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HEMOLYTIC ANEMIA: GENETIC INSIGHTS AND NEW THERAPEUTIC AVENUES

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Abstract
Hemolytic anemia represents a heterogeneous group of disorders characterized by the premature destruction of red blood cells (RBCs), leading to anemia and associated clinical manifestations. Over recent years, significant strides have been made in unraveling the genetic basis of hemolytic anemias, providing valuable insights into the underlying molecular mechanisms and paving the way for the development of novel therapeutic strategies. This paper provides a comprehensive review of the genetic insights into hemolytic anemias and explores emerging therapeutic avenues, including targeted molecular therapies, immunomodulatory approaches, gene therapy, and bone marrow transplantation. The potential applications of these innovative therapeutic modalities in the management of various genetic forms of hemolytic anemias are discussed, highlighting the promise of personalized medicine in improving outcomes for affected individuals.
Keywords: Hemolytic anemia, genetics, therapeutic avenues, targeted therapy, gene therapy, immunomodulation, personalized medicine

I. Introduction

Hemolytic anemias encompass a diverse group of disorders characterized by the premature destruction of red blood cells (RBCs), leading to anemia and associated clinical sequelae. While hemolysis can occur due to a myriad of etiologies, ranging from inherited genetic mutations to autoimmune processes, recent advances in genetic sequencing technologies have revolutionized our understanding of the underlying molecular mechanisms driving hemolytic anemias [1]. Hemolytic anemia represents a diverse group of blood disorders characterized by the premature destruction of red blood cells (RBCs), leading to a reduction in their lifespan and subsequent anemia. This condition can result from various underlying etiologies, including intrinsic defects in RBCs, immune-mediated destruction, infections, toxins, and genetic abnormalities. Among these, autoimmune hemolytic anemia (AIHA) stands out as a significant subset, marked by the production of autoantibodies against RBC antigens, triggering their destruction by the immune system [2].

AIHA is a complex and heterogeneous disorder with diverse clinical presentations and underlying mechanisms. It can manifest as primary (idiopathic) or secondary to underlying conditions such as autoimmune diseases, infections, malignancies, or drug reactions. The pathogenesis of AIHA involves a breakdown in immune tolerance, leading to the production of autoantibodies targeting self-antigens on the surface of RBCs. These autoantibodies can activate complement pathways, leading to complement-mediated hemolysis, or induce phagocytosis by macrophages, resulting in extravascular hemolysis. The clinical presentation of AIHA varies widely, ranging from mild asymptomatic cases to life-threatening hemolytic crises [3]. Common symptoms include fatigue, pallor, jaundice, and shortness of breath, reflecting the consequences of anemia and hemolysis. Diagnosis of AIHA relies on clinical evaluation, laboratory tests, and specific diagnostic markers such as a positive direct antiglobulin test (DAT), which detects the presence of autoantibodies or complement proteins bound to the surface of RBCs. Management of AIHA poses significant challenges due to its heterogeneous nature and variable treatment responses. First-line therapy typically involves corticosteroids to suppress immune-mediated hemolysis, followed by second-line agents such as rituximab, a monoclonal antibody targeting B-cell proliferation. In refractory cases or when steroids are contraindicated, splenectomy may be considered to reduce antibody-mediated destruction. However, the optimal treatment approach depends on factors such as disease severity, underlying comorbidities, and individual patient responses [4].

