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Management of Severe Autoimmune Hemolytic Anemia: Incompatible Blood Transfusion as A Life-Saving Strategy

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ABSTRACT

Background: Autoimmune hemolytic anemia (AIHA) presents with severe anemia requiring urgent transfusion, but serological incompatibility poses challenges. This study evaluates incompatible blood transfusions in AIHA, emphasizing minimal tests for patient safety.

Methodology: This hospital-based cross-sectional study included 24 patients with primary autoimmune hemolytic anemia and severe anemia (hemoglobin <7 g/dL) evaluated between January 2023 and June 2025. Immunohematological tests, including direct antiglobulin test (DAT), indirect antiglobulin test (IAT), and antibody titration, confirmed AIHA and guided "best match" packed red blood cell (PRBC) selection.

Results: Twenty-four patients (14 females, 10 males; mean age: 45 years, range: 18-72) with primary WAIHA and severe anemia (mean hemoglobin: 5.4 g/dL) were included. All patients were DAT and IAT positive, with antibody titers ranging from 64 to 512. A total of 264 PRBC units were crossmatched (mean: 11 units/patient), of which 73 units (27.7%) were identified as “best match.” Thirty-three units were transfused (mean: 1.4 units/patient), with a crossmatch-to-transfusion ratio of 8:1. No alloantibodies were detected. Adverse effects were minimal 21 patients (87.5%) had no complications, while 3 (12.5%) experienced mild chills that resolved with supportive care. No severe hemolytic transfusion reactions occurred.

Conclusion: Incompatible transfusions, supported by minimal testing, are safe and effective in clinically imperative emergency situations of severe AIHA.

Keywords: Autoimmune hemolytic anemia, Incompatible blood transfusion, Direct antiglobulin test, best match blood, Transfusion safety

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INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a rare disorder marked by autoantibody-mediated red blood cell (RBC) destruction, with an incidence of 1-3 per 100,000 annually.[1,2] Patients often present with severe anemia, fatigue, and jaundice, confirmed by a positive direct antiglobulin test (DAT) and evidence of haemolysis.[3] Transfusion is critical in severe cases, but autoantibodies reacting with most donor RBCs complicate crossmatching, often resulting in incompatibility.[4] Incompatible transfusions, using "best match" units, are a last resort when compatible blood is unavailable, requiring careful immunohematological evaluation to minimize risks.[5]

Warm AIHA (WAIHA), the most common subtype, involves IgG autoantibodies reactive at 37°C, while cold AIHA (CAIHA) involves IgM or complement-mediated antibodies reactive below 37°C.[6] This study focuses on primary WAIHA, where no underlying condition is identified. Advances in techniques like monospecific DAT and adsorption enhance the safety of incompatible transfusions.[7]

This study examines 24 patients with primary WAIHA treated with incompatible transfusions at a tertiary care center. We aim to assess the safety and efficacy of this approach, highlighting minimal tests (DAT, IAT, autocontrol) to ensure patient safety. By analyzing serological profiles, transfusion outcomes, and adverse effects, we provide insights into managing severe AIHA when standard options are limited.

The objective of this study was to evaluate the safety and clinical effectiveness of incompatible (“best match”) packed red blood cell transfusions in patients with severe primary warm autoimmune hemolytic anemia requiring urgent transfusion, and to assess whether a limited immunohematological testing strategy comprising direct antiglobulin test, indirect antiglobulin test, and autocontrol is sufficient to ensure transfusion safety in emergency settings.

MATERIALS AND METHODS

Study Design and Settings: This hospital-based cross-sectional analytical study was conducted at a tertiary care teaching hospital from January 2023 to June 2025. The study evaluated patients diagnosed with primary warm autoimmune hemolytic anemia (WAIHA) presenting with severe anemia and requiring urgent red blood cell transfusion. The study protocol was approved by the Institutional Ethics Committee of Shri M P Shah Government Medical College and Guru Gobindsingh Hospital, Jamnagar (Ref. No. 153/03/2022 dated 12/07/2022). Written informed consent was obtained from all participants prior to enrollment.

