Klinik: Jurnal Ilmiah Kedokteran dan Kesehatan
Volume 5, Nomor 1, Januari 2026
E-ISSN .: 2809-2090; P-ISSN .: 2809-235X, Hal. 563-576
DOI: https://doi.org/10.55606/klinik.v5i1.5760
Tersedia: https://journalcenter.org/index.php/klinik

Pathophysiologic Mechanisms and Serological Resolution Strategies for Cold Agglutinin-Mediated ABO Grouping Discrepancies in Transfusion Medicine

(Clinical Ramifications and Operational Considerations A Narrative Review)

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Abstract. *Cold agglutinin-mediated ABO grouping discrepancies pose persistent diagnostic and operational challenges in transfusion medicine. Cold-reactive autoantibodies, predominantly IgM with complement-binding capacity, cause false agglutination during forward and reverse grouping, potentially delaying crossmatching and jeopardizing transfusion safety. These issues are particularly relevant in laboratories with variable automation, such as in Indonesia, where manual methods remain common. This narrative review synthesized literature retrieved from electronic databases (Google Scholar, ScienceDirect, Scopus, and PubMed) on the pathophysiology, serological identification, and laboratory resolution strategies of cold agglutinin-mediated ABO grouping discrepancies, with emphasis on diagnostic, clinical, and operational implications across laboratory settings. Cold agglutinins cause spurious ABO grouping results through temperature-dependent erythrocyte agglutination and complement activation. Identification involves direct antiglobulin testing, saline replacement, and prewarming. Resolution requires warm-phase techniques, monospecific antisera, and adsorption/elution studies. Operationally, prolonged turnaround time, increased reagent use, and workflow strain have been reported, especially in resource-limited laboratories. Timely recognition and structured management of cold agglutinin-mediated discrepancies are essential to maintain transfusion accuracy. Implementation of standardized protocols, competency-based training, and evidence-based national guidelines can optimize patient safety and operational efficiency across varying healthcare infrastructures.*

Keywords*: ABO Blood Type; Cold Agglutinins; Laboratory Management; Serological Interference; Transfusion Medicine*

1. INTRODUCTION

The ABO blood group system holds fundamental importance in transfusion medicine, as it classifies blood group types according to the presence or absence of A and B antigens on erythrocytes and corresponding antibodies in the plasma (Desai et al., 2024; Fathima & Killeen, 2023; Hashim et al., 2025). Accurate grouping prevents hemolytic transfusion reactions and underpins all pretransfusion testing. Blood typing is performed through two complementary methods, which are forward grouping and reverse grouping (Fathima & Killeen, 2023; Hashim et al., 2025; Sahu et al., 2022). Forward grouping identifies cell surface antigens using known antisera, while reverse grouping detects corresponding antibodies in serum; concordance between these reactions is essential for correct blood typing (Desai et al., 2024; Fathima & Killeen, 2023).

Cold agglutinins (CA) are autoantibodies, predominantly of the immunoglobulin M (IgM) class, that bind to erythrocyte surface antigens, most commonly the I or i antigen, at temperatures below the physiological range, typically between 0°C and 30°C. Their binding can lead to complement activation and spontaneous red cell agglutination at room temperature (Berentsen et al., 2022; Gabbard & Booth, 2020). In transfusion laboratories, CAs represent a

Naskah Masuk: 29 September 2025; Revisi: 17 Oktober 2025; Diterima: 09 November 2025; Tersedia: 11 November 2025

well-documented source of serologic interference, particularly during ABO forward and reverse grouping (Gabbard & Booth, 2020). Studies have reported that cold autoantibodies account for a significant proportion of ABO discrepancy cases, contributing to pretransfusion testing errors and potentially compromising transfusion safety if unrecognized (Desai et al., 2024; Makroo et al., 2019).

