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Molecular mimicry as a central mechanism in autoimmune blood disorders: A comprehensive review

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Abstract

Autoimmune hemolytic anemia (AIHA) is an uncommon hematologic condition where autoantibodies cause red blood cells (RBCs) to be destroyed too soon. IgG, IgM, or sometimes IgA antibodies attach to RBC surface antigens, causing extravascular or intravascular hemolysis via complement activation and macrophage phagocytosis. AIHA may arise as a main idiopathic disorder or as a side effect of drug exposure, autoimmune diseases, hematologic malignancies, or infections.

Warm antibody AIHA (wAIHA), cold antibody AIHA (cAIHA, which includes CAD and CAS), mixed AIHA, paroxysmal cold hemoglobinuria, drug-induced AIHA, and other uncommon variants are among the subtypes of AIHA. While cold forms of wAIHA are IgM-mediated and act at lower temperatures, resulting in RBC agglutination and complement-induced lysis, wAIHA is primarily mediated by IgG antibodies that are active at body temperature and cause extravascular hemolysis. IgG and IgM antibodies are both involved in mixed AIHA, which is rare but frequently clinically severe. Female sex, advanced age, genetic susceptibility, hematologic malignancies, prior transfusions, and organ transplantation are risk factors. Molecular mimicry, in which infections create antigens that are structurally or sequentially similar to RBC proteins, is a key mechanism in the pathophysiology of AIHA. The immune system is misled by this resemblance into generating T cells and cross-reactive antibodies that attack host red blood cells.

Antibodies or immunoglobulins such as IgG or IgM play a significant role in mixed type of AIHA, this effect is rare, in fact if it occurs it frequently clinically severe. Female sex, advanced age, genetic susceptibility, hematologic malignancies, prior transfusions, and organ transplantation are risk factors. Molecular mimicry, that occurred after such an infection that led for the production of antigens particles that are structurally or functionally similar to red cell proteins, this phenomenon is considered as a key mechanism in the pathophysiology of AIHA. The cells of the immune system because of this defect lead to autoimmune disorder disease or AIHA (the resemblance of the new produced T cells and cross-reactive antibodies that attack host red blood cells).

Autoimmune hemolytic anemia (AIHA) is uncommon immune-mediated disorder that are characterized by premature destruction of the red blood cells due to autoantibodies. It includes warm, cold, and mixed types, and may be primary or secondary to underlying conditions. Understanding the diseases mechanisms with its risk factors is very essential for the accurate diagnosis and for effective management.

Keywords: Molecular mimicry, autoimmune hemolytic anemia (AIHA), autoantibodies, red blood cells (RBCs)

Introduction

Scientific definition of autoimmune hemolytic anemia

The AIHA is consider a very rare disorder but clinically relevant hematological condition that is characterized by autoantibodies against self-antigens that cause red blood cells (RBCs) to be destroyed too soon. The prevalence is higher in women, and the global incidence varies between 0.8 and 3 instances per 100,000 people per year, peaking in early childhood and elderly adults (Barcellini & Fattizzo, 2020; Jäger *et al.*, 2020)^[1, 2].

Immune anemia, also known as autoimmune hemolytic anemia (AIHA), is a rare hematologic disease that affects 1-3 people out of every 100,000 (Böttiger & Westerholm, 1973)^[9]. AIHA occurs when autoantibodies attack the patient's own red blood cells (RBCs),

causing them to be prematurely destroyed (lysed) and therefore reduced in circulation. In extreme situations, the RBCs' normally 100-120 day lifespan is shortened to a few days (Shoenfield, Cervera, & Gershwin, 2008;) [13]. During RBC lysis, the intracellular contents of RBCs rupture and spill into the blood and tissues, resulting in the majority of the disease's distinctive clinical characteristics.

Pathophysiologically, the immune response can initiate the

membrane assault complex by activating the conventional and/or alternative complement pathways. The ability of immunoglobulin molecules to activate complement is determined by their structural differences (Hill *et al.*, 2017) [3].

The extramedullary damage caused by the binding of IgG, IgM, or, less frequently, IgA antibodies to RBC surfaces is what defines AIHA (Branch & Parry, 2024) [5] figure 1.