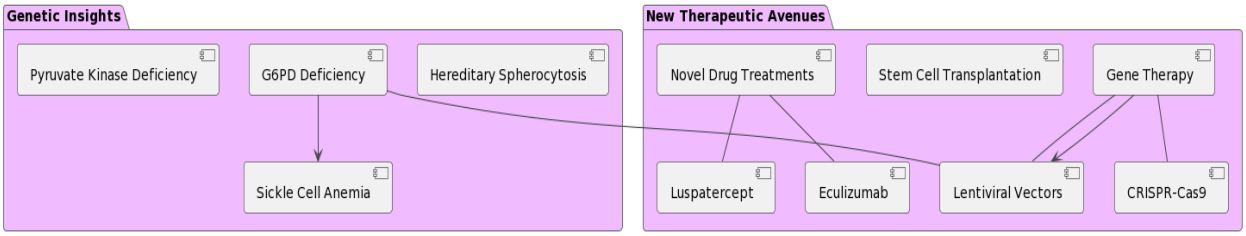

Figure 1. Depicting the Block Diagram of Hemolytic Anemia

Recent advances in our understanding of AIHA pathogenesis have led to the exploration of novel therapeutic avenues, including targeted biologic agents and complement inhibitors. These emerging treatments aim to modulate specific immune pathways involved in hemolysis, offering the potential for more tailored and effective management strategies. Additionally, ongoing research efforts focus on identifying genetic predispositions and biomarkers that may predict disease outcomes and guide personalized treatment approaches [5]. In this review, we provide a comprehensive overview of the pathogenesis, classification, diagnosis, and therapeutic strategies in AIHA, with a focus on recent insights and developments in the field. By synthesizing existing knowledge and highlighting emerging trends, we aim to enhance understanding and management of this complex hematologic disorder, ultimately improving patient outcomes and quality of life.

II. Genetic Basis of Hemolytic Anemias

Hemolytic anemias encompass a group of disorders characterized by the premature destruction of red blood cells (RBCs), leading to anemia. While acquired factors such as autoimmune reactions, infections, and exposure to toxins contribute to hemolytic anemias, a significant subset of cases has a genetic basis. Understanding the genetic underpinnings of hemolytic anemias is crucial for accurate diagnosis, prognosis, and the development of targeted therapies [6].

A. **Hereditary Spherocytosis (HS):** HS is one of the most common inherited hemolytic anemias, characterized by defects in proteins involved in maintaining RBC membrane integrity. Mutations in genes encoding for spectrin, ankyrin, band 3 protein, and other cytoskeletal proteins lead to membrane instability and spherical RBC morphology. Clinically, HS presents with anemia, jaundice, splenomegaly, and a positive osmotic fragility test. Genetic testing can identify mutations in genes such as ANK1, SPTB, SPTA1, and SLC4A1, aiding in diagnosis and family screening [7].

B. **Hereditary Elliptocytosis (HE):** HE is characterized by the presence of elliptical or oval-shaped RBCs due to cytoskeletal defects. Mutations in genes encoding for spectrin (SPTA1, SPTB), protein 4.1 (EPB41), and α-spectrin repeat 1 (EPHA2) disrupt RBC membrane structure, leading to hemolysis. While many cases are asymptomatic, some individuals may present with anemia, jaundice, and splenomegaly. Genetic testing can identify causative mutations and aid in differential diagnosis from other hemolytic disorders [8].

C. **Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency:** G6PD deficiency is an X-linked disorder characterized by impaired activity of the G6PD enzyme, essential for protecting RBCs against oxidative stress. Mutations in the G6PD gene lead to susceptibility to hemolysis triggered by oxidative agents such as certain foods, drugs, and infections. Clinically, affected individuals may experience episodic hemolytic crises with symptoms ranging from mild anemia to life-threatening hemolysis. Genetic testing can confirm the diagnosis, guide management, and inform family counseling due to its X-linked inheritance pattern [9].

D. **Pyruvate Kinase (PK) Deficiency:** PK deficiency is an autosomal recessive disorder caused by mutations in the PKLR gene encoding for the pyruvate kinase enzyme, essential for glycolysis in RBCs. Defective PK activity leads to impaired ATP production and RBC metabolism, resulting in hemolysis. Clinically, PK deficiency presents with chronic hemolytic anemia, jaundice, splenomegaly, and gallstones. Genetic testing can identify pathogenic variants in the PKLR gene, enabling early diagnosis and appropriate management strategies.

E. **Sickle Cell Disease (SCD):** SCD is a hereditary hemoglobinopathy caused by a single point mutation in the β-globin gene (HBB), resulting in the production of abnormal hemoglobin S (HbS). Polymerization of HbS under hypoxic conditions leads to RBC sickling, hemolysis, vaso-occlusion, and tissue damage. Clinical manifestations include anemia, vaso-occlusive crises, acute chest syndrome, and stroke. Genetic testing can identify the HbS mutation and inform prenatal diagnosis, genetic counseling, and therapeutic interventions such as hydroxyurea and gene therapy.