CA-mediated ABO discrepancies pose diagnostic and operational challenges in transfusion laboratories worldwide, particularly in settings with variable infrastructure and limited automation (Datta & Berentsen, 2024; WHO, 2022). Misinterpretation of serologic results due to cold autoantibodies may delay crossmatching and increase the risk of incompatible transfusion, emphasizing the need for standardized resolution strategies (Fathima & Killeen, 2023; Makroo et al., 2019). In Indonesia, a developing country, where manual and semi-automated methods remain common alongside emerging automated systems in tertiary centers, recognition of CA interference is critical to ensure transfusion safety and laboratory reliability (Amjad et al., 2024; Erdayanti et al., 2024). This review aims to delineate the pathophysiologic mechanisms, serological identification, and resolution strategies of CA-mediated ABO grouping discrepancies, integrating clinical and operational considerations relevant to modern transfusion practice.

2. METHODS

This review employed a narrative literature review design focusing on the pathophysiology, serological identification, and laboratory resolution strategies of CA-mediated ABO grouping discrepancies. Relevant literature was searched through electronic databases, including Google Scholar, ScienceDirect, Scopus, and PubMed, using combinations of the following keywords and phrases: *"cold agglutinin" OR "cold reactive autoantibody", "ABO grouping discrepancy" OR "ABO typing error" OR "ABO discrepancy", "transfusion medicine" OR "blood bank testing", "serological interference" OR "serologic testing error",* and *"resolution strategy" OR "prewarming technique" OR "adsorption method"*. Search strings also incorporated conceptual phrases such as "*cold agglutinin interference in ABO typing*", "*resolution strategies for ABO discrepancies*", *"management of cold antibody in transfusion testing"*, and *"operational challenges in blood grouping"* to capture integrative diagnostic and operational discussions. Articles published between 2015 and 2025 were considered, prioritizing full-text papers in English that addressed serological or clinical aspects of cold agglutinins and their impact on blood grouping accuracy. Data from the selected literature were critically reviewed and synthesized narratively to summarize pathophysiologic

mechanisms, diagnostic approaches, and laboratory management strategies. No quantitative or statistical analyses were performed, and ethical approval was not required, as this study did not involve human or animal subjects.

3. RESULTS AND DISCUSSION

Pathophysiology of Cold Agglutinins

About 15-30% of autoimmune hemolytic anemias (AIHA) are caused by cold agglutinin disease (CAD), an uncommon hemolytic condition. CA are autoantibodies that induce CAD because they may agglutinate erythrocytes at temperatures lower than body temperature (Berentsen et al., 2022; Chevalier et al., 2025; Sharma et al., 2023). Based on their titer and thermal range, CAs are divided into two categories: benign and pathological. While benign CAs have a very low titer (<64) and react at 4^{o}C, they can be identified in the serum of most normal, healthy individuals. Pathological CAs react at or near body temperature (30^{o}C to 37^{o}C) and have high titer values (Sharma et al., 2023).

In CAD, monoclonal IgM antibodies – and, less frequently, IgG or IgA – mediate CA activity (Berentsen et al., 2022; Gabbard & Booth, 2020; Zahid et al., 2021). Among patients with detectable clonal immunoglobulins, monoclonal IgM is identified in approximately 91%, IgG in 4.5%, and both IgM and IgG in 2.8% (Berentsen et al., 2022; Chevalier et al., 2025). The pentameric structure of IgM confers high avidity binding to repetitive epitopes on erythrocyte surface antigens, causing agglutination. The resulting IgM-antigen complex serves as a potent activator of the classic complement pathway through its interaction with the C1 complement complex, initiating a cascade that results in deposition of C3b and subsequent opsonization or intravascular hemolysis when complement activation proceeds to the membrane attack complex (Berentsen et al., 2020; Röth et al., 2021).