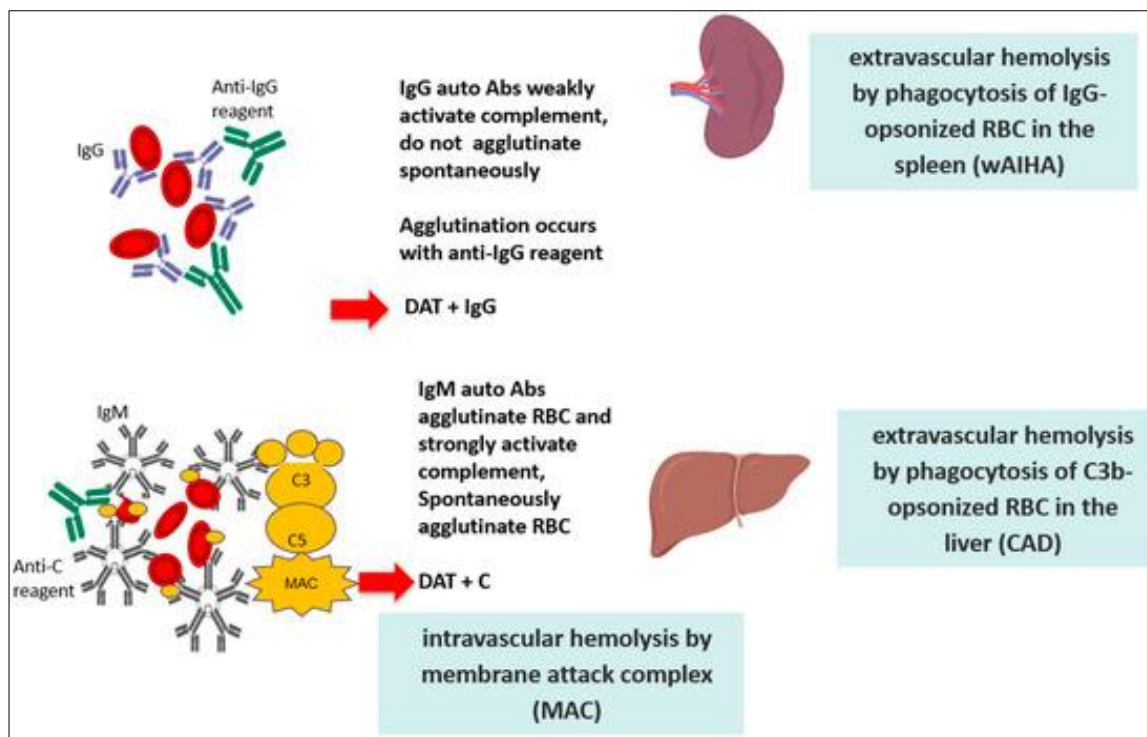


Fig 1: Pathogenic mechanism of Red blood Cell (RBC) destruction (Barcellini *et al.*, 2015) [14]

Patterns of autoimmune hemolytic anemia (AIHA)

• Warm-Antibody Autoimmune Hemolytic Anemia (wAIHA)

Warm autoimmune hemolytic anemia (wAIHA) is typified by increased RBC degradation brought on by warm agglutinins, which are essentially all immunoglobulin G (IgG) antibodies that interact best with erythrocyte antigens around 37 °C. According to annual reports, the frequency is roughly 1 to 3 per 100,000 people (Eaton *et al.*, 2007) [4]. Although the disease can strike at any age, the usual time of diagnosis is roughly 52 years, and most studies show a small female predominance. The majority of patients experience a relapsing, chronic illness pattern, while up to 30% of patients may get a durable remission with first medication (Barcellini).

Extravascular processes in wAIHA mainly cause hemolysis in the liver and spleen (Barcellini, 2015) [14]. Using Fcγ

receptors, splenic macrophages identify IgG-coated erythrocytes and either fully phagocytose the cell or partially remove the cell membrane. During succeeding circulations, the latter become microspherocytes, which are sequestered in the splenic sinusoids and are less deformable than regular RBCs. Additionally, antibody-dependent cell-mediated cytotoxicity by T cells with Fc receptors may be included in extravascular hemolysis (Costa *et al.*, 2025) [6].

The complement system can be triggered by specific IgG subclasses, which results in the deposition of C3 fragments on RBC membranes. Liver macrophages with C3 fragment receptors then eliminate these opsonized cells. Severe complement activation causes intravascular hemolysis, which is clinically characterized by hemoglobinuria and significantly high lactate dehydrogenase levels, as well as the building of the membrane assault complex (C5b-9) on the surface of the red blood cell (Brodsky, 2015), (Figure 2).