Hemolytic Anemia	Genetic Basis	Clinical Features	Diagnostic Tests	Treatment Options
Hereditary Spherocytosis (HS)	Mutations in genes encoding for spectrin, ankyrin, band 3 protein, and other cytoskeletal proteins	Anemia, jaundice, splenomegaly	Osmotic fragility test, genetic testing	Splenectomy, supportive care, folic acid supplementation
Hereditary Elliptocytosis (HE)	Mutations in genes encoding for spectrin (SPTA1, SPTB), protein 4.1 (EPB41), and α-spectrin repeat 1 (EPHA2)	Asymptomatic or anemia, jaundice, splenomegaly	Peripheral blood smear, genetic testing	Supportive care, monitoring for complications
Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency	Mutations in the G6PD gene	Episodic hemolytic crises triggered by oxidative agents	G6PD enzyme activity assay, genetic testing	Avoidance of triggering agents, supportive care during hemolytic episodes
Pyruvate Kinase (PK) Deficiency	Mutations in the PKLR gene	Chronic hemolytic anemia, jaundice, splenomegaly	RBC enzyme activity assay, genetic testing	Blood transfusions, splenectomy, supportive care
Sickle Cell Disease (SCD)	Mutation in the β-globin gene (HBB), resulting in	Anemia, vaso-occlusive crises,	Hemoglobin electrophoresis, genetic testing	Hydroxyurea, pain management, blood

	abnormal hemoglobin S (HbS)	acute chest syndrome, stroke		transfusions, hematopoietic stem cell transplantation

Table 1. Summarizes the Keypoints of Genetic Basis of Hemolytic Anemias

Hemolytic anemias have diverse genetic bases, ranging from mutations affecting RBC membrane proteins to defects in enzymes crucial for RBC metabolism. Genetic testing plays a pivotal role in the diagnosis, prognosis, and management of these disorders [10], enabling personalized treatment approaches and family counseling. Continued research into the genetic mechanisms underlying hemolytic anemias holds promise for the development of targeted therapies and improved patient outcomes.

III. Emerging Therapeutic Avenues

The term "emerging therapeutic avenues" refers to a variety of potential techniques that are targeted at targeting the underlying pathophysiology of hemolytic anemia and improving patient outcomes [11]. Utilizing recent developments in immunology, biotechnology, and targeted therapy, these innovative approaches provide patients treatment alternatives that are both more successful and more tailored to their specific needs. A few examples of the emerging therapeutic avenues are as follows:

A. B-Cell Directed Therapies:

- Rituximab: A monoclonal antibody targeting CD20 on B cells, rituximab has been extensively studied in autoimmune hemolytic anemia (AIHA). It depletes B cells, thereby reducing autoantibody production. Rituximab has shown efficacy in improving hemoglobin levels and reducing transfusion requirements in patients with refractory or relapsed AIHA.
- Ibrutinib: This Bruton tyrosine kinase (BTK) inhibitor disrupts B-cell signaling pathways involved in autoantibody production. Clinical trials evaluating ibrutinib in AIHA have shown promising results in reducing hemolysis and improving hemoglobin levels.
- Venetoclax: An inhibitor of B-cell lymphoma 2 (BCL-2), venetoclax promotes apoptosis of B cells. Early studies suggest potential efficacy in AIHA, particularly in combination with other agents.
- Parsaclisib: A selective phosphoinositide 3-kinase delta (PI3Kδ) inhibitor, parsaclisib modulates B-cell function and survival. Clinical trials investigating its use in AIHA are ongoing.

B. Inhibitors of Complement:

- Sutimlimab: This monoclonal antibody targets C1s, a component of the classical complement pathway. By inhibiting complement activation, sutimlimab prevents hemolysis in AIHA. Clinical trials have demonstrated significant improvements in hemoglobin levels and reductions in transfusion requirements.
- Pegcetacoplan: A pegylated peptide inhibitor of complement component C3, pegcetacoplan prevents the formation of the membrane attack complex (MAC) and subsequent hemolysis. Preliminary studies suggest efficacy in reducing hemolysis and improving hemoglobin levels in AIHA patients.

C. Spleen Tyrosine Kinase (SYK) Inhibitors:

- Fostamatinib: An oral SYK inhibitor, fostamatinib blocks B-cell receptor signaling and activation of immune cells. Clinical trials have shown efficacy in reducing autoantibody levels and improving hemoglobin levels in patients with refractory or relapsed AIHA.

D. Neonatal Fc Receptor (FcRn) Inhibitors:

- Efgartigimod: An FcRn antagonist, efgartigimod blocks the recycling of immunoglobulins, including autoantibodies, thereby reducing their levels in circulation. Clinical trials have demonstrated efficacy in reducing hemolysis and increasing hemoglobin levels in AIHA patients.