Thermal amplitude refers to the highest temperature at which erythrocyte agglutination occurs as a result of CA binding to its target antigen (Berentsen et al., 2020; Bizjak et al., 2021; Climent et al., 2022). Hematologic studies have demonstrated that the pathogenic potential of CAs is more closely associated with their thermal amplitude than with antibody titer (Bizjak et al., 2021; Climent et al., 2022). The clinical relevance of CAs is also influenced by antigen specificity, as IgM CAs predominantly recognize carbohydrate antigens of the Ii blood group system (Berentsen, 2020; Berentsen et al., 2020; Gertz, 2022). The i antigen, composed of linear poly-N-acetyllactosamine, is primarily expressed on neonatal erythrocytes, whereas the I antigen becomes the dominant form in adults (Berentsen, 2020; Gertz, 2022).

At low temperatures, IgM antibodies bind to these antigens and crosslink multiple erythrocytes simultaneously, leading to visible hemagglutination (Berentsen et al., 2020; Röth et al., 2022). This agglutination is usually reversible with warming, but antibodies with higher thermal amplitude remain active closer to physiologic temperatures, where they can trigger complement activation. Once initiated, complement components, particularly C3, may remain bound, although IgM dissociates from red cells upon rewarming to 37^{o}C, allowing hemolysis to continue despite the disappearance of visible agglutination (Gertz, 2022; Wasnik et al., 2021).

The degree of erythrocyte agglutination mediated by CAs is strongly influenced by temperature (Gabbard & Booth, 2020; Röth et al., 2022). CAs typically react optimally at 0-4^{o}C; however, pathogenic antibodies with higher thermal amplitude may remain active closer to physiologic temperature, resulting in clinically significant hemolysis and cold-induced symptoms, especially in cooler peripheral circulation such as nose, ears, or fingers (Berentsen, 2020; Gabbard & Booth, 2020).

Mechanism of ABO Discrepancies

ABO discrepancies arise when results from forward and reverse grouping do not correspond (Erdayanti et al., 2024; Fathima & Killeen, 2023; Shahshahani & Hayati, 2020). Discrepancies between forward and reverse grouping or crossmatch incompatibility are relatively common findings in clinical practice (Qiu et al., 2023). ABO discrepancies are categorized into four groups: Group I involves weak or missing antibodies; Group II is characterized by weak or missing antigens; Group III results from rouleaux formation or pseudo-agglutination; and Group IV encompasses miscellaneous causes that produce false reactions, including autoantibodies and polyagglutination (Fathima & Killeen, 2023; Kravchun et al., 2023). CAs, predominantly IgM with complement-binding capacity, are one of the most common causes of group IV blood group discrepancies and can lead to significant diagnostic confusion in transfusion medicine (Makroo et al., 2019; Shahshahani & Hayati, 2020).

In ABO forward grouping, the red blood cells are tested to determine antigen expression using anti-A and anti-B antisera (Fathima & Killeen, 2023; Hashim et al., 2025). CAs, usually IgM autoantibodies, can interfere with the forward grouping process by causing spontaneous agglutination with the patient's red cells, leading to false-positive result (Fathima & Killeen, 2023). The agglutination happened because CAs often bind across a broad range of erythrocyte surfaces, especially with the pentameric structure of IgM, resulting in aggregates that mimic genuine antigen-antibody reactions (Ying et al., 2021). The risk of misinterpretation is

heightened when CAs exhibit a broad thermal amplitude, which even with low-level binding can be detected by potent monoclonal antisera used in routine ABO typing.

Meanwhile, the reverse grouping identifies ABO antibodies present in a patient's serum by testing against reagent red cells, specifically A1 and B cells (Desai et al., 2024; Fathima & Killeen, 2023; Hashim et al., 2025). A study by Makroo et al. reported that cold autoantibodies are the most frequent causes of ABO typing discrepancies detected during reverse grouping. These antibodies may react with reagent A1 or B cells, thereby masking the expected agglutination pattern between the patient's plasma and the reagent red cells (Desai et al., 2024; Makroo et al., 2019; Shahshahani & Hayati, 2020). Such interference can lead to misclassification of an individual's blood group typing if unrecognized, underscoring the need for confirmatory testing strategies tailored to minimize CA interference.