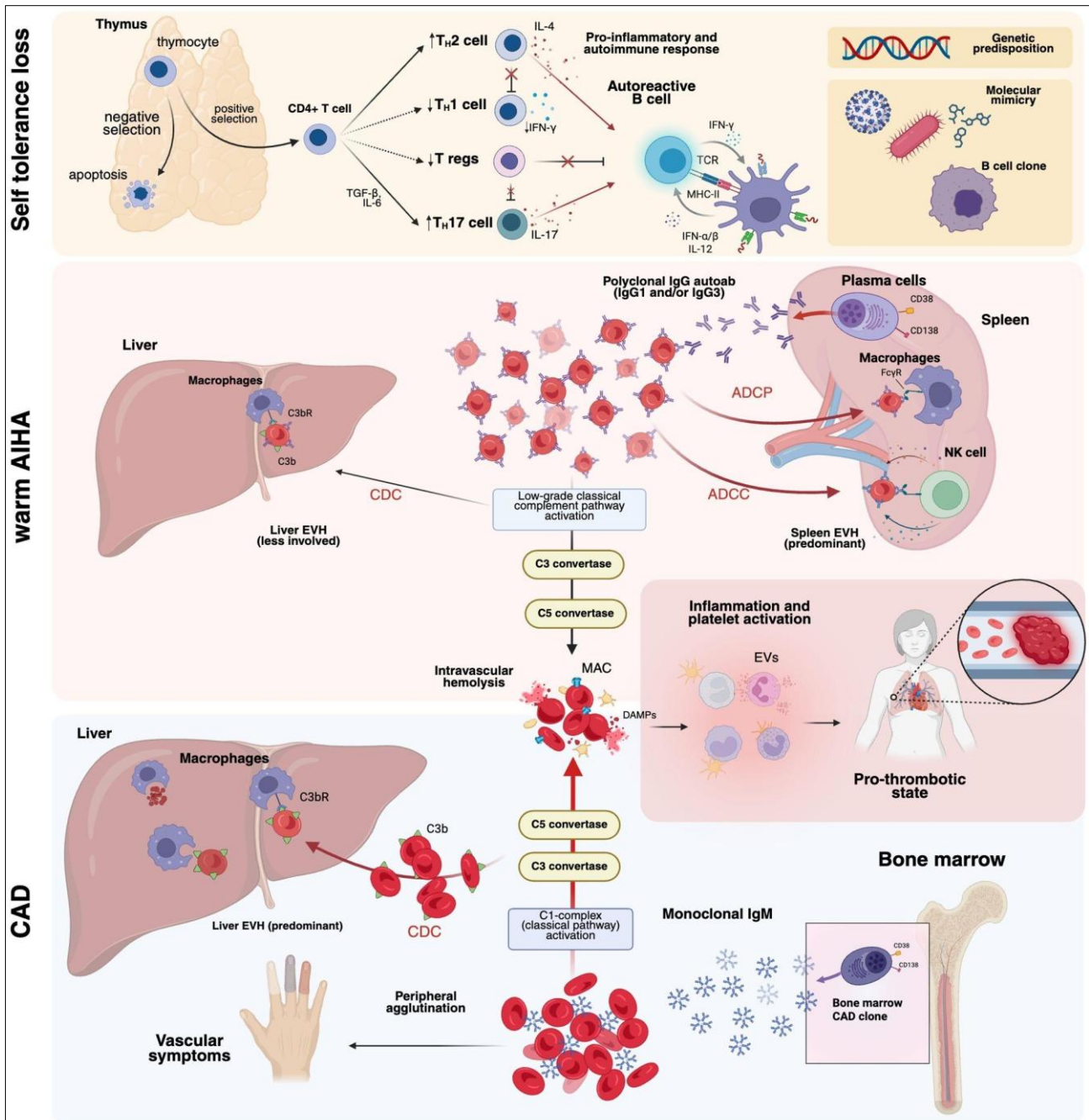


Fig 2: Overview of the pathogenesis of autoimmune hemolytic anemias (AIHAs) (Malecka *et al.*, 2023) ^[16]

• Cold-Antibody Autoimmune Hemolytic Anemia (CAIHA)

A rare form of AIHA known as cold-antibody autoimmune hemolytic anemia (CAIHA), which includes cold agglutinin syndrome (CAS) and cold agglutinin disease (CAD), is defined by elevated levels of cold-reactive autoantibodies, primarily immunoglobulin M (IgM), that are active at temperatures lower than 30 °C (86 °F). Red blood cell (RBC) surface antigens, especially the I and i antigens, are strongly reacted to by these antibodies (Petz & Branch, 1983) ^[17], causing complement activation, RBC agglutination, and subsequent intravascular and/or extravascular hemolysis. CAD and CAS, which today constitute two separate clinical entities, were formerly thought to be included in CAD (Nunes *et al.*, 2024) ^[18].