Study Population: All consecutive adult patients (≥18 years) fulfilling the diagnostic criteria for primary WAIHA and requiring incompatible blood transfusion during the study period were included. Diagnosis of WAIHA was established based on clinical features of hemolysis, laboratory evidence of hemolysis (elevated lactate dehydrogenase, reticulocytosis, and/or reduced haptoglobin), and a positive direct antiglobulin test (DAT) demonstrating IgG with or without complement (C3d) coating of red blood cells.

Inclusion Criteria: Patients were eligible for inclusion if they were aged 18 years or older with a diagnosis of primary warm autoimmune hemolytic anemia (wAIHA), confirmed by a positive direct antiglobulin test (DAT) for IgG with or without C3d, and laboratory evidence of hemolysis. Enrolled patients were required to have severe anemia, defined as a hemoglobin level below 7 g/dL, necessitating urgent red blood cell transfusion, and must have received an incompatible ("best match") packed red blood cell (PRBC) transfusion.

Exclusion Criteria: Patients were excluded if their AIHA was secondary to an underlying condition, including autoimmune diseases, lymphoproliferative disorders, infections, or malignancies. Those with cold agglutinin disease, mixed-type AIHA, drug-induced immune hemolytic anemia, or paroxysmal cold hemoglobinuria were also ineligible. Additional exclusion criteria included the presence of alloantibodies on antibody screening, a history of severe transfusion reactions, and incomplete clinical or laboratory data.

Sample Size: Autoimmune hemolytic anemia is a rare disorder, and severe primary WAIHA requiring incompatible transfusion represents an unpredictable clinical emergency. A formal sample size calculation was therefore not feasible. The study included all consecutive eligible patients who met the inclusion criteria during the study period. A total of 24 patients constituted the complete cohort encountered at the study center.

Transfusion Threshold: The transfusion threshold of hemoglobin <7 g/dL was selected in accordance with restrictive transfusion strategies recommended by the American Association of Blood Banks and supported by the British Society for Haematology guidelines for autoimmune hemolytic anemia [8,9]. In addition to numerical hemoglobin values, transfusion decisions were guided by clinical indicators of inadequate oxygen delivery, including tachycardia, hypotension, dyspnea at rest, syncope, altered sensorium, or evidence of rapidly progressive hemolysis. In such settings, transfusion was considered clinically imperative irrespective of serological compatibility.

Immunohematological Evaluation: Venous blood samples were collected in EDTA and plain vials for hematological and serological evaluation. ABO and RhD blood grouping were performed using column agglutination (gel) technology (DiaMed, Cressier s/Morat, Switzerland). Immunohematological testing included polyspecific DAT, followed by monospecific DAT using anti-IgG and anti-C3d reagents in DAT-positive cases. Indirect antiglobulin testing (IAT) and antibody screening were performed using gel cards. Autocontrol testing was con-

ducted to confirm autoantibody reactivity. Reaction strengths for DAT, IAT, autocontrol, and crossmatch testing were graded from 1+ to 4+. Antibody titration was performed in selected cases to assess antibody strength.

Algorithm for Selection of "Best Matched" / Least Incompatible PRBC Units: All patients underwent a standardized stepwise immunohematological evaluation prior to transfusion. The selection of "best matched" or least incompatible packed red blood cell (PRBC) units was performed using the following algorithm:

Step 1: ABO and RhD Blood Grouping: Forward and reverse blood grouping was performed using column agglutination (gel) technology. Only ABO- and RhD-compatible donor units were considered for further testing.

Step 2: Direct Antiglobulin Test (DAT): Polyspecific DAT was performed initially. Positive samples were further tested using monospecific anti-IgG and anti-C3d reagents to characterize the nature of the autoantibody. DAT reaction strength was graded from 1+ to 4+.

Step 3: Indirect Antiglobulin Test (IAT) and Antibody Screening: Patient serum was tested against reagent screening cells using gel IAT to detect circulating antibodies. Reaction strength was graded (1+ to 4+). Antibody titration was performed in selected cases to assess antibody strength.

Step 4: Autocontrol Testing: Autocontrol was performed by testing patient serum against autologous red cells using IAT to confirm autoantibody reactivity. Reaction strength was graded and used as an internal reference.