Several studies have documented instances where CAs led to ABO discrepancies. For example, a case study reports CAs and blood group discrepancies can be associated with diseases like COVID-19, and another study at a tertiary care oncology center noted that among ABO discrepancy cases, cold antibodies were responsible in several instances of Type IV discrepancies (Desai et al., 2024; Qiu et al., 2023; Raghuwanshi, 2020). These discrepancies naturally direct attention to laboratory identification strategies, where targeted testing such as direct antiglobulin test (DAT), saline replacement, and controlled-temperature assays provide the necessary tools to resolve these discrepancies.

Laboratory Identification

Discrepancies in forward and reverse ABO grouping that cannot be explained should raise the possibility that the patient's serum contains cold autoantibodies (Fathima & Killeen, 2023). Strong agglutination in forward grouping that persists at low temperature but resolves at 37^{o}C or pan-agglutination in reverse grouping are the common indicators. Such discrepancies often result from CA activity that obscures the true ABO grouping pattern. The clinical setting can further support suspicion, as CAD is frequently linked to infections, lymphoproliferative disorders, or autoimmune disorders. Early detection of these signs is essential for achieving accurate blood typing and preventing transfusion-related errors (Qiu et al., 2023).

The DAT or direct Coombs test is the most widely used laboratory test to confirm cold autoantibody activity (Gabbard & Booth, 2020; Jalink et al., 2024; Kerkar et al., 2022). A positive DAT, especially with C3d positivity, alongside a positive autocontrol, strongly suggests complement-coated red cells due to CAs (Fathima & Killeen, 2023; Gabbard & Booth, 2020). In contrast, rouleaux formation (a stacking artifact caused by elevated plasma proteins)

can mimic agglutination and is not immune-mediated (Gertz, 2022; Higuchi et al., 2023). Microscopic examination reveals rouleaux as coin-stacked cells, while cold agglutination shows irregular clumping (Heath et al., 2018). The use of monospecific antiglobulin reagents further helps distinguish complement-mediated (cold) from IgG-mediated reactions (Jalink et al., 2024; Wang et al., 2021).

Following the interpretation of DAT and autocontrol to identify cold autoantibody activity, several practical laboratory adjustments can further clarify ABO typing discrepancies (Fathima & Killeen, 2023). Saline replacement is effective for resolving rouleaux interference: the patient's plasma is replaced with isotonic saline, dispersing coin-stacked rouleaux, while true cold agglutination persists (Higuchi et al., 2023; Wang et al., 2025). For CAs, testing at 37^{o}C is particularly useful: prewarming patient plasma, red cells, and reagents prevents IgM-mediated cold binding, thereby restoring accurate forward and reverse grouping patterns (Fathima & Killeen, 2023; Heath et al., 2018). Additionally, performing ABO testing with washed red cells, preferably with warm saline, removes nonspecifically bound proteins, complement, and residual cold antibodies, reducing background reactivity and improving specificity (Fathima & Killeen, 2023; Johnson & Puca, 2022). These straightforward methods are widely applicable in both high- and low-resource laboratories, ensuring accurate resolution of serological discrepancies and supporting safe transfusion practice.

Resolution Strategies

Prewarming aims to prevent cold-reactive IgM autoantibodies from binding red cell antigens by maintaining the sample, reagents, and environment at 37^{o}C from the outset of testing (Raos et al., 2021; Subramaniyan, 2023). This thermal control reduces cold antibody interference in forward and reverse blood grouping (Qiu et al., 2023; Subramaniyan, 2023). For sample preparation, the patient's erythrocytes should be incubated at 37^{o}C for approximately 15 minutes to inactivate IgM antibodies. During forward grouping, repeated washing of the red cells with warm (37^{o}C) normal saline effectively removes antibody interference, while in reverse grouping, the patient's serum may be absorbed and reused multiple times to ensure accurate testing. If this step is unsuccessful, forward blood grouping should be repeated after the erythrocytes have been treated with Dithiothreitol (DTT) or 2-Mercaptoethanol (2-ME) to prevent agglutination due to IgM antibodies (Fathima & Killeen, 2023; Johnson & Puca, 2022; Qiu et al., 2023; Subramaniyan, 2023). These reagents disrupt the disulfide bonds within IgM antibodies, thereby eliminating autoagglutination observed during ABO forward grouping (Johnson & Puca, 2022; Subramaniyan, 2023). Prewarming