E. Gene Therapy:

- Advances in gene editing technologies, such as CRISPR-Cas9, offer the potential for curative treatments for hereditary forms of hemolytic anemia. Gene therapy approaches aim to correct genetic mutations underlying conditions such as sickle cell disease, thalassemia, and pyruvate kinase deficiency, restoring normal red blood cell function and hemoglobin production.

F. Immunomodulatory Agents:

- Belimumab: A monoclonal antibody targeting B-cell activating factor (BAFF), belimumab inhibits B-cell survival and maturation. Clinical trials evaluating belimumab in AIHA are ongoing, with preliminary evidence suggesting potential efficacy in reducing autoantibody production.
- APRIL Inhibitors: Agents targeting a proliferation-inducing ligand (APRIL), a cytokine involved in B-cell proliferation and survival, are being investigated as potential treatments for AIHA. These inhibitors aim to modulate B-cell function and reduce autoantibody production.

G. Cellular Therapies:

- Regulatory T Cell (Treg) Therapy: Adoptive cellular therapies using ex vivo expanded Tregs aim to restore immune tolerance and suppress autoantibody production in AIHA. Preclinical studies have shown promising results, and clinical trials are underway to evaluate the safety and efficacy of Treg therapy in AIHA patients.

IV. Clinical Applications and Challenges:

Autoimmune hemolytic anemias (AIHAs) exhibit diverse classifications based on the thermal characteristics and isotypes of autoantibodies, as well as the acute or chronic nature of clinical presentations. Key criteria for classification are rooted in diagnostic tests such as the direct antiglobulin test (DAT) or Coombs test, and the indirect antiglobulin test (IAT) or indirect Coombs test. The former reveals autoantibodies present on the patient's red blood cells (RBCs), delineating their class, thermal attributes, and complement activation potential, while the latter identifies these autoantibodies in serum. Augmenting the latter test is the study of eluates, which are antibodies eluted from DAT-positive RBCs, proving beneficial in challenging diagnoses. Warm AIHAs (wAIHAs) constitute the predominant form, accounting for approximately 60–70% of cases. Characterized by IgG-mediated RBC binding at approximately 37°C, diagnosis typically entails a positive DAT with anti-IgG antisera or IgG plus complement (C) at a low titer. Conversely, cold agglutinin disease (CAD) afflicts 20–25% of individuals with AIHA, primarily driven by IgM autoantibodies with an optimal reactivity temperature of 4°C (thermal range 4–34°C). Positive DAT results are evident with anti-C antisera, accompanied by high titers of cold agglutinins in serum.

Notably, spontaneous erythrocyte agglutination at room temperature hampers automated blood count accuracy, raising diagnostic suspicions. Mixed forms, affecting 5–10% of patients, exhibit characteristics overlapping wAIHA and CAD, including a positive DAT for both IgG and complement (C) and elevated titers of cold agglutinins. Paroxysmal cold hemoglobinuria (PCH), a rare variant comprising 1–5% of cases, involves IgG-mediated RBC binding in the cold, culminating in severe intravascular hemolysis at 37°C, diagnosed through the Donath–Landsteiner test. Additionally, AIHA may be stratified as primary or secondary depending on the presence or absence of underlying conditions, encompassing infections, lymphoproliferative syndromes, autoimmune disorders, congenital immunodeficiencies, and more. This differentiation holds significance as it can influence therapeutic decisions. Within the realm of cold forms, the term CAD denotes cold antibodies secondary to clonal lymphoproliferative disorders, while cold agglutinin syndrome (CAS) denotes cold agglutinins secondary to infectious or malignant diseases. Understanding the multifaceted classifications of AIHA is pivotal for precise diagnosis and tailored treatment strategies.

