimmunization and hyperhemolysis in sickle cell disease. Hematology Am Soc Hematol Educ Program 2023: 653-659.
19. Tsitsikas DA, Mihalca D, Hibbs S, Freeman T, Bello-Sanyaolu O, et al. (2023) Therapeutic plasma exchange in the management of acute hyperhaemolytic syndrome in sickle cell disease. Br J Haematol 5: 3-5.
20. Chan Gomez J, Saleem T, Snyder S, Joseph M, Kanderi T (2020) Drug-induced immune hemolytic anemia due to amoxicillin-clavulanate: a case report and review. Cureus 12: e8666.
21. Vellanki S, Thalambedu N, Trikannad Ashwini Kumar A, Honhar M, Hendrix R, et al. (2025) Navigating hyperhemolysis in sickle cell disease: insights from literature. Diagnostics doi: 10.3390/diagnostics15141835.
22. Daly BM, Thompson S, Abu SA (2023) Severe hyperhemolysis syndrome in sickle cell anemia. Am J Hematol https://journal.chestnet.org/article/S0012-3692(23)02443-1/fulltext.
23. Yazdanbakhsh K, Ware RE, Noizat-Pirenne F (2012) Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. Blood 120: 528-537.
24. Hendrickson JE, Fasano RM (2021) Management of hemolytic transfusion reactions. Hematology Am Soc Hematol Educ Program 704 -709.
25. Linder GE, Chou ST (2021) Red cell transfusion and alloimmunization in sickle cell disease. Haematologica 106: 1135-1146.
26. Röth A, Berentsen S, Barcellini W, D Sa S, Jilma B, et al. (2022) Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. Blood 140: 980-991.
27. Petz LD, Garratty G (2004) Immune Hemolytic Anemias. 2nd ed. Philadelphia: Churchill Livingstone https://doi.org/10.1016/B978-0-443-08559-8.50012-1.
28. Leicht HB, Weinig E, Mayer B, Viebahn J, Geier A, et al. (2018) Ceftriaxone-induced hemolytic anemia with severe renal failure: a case report and review of literature. BMC Pharmacol Toxicol doi: 10.1186/s40360-018-0257-7.
29. Chonat S, Chandrakasan S, Kalinyak KA (2018) Contribution of alternative complement pathway to delayed hemolytic transfusion reaction in sickle cell disease. Haematologica 103: e483-485.
30. Pirenne F (2019) Prevention of delayed hemolytic transfusion reaction. Transfus Clin Biol 26: 99-101.
31. Fust A, Huber D, Arlettaz Mieth R (2023) Three different pathways of IgM-antibody-dependent hemolysis are mainly regulated by complement. Front Immunol 1114509.
32. Gavriilaki E, Brodsky RA (2020) Novel insights into the treatment of complement-mediated hemolytic anemias. Ther Adv Hematol 2040620720919517.
33. Cunnion KM, Feagin LM, Chicella MF, Kaszowski CL, Hair PS, et al. (2019) Ceftriaxone-induced immune hemolytic anemia: in vitro reversal with peptide inhibitor of complement C1 (PIC1). Case Rep Hematol doi: 10.1155/2019/4105653.
34. Pirenne F, Yazdanbakhsh K (2018) How I safely transfuse patients with sickle-cell disease and manage delayed hemolytic transfusion reactions. Blood 131: 2773-2781.
35. Piel FB, Steinberg MH, Rees DC (2017) Sickle cell disease. N Engl J Med 376: 1561-1573.
36. Howard J (2016) Sickle cell disease: when and how to transfuse. Hematology Am Soc Hematol Educ Program 625-631.
37. Vlachaki E, Gavriilaki E, Kafantari K, Adamidou D, Tsitsikas D, et al. (2018) Successful outcome of hyperhemolysis in sickle cell disease following multiple lines of treatment: the role of complement inhibition. Hemoglobin 42: 138-140.
38. Ballas SK, Marcolina MJ (2006) Hyperhemolysis during the evolution of uncomplicated acute painful episodes in patients with sickle cell anemia. Transfusion 46: 105-110.
39. Rother RP, Bell L, Hillmen P, Gladwin MT (2005) The Clinical Sequelae of Intravascular Hemolysis and Extracellular Plasma Hemoglobin: A Novel Mechanism of Human Disease. JAMA 293: 1653-1662.
40. Barcellini W, Fattizzo B (2015) Clinical Applications of Hemolytic Markers in the Differential Diagnosis and Management of Hemolytic Anemia. Dis Markers 635-670.