A. Cold agglutinin syndrome (CAS) is a secondary, transient illness most often seen in the setting of bacterial or viral infections such as *Mycoplasma*

pneumoniae or Epstein-Barr virus-associated mononucleosis (Petz & Garratty, 2004). CAS can also be seen in the setting of certain malignancies or autoimmune illnesses (Swiecicki *et al.*, 2013) ^[19]. CAS is generally self-limited with resolution after clearance of the inciting infection.

B. Cold agglutinin disease (CAD) is a chronic, primary condition where there is a clonal expansion of B lymphocytes producing monoclonal IgM autoantibodies reacting at temperatures ≤ 30 °C, again against the I or i antigens. These monoclonal antibodies activate the complement pathway with resultant potential intravascular hemolysis of scale (Malecka *et al.*, 2023) ^[16].

Although the causes of CAS and CAD are different—CAS is caused by polyclonal IgM, whereas CAD is caused by monoclonal IgM—they have similar diagnostic

characteristics. IgM antibodies attach to red blood cells and activate complement in both disorders, causing significant

intravascular hemolysis (Broome, 2023) (Figure 3).

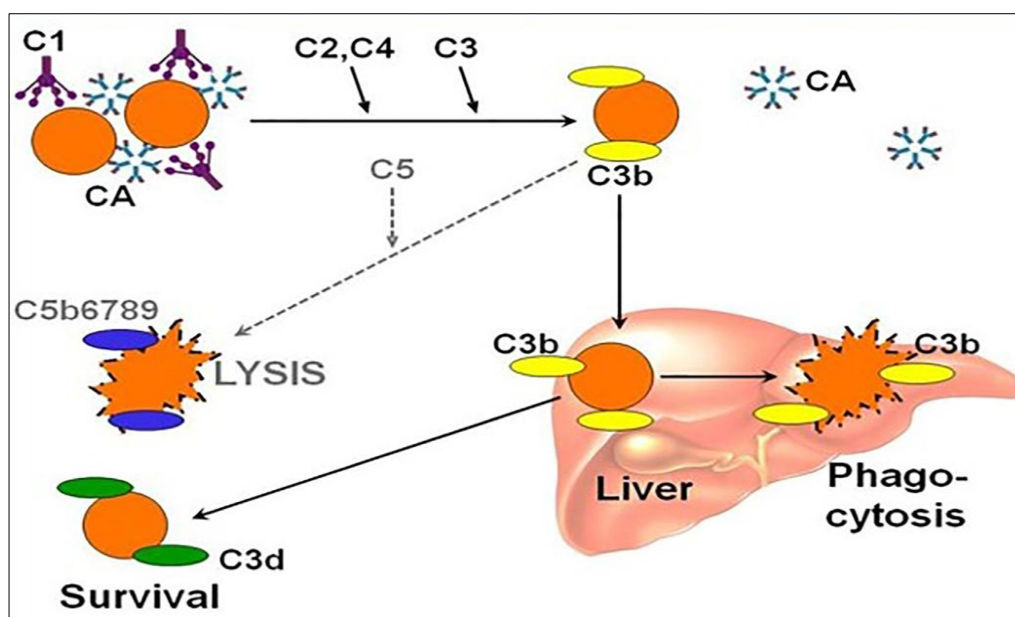


Fig 3: Pathophysiology of cold agglutinin in disease (Barcellini, 2015) ^[14].

• Mixed Autoimmune Hemolytic Anemia (mAIHA)

Immunoglobulin G (IgG) and immunoglobulin M (IgM) subtypes that are both warm- and cold-reactive autoantibodies coexist in mixed autoimmune hemolytic anemia (mAIHA). Less than 5% of all instances of AIHA are of this kind, and it is significantly less common in children (Mayer *et al.*, 2008). mAIHA may manifest as an idiopathic condition may develop secondary to autoimmune disorders or cancers like lymphoma or systemic lupus erythematosus (SLE). It can be difficult to identify the particular heat range that causes hemolysis as well as the main pathogenic antibody class (IgG or IgM). Patients frequently have both warm and cold antibody components, which can target various red blood cell antigens at the same time) (Rinaldi & Kerr, 2023) ^[11].