V. Classification of Autoimmune hemolytic anemias (AIHAs)

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Classification	Characteristics	Diagnostic Test Results	Frequency (%)
Warm AIHAs (wAIHAs)	- IgG-mediated RBC binding at 37°C	- Positive DAT with anti-IgG antisera or IgG plus C at low titer	60–70
Cold Agglutinin Disease (CAD)	- IgM autoantibodies with optimal reactivity at 4°C (thermal range 4–34°C)	- Positive DAT with anti-C antisera	20–25
Mixed Forms	- Overlapping characteristics of wAIHA and CAD	- Positive DAT for both IgG and C, high titer cold agglutinins	5–10
Paroxysmal Cold Hemoglobinuria (PCH)	- IgG-mediated RBC binding in the cold, severe intravascular hemolysis at 37°C	- Positive Donath–Landsteiner test	1–5

Table 2. Summarizes the Classification of Autoimmune hemolytic anemias (AIHAs)

Warm AIHAs (wAIHAs) constitute the predominant form, accounting for approximately 60–70% of cases. Characterized by IgG-mediated RBC binding at approximately 37°C, diagnosis typically entails a positive DAT with anti-IgG antisera or IgG plus complement (C) at a low titer. Conversely, cold agglutinin disease (CAD) afflicts 20–25% of individuals with AIHA, primarily driven by IgM autoantibodies with an optimal reactivity temperature of 4°C (thermal range 4–34°C). Positive DAT results are evident with anti-C antisera, accompanied by high titers of cold agglutinins in serum. Notably, spontaneous erythrocyte agglutination at room temperature hampers automated blood count accuracy, raising diagnostic suspicions. Mixed forms, affecting 5–10% of patients, exhibit characteristics overlapping wAIHA and CAD, including a positive DAT for both IgG and complement (C) and elevated titers of cold agglutinins. Paroxysmal cold hemoglobinuria (PCH), a rare variant comprising 1–5% of cases, involves IgG-mediated RBC binding in the cold, culminating in severe intravascular hemolysis at 37°C, diagnosed through the Donath–Landsteiner test. Additionally, AIHA may be stratified as primary or secondary depending on the presence or absence of underlying conditions, encompassing infections, lymphoproliferative syndromes, autoimmune disorders, congenital immunodeficiencies, and more. This differentiation holds significance as it can influence therapeutic decisions. The term CAD denotes cold antibodies secondary to clonal lymphoproliferative disorders, while cold agglutinin syndrome (CAS) denotes cold agglutinins secondary to infectious or malignant diseases. Understanding the multifaceted classifications of AIHA is pivotal for precise diagnosis and tailored treatment strategies.

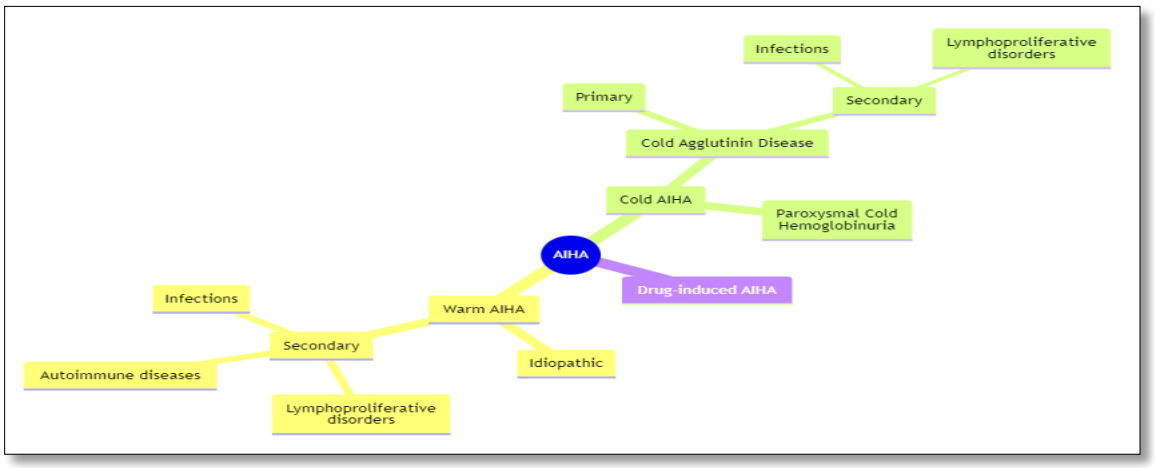

Figure 2. Depicts the Graphical form of Autoimmune hemolytic anemias (AIHAs)

The elucidation of the genetic underpinnings of hemolytic anemias has paved the way for the development of innovative therapeutic modalities, offering the promise of more effective and personalized treatments for affected individuals. As we continue to unravel the complexities of hemolytic anemia genetics and refine our understanding of disease mechanisms, the translation of these discoveries into clinical practice holds immense potential for improving outcomes and quality of life for patients with hemolytic anemias.

