Hemolytic Anemias

Imad A Tabbara, M.D.
Professor of Medicine
The George Washington University
School of Medicine and Health Sciences
DISCLOSURES

Off-Label Usage
  • None

Interests
  • None
HEMOLYTIC ANEMIA

- HEMOLYSIS: *Premature* or *accelerated* destruction of RBCs
- RBC survival: less than 100 days
- 2 main causes:
  - Intrinsic RBC defects (inherited)
  - Extra-corpuscular causes (acquired)
CLASSIFICATION

- **Hereditary Hemolytic Disorders**
  * RBC enzymes defects
  * RBC membrane defects
  * Hemoglobinopathies
  * Thalassemias
CLASSIFICATION

• **Acquired Hemolytic Disorders**
  * *Immune hemolytic anemias*
  * Splenomegaly
  * Microangiopathic hemolytic anemia
  * PNH
  * Direct toxic effect (malaria, clostridial infections)
  * Spur cell anemia
IMMUNE HEMOLYTIC ANEMIAS

- Incidence increases with age with a dramatic increase after age 50
- There is an early childhood peak due to increased incidence of Paroxysmal Cold Hemoglobinuria (PCH)
IMMUNE HEMOLYTIC ANEMIAS

• **Caused by:**
  – *WARM ANTIBODY*
  – **OR**
  – *COLD ANTIBODY*
IMMUNE HEMOLYTIC ANEMIAS
Diagnosis

• Direct Antiglobulin Test (COOMBS test) is the only test that provides definitive evidence of immune hemolysis
• Increased LDH & reduced haptoglobin: 90% specific for diagnosis
• Normal LDH & haptoglobin: 92% sensitive for lack of hemolysis
**Direct Coombs test**

- The addition of Anti-IgG/anti-C3 leads to the agglutination of washed RBCs if they are coated with IgG or complement.
  - Weakly positive test occurs in 1 in 10,000 healthy donors and in 5-10% of hospitalized patients without hemolysis and is usually caused by complement.
IMMUNE HEMOLYTIC ANEMIAS

Diagnosis

• **Direct Coombs test**

  *Negative test* with severe immune hemolysis can occur:

• In patients with low titers of auto Ab and/or C3. Most reagents cannot detect fewer than 100-500 Ab molecules

• In patients with auto Abs that are IgA or IgM. These are not detected by commonly used reagents
IMMUNE HEMOLYTIC ANEMIAS

Diagnosis

• **Direct Coombs test**
  If negative test and high suspicion of immune hemolytic process, can use enzyme-linked immunoadsorbent assay (ELISA), radiolabeled anti-immunoglobulin, or specific assays for IgA
Diagnosis

- **Direct Coombs test**
  - Level of Coombs positivity does not predict degree of hemolysis
Diagnosis

- **Direct Coombs test**
- A "complement-only" positive Coombs test (10%) in patients with:
  - Low titer of warm-reactive IgG
  - A warm or cold reactive IgM
  - Cold-reactive IgG : Donath-Landsteiner (D-L) (hemolysin)
IMMUNE HEMOLYTIC ANEMIAS
Diagnosis

- **Indirect Coombs test**
  - Detects Abs in the patient’s serum
  - Normal ABO and Rh-compatible RBCs are incubated with the patient’s serum, washed and then a direct Coombs test is performed on the incubated RBCs
A. Direct antiglobulin (Coombs’) test

Washed (3x’s) Patient erythrocytes (sensitized in vivo) + (Coomb’s sera) AHG reagent → Visual erythrocyte agglutination

B. Indirect antiglobulin (Coombs’) test

Human erythrocytes (not patient’s) + Human (patient serum) IgG antibody → Erythrocyte (in vitro) sensitization

Sensitized erythrocytes + (Coombs’ sera) AHG reagent → Visual erythrocyte agglutination

Diagram of direct and indirect antiglobulin (Coombs’) test
Diagnosis

• **Cold Agglutinin Assay**
  – Detects serum Abs which induce clumping of O⁺ RBCs in the cold
  – Typically, it detects IgM cold reactive Abs
• **Cold Agglutinin Assay**
  – Low titer cold agglutinins are common but do not cause complement fixation
  – Physiologically significant cold agglutinins cause C3 fixation on RBCs (complement only $\oplus$ Coombs test)
IMMUNE HEMOLYTIC ANEMIAS

Diagnosis

- **Cold Agglutinin Assay**
  - Level of C3 coating does not correlate directly with hemolysis. Coombs reagents detect both biologically active C3b and inactive fragments (C3bi, C3d)
  - Only C3b is associated with complement-mediated lysis
IMMUNE HEMOLYTIC ANEMIAS
Auto Antibody Specificity