may be ineffective with very high-titer or broad-thermal-range antibodies and can occasionally mask weak alloantibodies, so results should be interpreted with caution (Subramaniyan, 2023).

When additional clarification is needed, targeted antibody detection can be enhanced with monospecific reagents. These reagents minimize false reactivity from cold autoantibodies: in the DAT context, monospecific anti-C3d and anti-IgG reagents differentiate complement-coated cells (typical of CAs) from IgG-mediated processes, avoiding ambiguous polyspecific results. When the sample is maintained at 37^{o}C after collection, a polyspecific DAT is performed first; if positive, monospecific testing for C3d and IgG follows (Gabbard & Booth, 2020). Clinically, replacing polyspecific AHG with monospecific reagents clarifies whether complement fixation is the dominant mechanism and guides subsequent resolution steps (Wang et al., 2021). If cold autoantibody interference persists or further characterization is required, adsorption and elution methods provide additional resolution.

When cold autoantibody interference cannot be resolved – particularly in cases where reverse grouping discrepancies persist – retesting should be conducted at body temperature, as this generally eliminates the reactivity of cold autoantibodies (Desai et al., 2024; Fathima & Killeen, 2023). If discrepancies remain, a cold autoabsorption procedure can be performed by incubating the patient's erythrocytes with their own serum, allowing autoantibodies to bind and thereby reducing their concentration; the supernatant serum is then used for repeat reverse grouping (Fathima & Killeen, 2023). To verify that a positive DAT results from an autoantibody, an elution procedure may be employed, in which bound antibodies are released from erythrocytes using a dilute acid solution, and the resulting eluate is tested for antibody identification. Adsorption studies remain one of the most reliable approaches to remove autoantibodies from plasma while preserving any underlying alloantibodies. In recently transfused patients, allogeneic adsorption using donor cells of known phenotypes is preferred, whereas in non-transfused patients, autologous adsorption is used to confirm the autoimmune origin of the antibody and prevent depletion of alloantibodies to high-prevalence antigens. Patient erythrocytes are commonly treated with ZZAP (DTT/2-ME + ficin/papain) or with ficin or papain alone to remove bound antibodies and expose antigen sites; multiple adsorption cycles may be necessary depending on the antibody strength and titer, often requiring several hours to complete (Johnson & Puca, 2022; Raos et al., 2021).

Maintaining the specimen and all testing steps at body temperature is critical to prevent renewed binding of cold-reactive antibodies. Blood samples from patients with suspected or confirmed CA interference should be collected in pre-warmed tubes, kept at 37^{o}C during transport, and promptly processed (Agarwal et al., 2020; Gabbard & Booth, 2020; Raos et al.,

2021). Centrifugation, plasma or serum separation, and cell washing are performed in temperature-controlled equipment to avoid cooling (Raghuwanshi, 2020; Raos et al., 2021). Instruments and reagents used for grouping and antibody testing are equilibrated to 37^{o}C before use (Agarwal et al., 2020; Raos et al., 2021). Communication between phlebotomy, transport, and transfusion service staff ensures that specimens are never exposed to refrigeration or ambient temperatures that can reactivate IgM cold autoantibodies (Agarwal et al., 2020). These workflow measures help preserve accurate serologic results and reduce the risk of recurring ABO discrepancies.