Causes of autoimmune hemolytic anemia

There is currently no explanation for the pathophysiology of autoimmune anemia. It could be the primary or secondary ailment. Idiopathic primary immunological anemia makes up around half of all cases (Gupta *et al.*, 2011) ^[22].

Both warm and cold immune anemias can be caused by a variety of different illnesses, the most prevalent of which are as follows: The most prevalent causes of warm secondary

immune anemia include autoimmune conditions like lupus, arthritis, scleroderma, and ulcerative colitis, as well as lymphoid disorders like lymphoma and chronic lymphocytic leukemia. Infections and non-lymphoid cancers are less frequent causes of warm secondary immunological anemia. Although lymphatic diseases can produce secondary cold immune anemia, infections, including mycoplasmosis, viral pneumonia, infectious mononucleosis, and other respiratory infections, are typically the cause. Less frequently, related autoimmune illnesses could be the culprit (Sokol *et al.*, 1981) ^[8].

Although uncommon, a variety of medications, such as penicillin and methyldopa, have been known to cause drug-induced autoimmune hemolytic anemia. Drug molecules attach themselves to the surface of red blood cells and function as antigens in this type II hypersensitivity reaction. The complement system is being activated by antibodies directed against red blood cells. While the remaining complement system proteins (C6, C7, C8, and C9) either form the membrane attack complex (MAC) or bind antibodies to aid macrophage phagocytosis (C3b), small complement system components like C3a, C4a, and C5a activate granular leukocytes (such as neutrophils). One kind of penicillin allergy is this one (Figure 4).