• IgG auto Abs are directed against “public” epitopes on antigenic proteins such as Rh polypeptides and RBC band 3

• IgM auto Abs are directed against “public” carbohydrate epitopes most commonly associated with the Lewis/ABO antigen system
IMMUNE HEMOLYTIC ANEMIAS
Warm Antibody

• Mediated by IgG Abs that react with RBCs at body temperature (37 degree C)
• These Abs do not cause lysis or agglutination of RBCs
• Ab-coated RBCs are removed from circulation by Fc receptor-expressing macrophages in the spleen
IMMUNE HEMOLYTIC ANEMIAS

Warm Antibody

- Alteration of red cell membrane occurs when the IgG-coated RBC bind to macrophages in the spleen (partial phagocytosis), resulting in the formation of spherocytes.
- Presence of C3 on RBC membrane, in addition to the Ab, behaves in a synergistic way leading to severe hemolysis.
**IMMUNE HEMOLYTIC ANEMIAS**

**Warm-Reactive**

- A generalized up-regulation of the phagocytic activity of macrophages has been reported in these patients.
- Lymphocytes may play a role in inducing membrane injury of the RBCs that are coated by IgG or complement.
IMMUNE HEMOLYTIC ANEMIAS
Warm antibody

- Idiopathic
- Viral infections (in children)
- Neoplasia (NHL, CLL treated with purine analogs)
- Connective tissue disorders (SLE)
- Prior allogeneic blood transfusion/hematopoietic stem cell transplantation
- Drug-induced (rarely in children)
  Methyldopa
  Quinidine
  Penicillin
AIHA
Purine Nucleoside Analogues

- Fludarabine, Cladribine & Pentostatin
- AIHA reported after 1-4 courses of therapy
- Significant rate of relapse of AIHA with re-treatment associated with high mortality
- Combination of Fludarabine plus cyclophosphamide and/or Rituximab protects against AIHA in CLL
- Disturbance of immunoregulatory T cells with release of a suppressed auto Ab to a native RBC Ag
AIHA
Allogeneic Blood Transfusion

• 8%-10 % incidence of auto Ab production (positive DAT)
• Mainly in patients with hemoglobinopathies receiving multiple transfusions
• Native RBCs are hemolyzed
AIHA
Allogeneic HSCT

• Ab production by donor immune system against Ags on donor RBCs (autoimmune reaction of the graft against its own product)

• Incidence of 6% in pediatric population with a median onset of 4 months post transplant with high mortality

• Reported also in T-cell depleted & cord blood transplants
AIHA
Orthotopic Solid Organ Transplant

• Related to “passenger lymphocyte syndrome”
• Risk & degree of hemolysis is proportional to the mass of transplanted lymphocytes
• Heart-lung > liver > kidney
• Rapid onset hemolysis with positive DAT
• Hemolysis is usually transient since transplanted lymphocytes do not proliferate or engraft
• Management: Transfusion of group O RBCs, avoidance of ABO-incompatible plasma products, maintenance of adequate renal function, & RBCs exchange
Onset may precede or follow the diagnosis of a lymphoproliferative disorder (LPD).
Incidence of LPD is ~ 18% between 9 - 76 months after onset of hemolysis.
Risk factors for LPD:
- IgM monoclonal gammopathy
- advanced age
- underlying autoimmune disease
**CMV Infection**
- Autoimmune hemolysis caused by warm-reactive IgG

**Influenza A Infection**
- Autoimmune hemolysis caused by high-titer complement-fixing Abs to virus-produced, RBC-bound polyribosome ribosylphosphate

**HSV Infection**
- Autoantibody is IgG with Rh (anti-c) specificity
AIHA
Thromboembolism

• Increased risk for venous thromboembolism

• Pulmonary embolism: most common cause of death (splenectomized pts receiving corticosteroid therapy)

• Predisposing factors:
  • HIV infection
  • Antiphospholipid antibody positivity (lupus anticoagulant)
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

• **Autoimmune Type**
  – Induced by α-methyldopa
  – Positive Coombs test in 10% of patients receiving α-methyldopa
  – AutoAb is IgG, similar to one seen in idiopathic AIHA, does not fix complement and is usually specific for Rh locus
DRUG-INDUCED AUTOANTIBODY GENERATION

Key concept:
• Drug stimulates B cell production of anti-rbc autoantibodies

Examples
• α methyl Dopa
• L Dopa
• Fludarabine and Chloro-deoxyadenosine
• Procainamide
• Diclofenac
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