Clinical Significance

CAs are frequently observed in both primary cold agglutinin disease (CAD), which occurs in the absence of an identifiable underlying condition, and secondary cold agglutinin syndrome (CAS), which arises in association with infections, autoimmune disorder, lymphoproliferative diseases, and Waldenstrom macroglobulinemia. Among infectious etiologies, *Mycoplasma pneumoniae,* Epstein-Barr virus (EBV), and cytomegalovirus (CMV) are the most commonly implicated triggers (Gertz, 2019; Kaur et al., 2021). Even when clinically silent, these autoantibodies can react strongly at temperatures below 37^{o}C and interfere with ABO grouping, creating forward or reverse discrepancies (Agarwal et al., 2020). Recognition of their clinical and serologic significance is critical, as identification of a cold autoantibody may reflect an occult infection or lymphoproliferative disorder in secondary CAS, represent primary CAD, or simply explain unexplained ABO grouping discrepancies that require further evaluation.

Cold-reactive IgM autoantibodies potently trigger the classical complement pathway, causing primarily C3b-mediated extravascular hemolysis and, in severe cases, progression to intravascular hemolysis (Gabbard & Booth, 2020; Gertz, 2019). In transfusion settings, unrecognized CA interference can delay the provision of compatible units or result in the inadvertent selection of ABO-incompatible blood (Basavarajegowda & Shastry, 2022; Zahid et al., 2021). Acute hemolytic reactions may manifest with hemoglobinuria, jaundice, or a rapid fall in hemoglobin, posing significant morbidity or even mortality (Gertz, 2019; Pham et al., 2022). Donor red cells are equally vulnerable, and passive cooling of blood during storage or infusion can intensify antibody binding. Mitigation strategies include maintaining patient specimens and transfusion components at 37^{o}C, using in-line blood warmers, and close monitoring for biochemical or clinical evidence of hemolysis (Gertz, 2019; Shima et al., 2025). Identifying CA-mediated ABO discrepancies is therefore not merely an analytical challenge but a critical patient-safety imperative (Shima et al., 2025).

Patients with clinically significant CAs require careful transfusion planning to prevent hemolysis and avoid misleading compatibility results (Iberahim et al., 2024). Blood samples should be collected and maintained at 37^{o}C until serum separation, and pretransfusion testing performed with pre-warmed methods and 37^{o}C saline washes (Shima et al., 2025; Ying et al., 2021). A DAT followed by monospecific antiglobulin reagents (anti-IgG and anti-C3d) aids in distinguishing complement-only coating characteristic of cold IgM from IgG-mediated reactions (Gabbard & Booth, 2020). Red-cell units must be ABO/Rh matched and transfused through an approved blood warmer and patient core temperature maintained to reduce cold antibody activity (Shima et al., 2025; Ying et al., 2021). Transfusion should be restricted to clear indications, and close communication between the laboratory and clinical teams is essential to minimize hemolysis risk and ensure timely, safe delivery of compatible blood (Ying et al., 2021).

CAs can create persistent ABO and crossmatch incompatibilities that complicate routine pretransfusion testing and strain blood supply logistics. Broad-thermal-amplitude IgM antibodies frequently cause panagglutination in antibody screening and positive autocontrols, masking underlying alloantibodies and necessitating extended-warm-phase crossmatching or adsorption studies (Kokoris et al., 2022; Yousuf et al., 2024). These additional procedures consume specialized reagents, technologist time, and equipment, while delaying the release of compatible units. In urgent settings, least-incompatible or group O red cells may be issued, a practice that – though not systematically quantified – can place additional pressure on universal donor stocks (Kim et al., 2023). These operational challenges highlight the need for proactive coordination between transfusion services and clinicians to mitigate delays and ensure safe, timely blood provision.