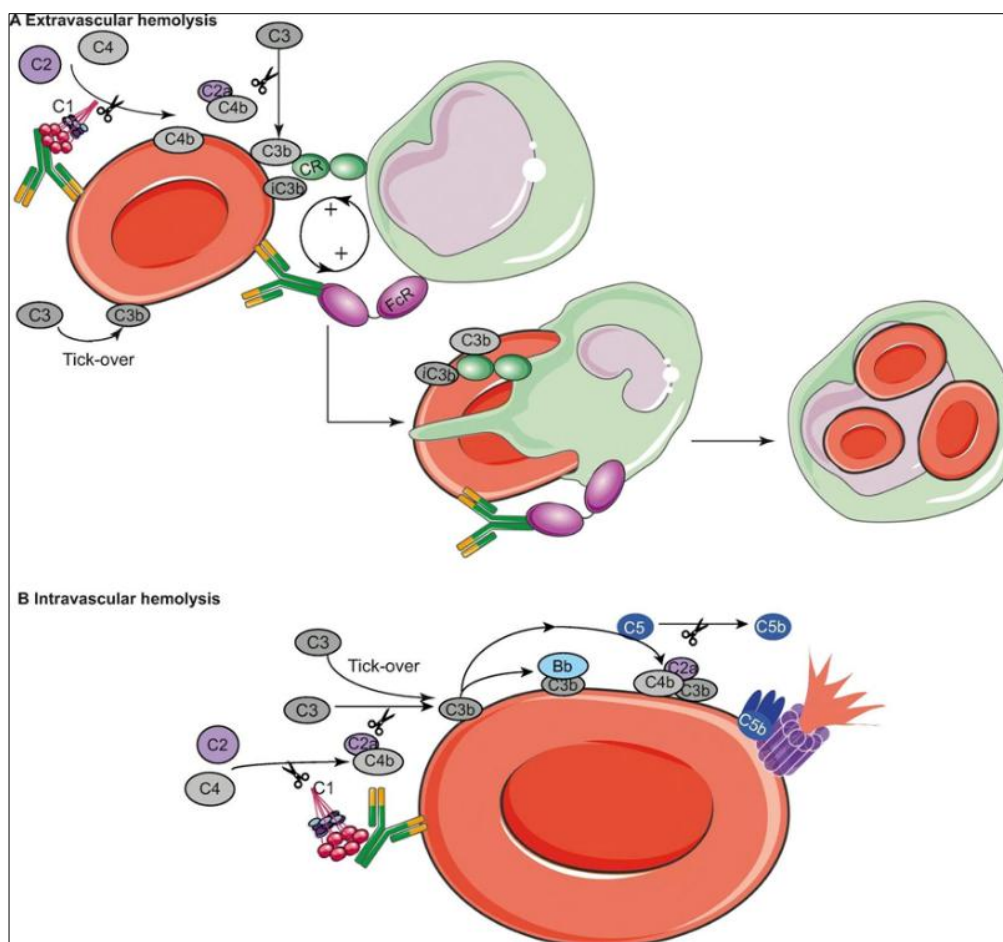


Fig 4: Mechanisms of extravascular and intravascular hemolysis (Patidar *et al.*, 2025)^[12].

Incidence of Autoimmune Hemolytic Anemia

The size of the population under study, the distribution of ages, and variations in national health care systems all have a substantial impact on the incidence and prevalence of autoimmune hemolytic anemia. Since the majority of current research is conducted in hospitals, primary healthcare providers may not fully recognize AIHA. Therefore, if hospital cases are not selected from trustworthy local community samples, many patients might not be included in epidemiological data (Barcellini & Fattizzo, 2020)^[1]. Autoimmune hemolytic anemia (AIHA) is a rare but significant Iraqi hematologic disease, with limited epidemiologic data. An incidence of 2% in patients with ulcerative colitis was documented in one Baghdad Medical City study, underscoring AIHA as an uncommon aftereffect of inflammatory bowel illness (Al-Khazraji, 2008)^[23]. While the US Immune Hematology database estimates an incidence of 17.8 cases per million, reported incidence rates of AIHA include roughly 0.8 occurrences per 100,000 person-years in northern France and 3.9 cases per 100,000 in Spain. There are two known occurrence peaks: the first primarily occurs in children under the age of ten, and the second occurs in people 70 years of age and older. With a female-to-male ratio of more than 1.5, AIHA is more prevalent in females than in males (Barcellini & Fattizzo, 2020)^[1].

Clinical Symptoms of Autoimmune Hemolytic Anemia

A vast but wildly varied variety of symptoms are present in AIHA patients. Dizziness, weakness, weariness, and dyspnea (shortness of breath) are the most often reported

symptoms, which indicate general anemia and decreased tissue oxygen delivery (Costa *et al.*, 2025)^[6].

Hemolysis symptoms typically include pallor, jaundice, and colored urine, which are signs of high bilirubin and accelerated red blood cell breakdown (Loriamini *et al.*, 2024). Physical signs like splenomegaly can also appear in severe or persistent illnesses (Merck Manual, reviewed April 2024).

Patients may present with fever, tachycardia, and chest pain after acute or severe hemolysis events, such as acute crises or COVID-associated AIHA, exhibiting more pronounced clinical decompensation (Ayyad *et al.*, 2025)^[24].

Diagnosis of Autoimmune Hemolytic Anemia

The diagnosis of AIHA include different ways for example the Clinical assessment, laboratory or immunological testing, For therapy to be guided and results to improve, an early and precise diagnosis is essential (Hill *et al.*, 2017)^[3].

- **Clinical Evaluation:** Symptoms including pallor, jaundice, and exhaustion are common when patients first arrive. Potential triggers such autoimmune illnesses, infections, cancers, or drugs should be investigated during a comprehensive history and physical examination (Barcellini & Fattizzo, 2020)^[1].
- **Laboratory Findings:** A complete blood count (CBC) in general recorded a reticulocytosis and or anemia. In some time the hemolysis include decreased haptoglobin or increased indirect bilirubin, in addition to lactate dehydrogenase (LDH) elevation (Jäger *et al.*, 2020)^[2].
- **Direct Antiglobulin Test (DAT):** The Coombs test, in some reference called direct antiglobulin test these test

considered a crucial for diagnosing AIHA. in these test the AIHA could be distinguished from other type of blood disease such as anemias by a positive DAT, that mean the presence of autoantibodies or complement protein in the cells (Hill *et al.*, 2017)^[3].

- **Immunological Testing:** by identifying the type of autoantibodies involved (IgG, IgM) and complementing elements like C3d (Hill *et al.*, 2023)^[10].
- **Imaging Studies:** Abdominal ultrasound figure or CT scans check for splenomegaly or hepatomegaly, that give an idea about the severity of the disease or goose its secondary causes (Barcellini & Fattizzo, 2020)^[1].

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