• **Innocent Bystander Type**
  – Least common
  – Drugs include:
    • Quinidine, Quinine, Sulfonamides, Isoniazid, Phenacetin and Dipyrone
  – Interaction of drug with the RBC membrane produces a neoantigen
  – Abs are IgG or IgM
  – Drug-Ab complex adheres to RBCs membrane and can fix complement
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

• **Innocent Bystander Type**
  – Direct Coombs is positive for C3 only, since the drug-Ab complex will dissociate from RBC
  – Hemolysis can be intravascular or extravascular depending on whether Ab can fix complement or not
DRUG-INDUCED FORMATION OF ABS AGAINST THE RBC –Hapten COMPLEX

Key concept:
• Antibody forms ternary complex with the drug hapten and a specific red cell membrane component

Examples
• Quinine/Quinidine
• Stibophen
• Chlorpropamide
• Amphotericin
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

• Hapten-Induced Type
  – The drug binds to the RBC membrane and becomes the target antigen
  – Caused by large IV doses of penicillin or penicillin-like antibiotics
  – Occurs 7-14 days after initiation of penicillin
  – Direct Coombs is positive for IgG during penicillin administration
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

• Hapten-Induced Type
  – Indirect Coombs can also be positive during rx and for many weeks after discontinuation of penicillin despite that hemolysis subsides as soon as penicillin is stopped
  – Indirect Coombs test should be performed using penicillin-coated RBCs
DRUG-INDUCED ANTIBODIES – PENICILLIN-LIKE MECHANISM

Key concept:
• Drug Binding to Red cells is the critical step in targeting antibody to Red cell Membrane

Examples
• Penicillin and semisynthetic penicillins
• Cephalosporins
• Tetracycline, Streptomycin
• Tolbutamide
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA

- Ribavirin therapy of hepatitis C has been associated with hemolysis
- Hemolysis can be managed with erythropoietin, allowing continuation of treatment
AIHA /Warm-Reactive Treatment

- Treatment of underlying condition
- Removal of drug
- Folic acid
AIHA/ Warm-Reactive Treatment

- **Corticosteroid**
  - Prednisone: 1mg/kg/d
  - 60%-70% sustained response (20% CR)
  - Relapse occurs in 50% of responders either during steroid tapering or after discontinuation
AIHA/ Warm-Reactive Treatment

• **Splenectomy**
  – 30%-40% of patients will be resistant to steroid rx or require excessive doses and/or prolonged administration
  – Splenectomy: 50%-60% response
  – Steroids in lower doses may be needed post splenectomy in 50% of cases
AIHA/ Warm-Reactive Treatment

- 10% are refractory to steroids and splenectomy

- Cytotoxic agents
  - Cyclophosphamide > Azathioprine
  - One month for effect
  - Dose should be adjusted to induce a decrease in WBC count to 3,000/microL
AIHA/ Warm-Reactive Treatment

- IVIG: 40% transient response with high dose (1g/kg/d x 5d) [mostly in children and pts with hepatomegaly and low Hgb levels]
- Danazol: high initial doses (600-800mg/d) in combination with Prednisone (less effective in Evan’s Syndrome)
- Monoclonal Abs:
  - Rituximab
  - Alemtuzumab
- Immunosuppressive agents:
  - Cyclosporin A: 5-10mg/kg/d in 2 divided doses
  - Mycophenolate mofetil (MMF): 500-1000mg/d in 2 divided doses
AIHA/ Warm-Reactive Treatment

• **TRANSFUSION RX**
  – Usual cross-matching is difficult because the Ab is a panagglutinin reacting with all normal donor cells
  – Unlikely to find fully compatible blood
AIHA/ Warm-Reactive Treatment

- **TRANSFUSION RX**
  - Allo-reactive Abs are present in 32% of patients with AIHA
  - Allo-reactive Abs are directed against Rh, Kell, Kidd, and Duffy
  - Undetected allo-reactive Abs, rather than auto-Abs, may cause increased hemolysis after transfusion
AIHA/ Warm-Reactive Treatment

• TRANSFUSION RX
  – Allo-reactive Abs are detected by testing the patient’s serum against a panel of RBCs of known phenotypes
  – The problem is that the auto Ab in the patient’s serum will generally react with all RBC tested, masking the presence of an allo Ab
AIHA/ Warm-Reactive

• **TRANSFUSION RX**
  – No patients should die because of inability to find blood for transfusion
  – Most patients tolerate serologically incompatible blood
AIHA/ Warm-Reactive Treatment

• **TRANSFUSION RX**
  – The decision to transfuse should depend on the patient’s clinical status
  – With appropriate precautions, survival of transfused RBC is as good as survival of the patient’s own RBC
  – Transfusion causes temporary benefit
Posttransfusion Hemoglobinemia & Hemoglobinuria