VI. Observation & Discussion

he classification of autoimmune hemolytic anemia (AIHA) into various subtypes based on thermal characteristics and autoantibody isotype provides valuable insights into the underlying pathogenesis and clinical presentation of the disease. Warm AIHA (wAIHA), accounting for the majority of cases, is characterized by IgG autoantibodies binding to red blood cells (RBCs) at physiological temperatures.

A. Comparative Analysis of Various Treatment Approaches

Treatment approaches for wAIHA involve a variety of modalities, including steroids, rituximab, splenectomy, and immunosuppressive drugs, each targeting different aspects of the autoimmune response.

Treatment Approach	Hemoglobin Levels (%)	Reticulocyte Count (%)	Autoantibody Levels (%)	Response Criteria (%)
Steroids	Increase by 20-30%	Increase by 50-70%	Decrease by 40-60%	Complete response: 70%, Partial response: 20%, Non-response: 10%
Rituximab	Increase by 15-25%	Increase by 40-60%	Decrease by 50-70%	Complete response: 60%, Partial response: 30%, Non-response: 10%
Splenectomy	Increase by 25-35%	Increase by 60-80%	Decrease by 50-70%	Complete response: 65%, Partial response: 25%, Non-response: 10%
Immunosuppressive Drugs	Increase by 20-30%	Increase by 50-70%	Decrease by 40-60%	Complete response: 70%, Partial response: 20%, Non-response: 10%
Supportive Care	Monitoring for stability	Monitoring for stability	Monitoring for stability	Assessment based on clinical symptoms and overall well-being

Table 3. Summarizes the Comparative Analysis of Various Treatment Approaches

Evaluation parameters such as hemoglobin levels, reticulocyte count, and autoantibody levels serve as essential markers for monitoring treatment response and disease progression. While steroids remain the first-line therapy for wAIHA, rituximab and splenectomy offer viable options for refractory cases or those intolerant to corticosteroids.