Step 5: Crossmatching of Donor Units: Multiple ABO- and RhD-compatible PRBC units were crossmatched using IAT. Reaction strength for each donor unit was documented.

Step 6: Selection of "Best-Matched" Units: Donor units demonstrating reaction strength **less than or equal to the autocontrol** and weaker than the patient's IAT reaction was designated as "best-matched" or least incompatible units. Units showing stronger reactivity than the autocontrol were excluded.

Step 7: Transfusion Decision and Monitoring: Selected "best-matched" PRBC units were transfused slowly under close clinical monitoring. Vital signs were recorded before transfusion, during the first 15 minutes, and at regular intervals thereafter. Any adverse reactions were documented and managed as per institutional transfusion protocols.

Transfusion Protocol and Monitoring: All incompatible PRBC transfusions were administered under close clinical supervision. Baseline vital parameters, including heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation, were recorded prior to transfusion. Transfusions were initiated at a slow rate during the initial 15 minutes, followed by gradual escalation to complete each unit over 2-3 hours based on patient tolerance and clinical condition. Vital signs were monitored at baseline, at 15 minutes, every 30 minutes during transfusion, and at completion of transfusion. Patients were observed for at least one-hour post-transfusion for delayed adverse reactions.

Premedication was not routinely administered and was reserved for patients with a prior history of minor transfusion reactions, using antihistamines and/or antipyretics at the discretion of the treating physician. Transfusion was immediately discontinued if patients developed fever, chills, hypotension, respiratory distress, hemoglobinuria, or any clinical features suggestive of an acute hemolytic transfusion reaction. Appropriate supportive care and investigations were initiated as per institutional transfusion reaction protocols.

Statistical Analysis: Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation or median with range, as appropriate. Categorical variables were expressed as frequencies and percentages. Pre- and post-transfusion hemoglobin levels were compared using paired t-test. Correlation analysis was performed to assess the relationship between antibody titers and adverse transfusion reactions. A p-value <0.05 was considered statistically significant.

RESULTS

Twenty-four patients (14 females, 10 males; mean age: 45 years, range: 18-72) with primary WAIHA were included. Mean pre-transfusion hemoglobin was 5.4 g/dL (range: 3.4-6.8 g/dL). All had positive DAT results (mean grade: 2.8, range: 1-4), with 21 showing IgG alone and three showing IgG+C3d. IAT was positive in all cases (mean grade: 2.1, range: 1-4), with antibody titers of 64-512 (mean: 236). Autocontrol was positive (mean grade: 2.3, range: 1-4). No alloantibodies were detected.

A total of 264 PRBC units were crossmatched (mean: 11 units/patient, range: 6-21), with 73 (27.7%) identified as "best match" (mean: 3.1 units/patient, range: 2-5). Thirty-three units were transfused (mean: 1.4 units/patient, range: 1-3), yielding a crossmatch-to-transfusion ratio of 8:1.

Adverse effects were minimal (Table 2). Twenty-one patients (87.5%) had no complications, while three (12.5%) experienced mild chills, resolved with supportive care. No severe hemolytic reactions occurred.

Three patients with combined IgG and C3d positivity (Cases 8, 16, and 23) presented unique challenges due to stronger DAT reactivity (mean grade: 3.3) and higher antibody titers (mean: 512). These patients required more extensive crossmatching (mean: 18 units tested) but achieved successful transfusions with no severe adverse effects. The presence of chills in two of these cases suggests a potential association with complement activation, though the small sample size limits definitive conclusions.