Operational Considerations

CA interference can markedly prolong compatibility testing, resulting in longer turnaround times (TATs) for issuing blood and potentially compromising urgent transfusion support (Tripathi & Chuda, 2024; Yousuf et al., 2024). Further investigation and resolution of certain discrepancies can be labor-intensive and time-consuming, potentially delaying essential care for critically ill patients (Fathima & Killeen, 2023; Tripathi & Chuda, 2024). These challenges also increase reagent consumption and require technologists to be proficient in specialized testing (Tripathi & Chuda, 2024). In Indonesia, this problem is compounded by limited resources. A study at Dr. Sardjito General Hospital, Yogyakarta, reported that the average TAT for packed red-cell provision was significantly prolonged when extended serological workups were required, highlighting operational strain in transfusion services

(Kaslam et al., 2023). These findings underline the need for capacity-building and workflow optimization to ensure timely, safe transfusion support under conditions complicated by CAs.

Approaches to managing CA-mediated ABO discrepancies depend heavily on laboratory capacity. In low-resource settings, emphasis should be placed on pragmatic measures such as strict prewarming protocols, prompt communication between clinical and laboratory teams, and prioritization of universal donor units in emergencies when compatibility testing is delayed (Amjad et al., 2024; Datta & Berentsen, 2024; Fathima & Killeen, 2023). Capacity-building through staff training and standard operating procedures is critical to minimize errors (Amjad et al., 2024; Datta & Berentsen, 2024; Tripathi & Chuda, 2024). High-resource settings, by contrast, can integrate advanced tools including automated immunohematology platforms, adsorption techniques, and molecular typing to resolve complex discrepancies more rapidly (Berentsen et al., 2019; Fathima & Killeen, 2023). The differing strategies underscore the importance of tailoring operational practices to local infrastructure while maintaining patient safety.

Recommendations & Future Perspectives

Early recognition of CA-mediated ABO discrepancies is essential to prevent transfusion delays and potential hemolytic complications. Laboratories should adopt structured algorithms that include maintaining temperature control of specimens and reagents, the routine use of prewarming or saline replacement when indicated, and direct antiglobulin testing with both polyspecific and monospecific reagents. When standard serology remains inconclusive, escalation to adsorption/elution studies or referral for molecular typing should be undertaken. Standard operating procedures, competency-based staff training, and clear clinical-laboratory communication pathways are vital to ensure consistent practice. Where feasible, regional referral networks should be developed to manage complex cases and reduce turnaround time, thereby safeguarding transfusion safety.

Despite advances, significant gaps remain in defining standardized practices for CA-related discrepancies. Data quantifying their true incidence, operational costs, and clinical consequences are limited, and consensus thresholds for thermal amplitude or decision-making algorithms remain variable. Comparative studies are needed to evaluate the effectiveness and cost-utility of prewarming, adsorption/elution, automated platforms, and molecular typing across both low- and high-resource environments. Implementation research should also assess how structured training, workflow redesign, and referral pathways affect turnaround times and patient outcomes. Looking forward, the development of evidence-based consensus guidelines

that integrate laboratory, clinical, and operational perspectives is essential to harmonize management strategies and optimize transfusion safety globally.

4. CONCLUSION

CA-mediated ABO grouping discrepancies represent a persistent challenge in transfusion medicine, with implications that extend beyond laboratory complexity to directly affect patient safety. The presence of cold-reactive autoantibodies can delay compatibility testing, increase reagent and staffing demands, and, in critical settings, compromise timely transfusion support. Effective recognition and resolution require a structured diagnostic approach, skilled personnel, and reliable access to confirmatory methods such as prewarming, adsorption/elution, or molecular typing. While high-resource centers may increasingly rely on automated immunohematology platforms and advanced molecular assays, most laboratories in Indonesia and other low- to middle-income countries must depend on pragmatic strategies, staff training, and clear communication pathways to mitigate risk. Strengthening operational capacity, developing referral networks for complex cases, and fostering evidence-based national guidelines is an essential step to ensure safe and timely transfusion. Ultimately, bridging laboratory rigor with practical implementations across resource settings is key to reducing delays and safeguarding transfusion outcomes in patients affected by CAs.

Acknowledgments: The author expresses sincere gratitude to all parties who, directly or indirectly, provided support and input during the preparation of this manuscript. Constructive suggestions and feedback for future improvements are highly appreciated.

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