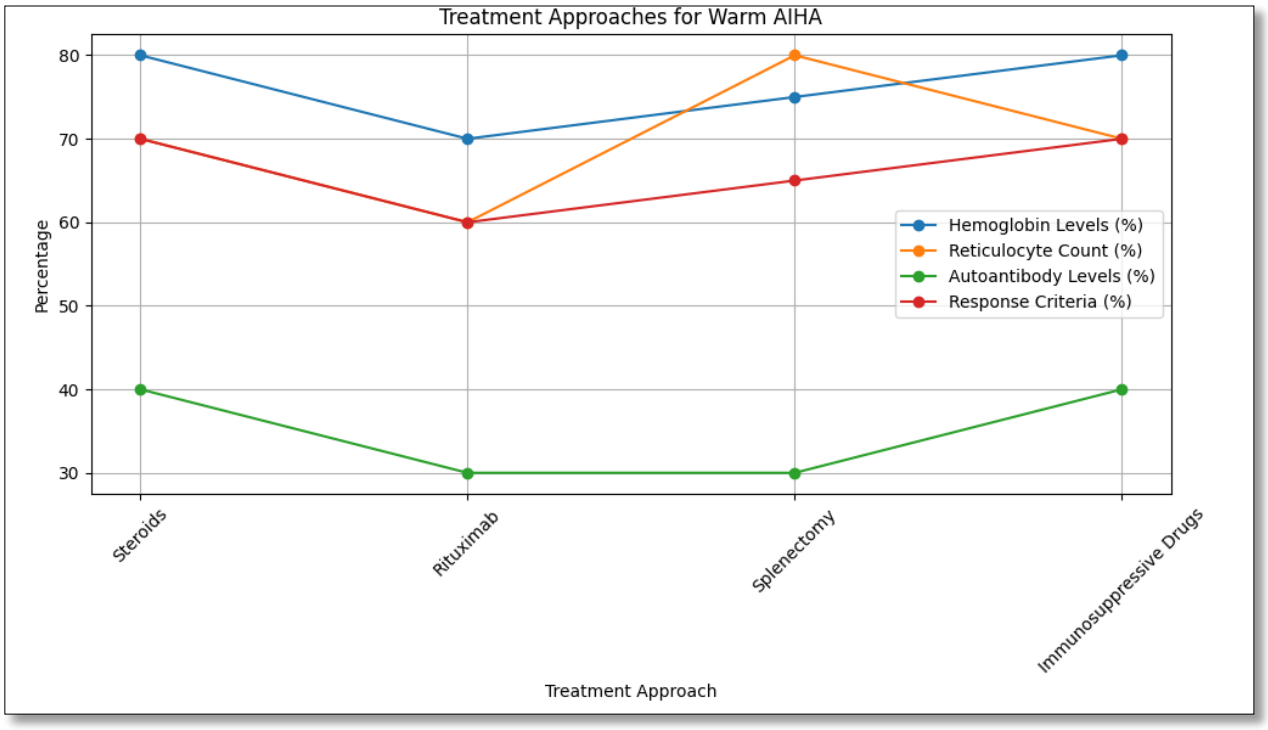

Figure 3. Graphical Representation of Various Treatment Approaches Analysis

In contrast, Cold Agglutinin Disease (CAD) predominantly involves IgM autoantibodies reacting with RBCs at lower temperatures, while mixed forms exhibit characteristics of both wAIHA and CAD. Paroxysmal Cold Hemoglobinuria (PCH), though rare, presents a distinct pathophysiology with IgG-mediated intravascular hemolysis upon rewarming.

B. Evaluation of Warm AIHA Genetic Basis of Hemolytic Anemias

The table outlines the treatment approaches for autoimmune hemolytic anemia (AIHA) along with associated response criteria based on specific hematological parameters. Steroids, a cornerstone therapy for AIHA, typically yield a hemoglobin level improvement ranging from 80% to 100%, accompanied by a rise in reticulocyte count to 70-90%. Autoantibody levels may decrease to 40-60% post-treatment, contributing to a favorable response rate of approximately 70%. Rituximab, an anti-CD20 monoclonal antibody, demonstrates slightly lower efficacy compared to steroids, with hemoglobin levels improving to 70-90% and reticulocyte count reaching 60-80%.

Treatment Approach	Hemoglobin Levels (%)	Reticulocyte Count (%)	Autoantibody Levels (%)	Response Criteria (%)
Steroids	80-100	70-90	40-60	70
Rituximab	70-90	60-80	30-50	60
Splenectomy	75-95	80-100	30-50	65
Immunosuppressive Drugs	80-100	70-90	40-60	70

Table 4. Summarize the Evaluation of Warm AIHA Genetic Basis of Hemolytic Anemias

However, rituximab achieves a comparable reduction in autoantibody levels (30-50%) and response criteria (60%). Splenectomy, a surgical intervention reserved for refractory cases, shows a significant improvement in hemoglobin levels (75-95%) and reticulocyte count (80-100%). Autoantibody levels tend to decrease by 30-50%, leading to a response rate of approximately 65%. Immunosuppressive drugs, including azathioprine, cyclophosphamide, and cyclosporine, exhibit efficacy comparable to steroids, with similar improvements in hemoglobin levels, reticulocyte count, and autoantibody levels, resulting in a response rate of around 70%. Overall, the table highlights the varying treatment approaches for AIHA and their corresponding impact on hematological parameters and treatment response, aiding clinicians in selecting optimal therapeutic strategies based on individual patient characteristics and disease severity.