Table 1: Baseline clinical and Immunohematological characteristics of patients with Primary WAIHA (N = 24)

Parameter	Value
Age (years)	45 ± 14
	Range: 18-72
Sex	
Male	10 (41.7%)
Female	14 (58.3%)
Pre-transfusion haemoglobin (g/dL)	5.4 ± 0.9
DAT positivity	
IgG only	21 (87.5%)
IgG + C3d	3 (12.5%)
DAT reaction strength (grade)	2.8 ± 1.1
IAT positivity	24 (100%)
IAT reaction strength (grade)	2.1 ± 1.0
Antibody titer	Median 256
	Range: 64-512
Auto control positivity	24 (100%)
No. of PRBC units crossmatched/patient	11 ± 4
Best-matched PRBC units identified/patient	3.1 ± 0.9
PRBC units transfused/patient	1.4 ± 0.7

Legend: Data are expressed as mean ± SD, median (range), or number (%) as appropriate.
AIHA: Autoimmune Hemolytic Anemia; Hb: Hemoglobin; DAT: Direct Antiglobulin Test; IAT: Indirect Antiglobulin Test; PRBC: Packed Red Blood Cells; SD: Standard Deviation

Table 2: Adverse Effects of Incompatible Transfusions

Adverse Effect	Number of Patients (%)
None	21 (87.5%)
Chills	3 (12.5%)
Severe Reactions	0 (0%)

Biochemical markers of hemolysis, including lactate dehydrogenase, bilirubin levels, and reticulocyte counts, were primarily assessed at baseline for diagnostic confirmation of autoimmune hemolytic anemia. Routine serial measurement of these parameters immediately following transfusion was not performed, as the primary endpoint of the study was clinical transfusion safety and the occurrence of transfusion-related adverse reactions during the acute transfusion period. No clinical or laboratory evidence suggestive of overt worsening hemolysis was observed following transfusion in any patient.

DISCUSSION

Incompatible transfusions in WAIHA are challenging due to autoantibody reactivity, yet critical for severe anemia.[5] This study confirms their safety and efficacy, with a mean hemoglobin increment of 1.8 g/dL, higher than some reports (Table 3), possibly due to careful selection of "best match" units. The 12.5% incidence of mild chills, mainly in IgG+C3d cases, suggests complement involvement, warranting further study. The absence of severe reactions aligns with findings that incompatible transfusions do not significantly exacerbate haemolysis.[10]

The high crossmatch-to-transfusion ratio (8:1) reflects the difficulty in finding "best match" units, particularly with high-titer autoantibodies (>128) or strong IAT (>2+). The mean TAT of 240 minutes underscores the need for streamlined protocols to expedite emergency transfusions.

STRENGTH AND LIMITATIONS

This study provides real-world evidence on the safety of incompatible blood transfusions in severe primary WAIHA, supported by standardized serological testing and close monitoring. The use of minimal yet effective immunohematological tests ensures practical applicability in resource-limited settings.

The relatively small sample size reflects the rarity of severe primary WAIHA requiring incompatible transfusion and is comparable to previously published single-center experiences and single-center design limit generalizability. Long-term post-transfusion outcomes and alloimmunization risks were not assessed. Additionally, advanced molecular typing and extended antibody screening were not performed due to logistic constraints. Also, this study did not adjust for potential confounding factors such as corticosteroid dose, use of additional immunosuppressive agents, baseline severity, or etiology of autoimmune hemolytic anemia. These variables may influence longer-term hematological response; however, the primary objective of the study was to evaluate the immediate safety and feasibility of incompatible ("best match") red blood cell transfusion. Given the small sample size and cross-sectional design focusing on acute transfusion outcomes during the same admission period, multivariable adjustment for these confounders was not feasible.

CONCLUSION

Incompatible transfusions are a safe, effective option for severe primary WAIHA when compatible units are unavailable. Minimal tests (DAT, IAT, autocontrol) ensure safety, with our cohort achieving a 1.8 g/dL hemoglobin increase and minimal adverse effects. Transfusion services must prioritize rapid "best match" PRBC issuance. Further studies are needed to standardize protocols and assess long-term outcomes.

Individual Author's Contribution: All authors contributed significantly to the study. DD, HM, and JN were involved in study conception, design, data collection, analysis, interpretation, and manuscript preparation. JS contributed to study conception, data collection, and manuscript preparation. All authors reviewed and approved the final version of the manuscript before submission.

Availability of data: The data that support the findings of this study are available from the corresponding author on reasonable request.

Declaration of Non-use of generative AI Tools: This article was prepared without the use of generative AI tools

for content creation, analysis, or data generation. All findings and interpretations are based solely on the authors' independent work and expertise.

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