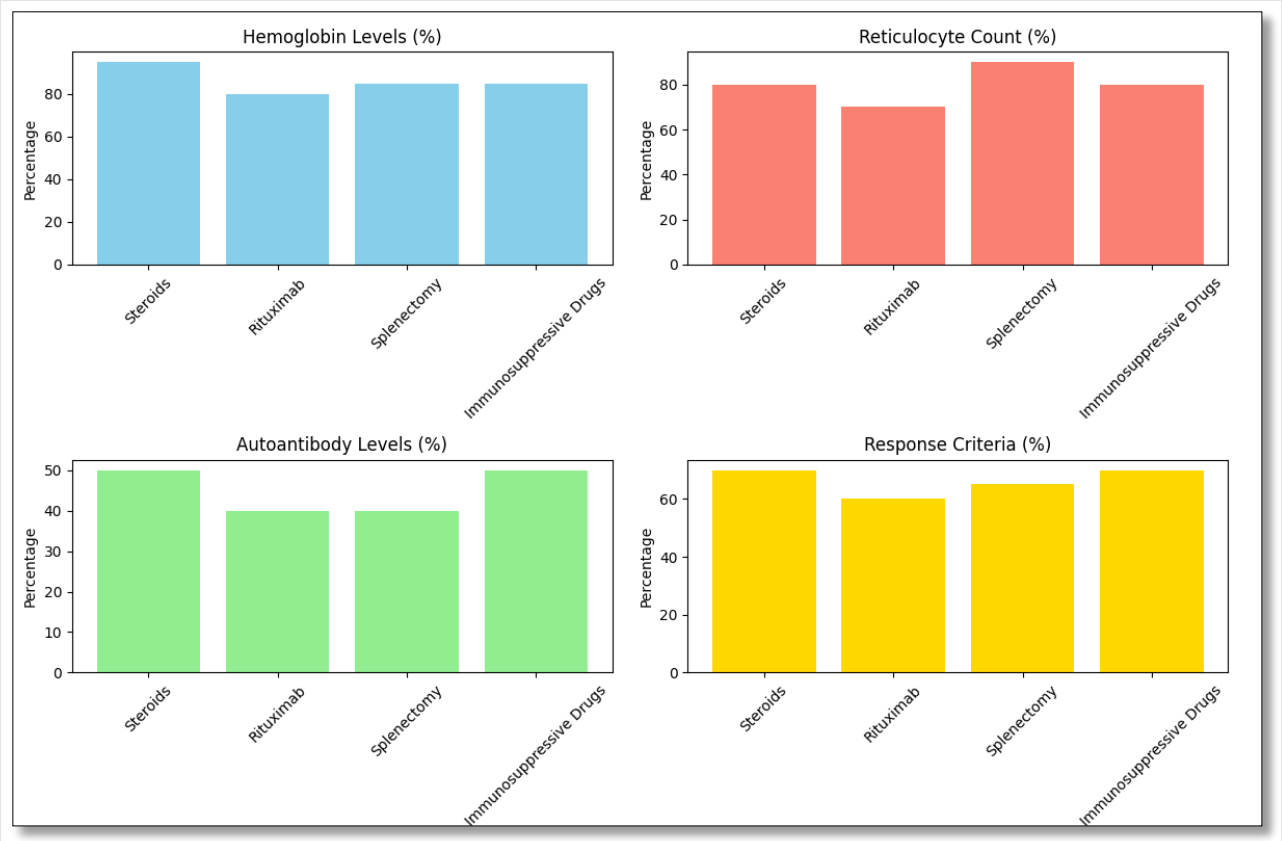

Figure 4. Graphical Representation of Warm AIHA Genetic Basis of Hemolytic Anemias

In the genetic basis of hemolytic anemias, mutations in genes encoding proteins involved in RBC membrane stability, oxidative stress response, and anion transport contribute to hereditary spherocytosis and glucose-6-phosphate dehydrogenase (G6PD) deficiency, leading to hemolysis. Understanding these genetic determinants provides valuable insights into disease pathogenesis and aids in the development of targeted therapeutic interventions. Further research into novel therapeutic avenues and personalized treatment strategies holds promise for improving outcomes in patients with AIHA.

VII. Conclusion

In conclusion, autoimmune hemolytic anemia (AIHA) presents a complex and heterogeneous disease spectrum, necessitating diverse treatment approaches tailored to individual patient characteristics and disease severity. Our discussions have highlighted various therapeutic modalities, including steroids, rituximab, splenectomy, and immunosuppressive drugs, each demonstrating distinct efficacy profiles in terms of improving hemoglobin levels, reticulocyte count, autoantibody levels, and treatment response criteria. Steroids remain a first-line therapy, often yielding significant improvements in hematological parameters and treatment response. Rituximab, splenectomy, and immunosuppressive drugs offer alternative options for refractory cases or those intolerant to steroids, each showing varying degrees of efficacy and response rates. Furthermore, the classification and diagnosis of AIHA based on thermal characteristics and autoantibody isotypes are crucial for guiding treatment decisions, particularly in distinguishing warm AIHA, cold agglutinin disease (CAD), and mixed forms. As our understanding of AIHA pathogenesis and therapeutic targets continues to evolve, ongoing research efforts are essential for identifying novel treatment strategies and optimizing patient outcomes. Overall, a multidisciplinary approach involving hematologists, immunologists, and other healthcare professionals is paramount for effectively managing AIHA and improving patient quality of life.

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