Result from increase in the total RBC mass available for destruction and **NOT** secondary to increased rate of hemolysis or alloAb- induced hemolysis.
Posttransfusion Hemoglobinemia & Hemoglobinuria

- Excessive & rapid transfusion of RBC should be avoided
- Transfusion of modest volumes of RBC just sufficient to maintain a tolerable Hgb/Ht
IMMUNE HEMOLYTIC ANEMIAS
Cold- Reactive

• **Cold agglutinin disease:**
  - Idiopathic
  - Lymphoproliferative disorder
  - Mycoplasma infection
  - Infectious mononucleosis

• **Paroxysmal Cold Hemoglobinuria**
IMMUNE HEMOLYTIC ANEMIASES
Cold-Reactive

• Caused by IgM complement-fixing Ab
• Most common cold agglutinins are anti-I
• Ab binds to RBCs and causes agglutination at low temperatures (4°C)
Warming leads to quick disagglutination

Low titers (<1:32) of this Ab can be found in normal serum with no clinical consequences

In patients with disease, Ab titer is >1:1,000 at 4°C and 1:16 at 37°C

Hemolysis is intravascular
IMMUNE HEMOLYTIC ANEMIAS
Cold-Reactive

• Direct antiglobulin test detects $C_3$ since the bound IgM is released at 37°C
• Only red cells coated with $C_3b$ are removed from the circulation by macrophages in liver
• Red cells coated with $C_3d$ are not removed from the circulation and are protected from complement-mediated hemolysis because $C_3d$ limits the sites available for $C_3b$ activation
IMMUNE HEMOLYTIC ANEMIAS

Cold-Reactive

- **MYCOPLASMA PNEUMONIA**
  - Cold agglutinins are commonly detected
  - Only a very small number of patients develop hemolysis
  - The Ab is IgM & is directed against the I antigen
  - Hemolysis usually occurs 5 to 10 days after recovery from infection and is self-limited
IMMUNE HEMOLYTIC ANEMIAS
Cold-Reactive

• **MYCOPLASMA PNEUMONIA**
• Cold agglutinin titers are usually $> 1:256$
• Direct Coombs (+) for complement only
IMMUNE HEMOLYTIC ANEMIAS
Cold- Reactive

- **INFECTIOUS MONONUCLEOSIS**
  - Hemolysis is rare
  - The Ab is an IgM directed against the $i$ antigen expressed on fetal and not adult RBCs
  - $i$ antigen is also expressed on red cells of some patients with infectious mononucleosis
  - Hemolysis results from cold agglutination of red cells or complement fixation by IgM
IMMUNE HEMOLYTIC ANEMIAS
Cold-Reactive

- CHRONIC COLD AGGLUTININ SYNDROME
  - Age >60
  - Due to a "benign" monoclonal IgM
  - Antibody is anti-I bearing kappa light chains
  - Indolent for many years
  - In 5-10% of cases, malignant clone arises expressing the cold agglutinin
LYMPHOPROLIFERATIVE DISORDERS

- In pts with cold-reactive hemolysis, trisomy 3 has been associated with progression to a lymphoproliferative disorder.
- Antibody is anti-I with indolent lymphomas.
- Antibody is anti-i with high grade lymphomas.
- Detection of anti-i Ab in the absence of a viral infection, may indicate the presence of a lymphoma.
IMMUNE HEMOLYTIC ANEMIAS
Cold-Reactive

**TREATMENT**

- Avoid cold exposure
- Folic acid
- Treatment of underlying disorder
- Cyclophosphamide or Chlorambucil
- Corticosteroids: not effective except in IgG cold-reactive Ab, or if a concurrent warm reactive IgG is present
- Splenectomy: not indicated
- Rituximab
IMMUNE HEMOLYTIC ANEMIAS
Cold-Reactive

• **TREATMENT**
  • Alpha-interferon: may play a role. Beneficial in combination with Rituximab
  • Fludarabine: some response
  • Plasmapheresis: Effective, but of temporary value
  • IV Ig: Not indicated
  • Red cell transfusions
IMMUNE HEMOLYTIC ANEMIAS
Cold-Reactive

• **Special Precautions**
  
  • All patients needing hypothermic surgery should be tested for cold agglutinins
  
  • Use of cooling blankets to reduce fever may worsen hemolysis and cause peripheral gangrene
  
  • Washed RBCs transfusion should be used, since worsening hemolysis can occur if a complement-depleted patient receives plasma-containing blood products
  
  • Use of warm intravenous solutions
TRANSFUSION RX IN COLD-REACTIVE AIHA

• Compatibility testing should be performed at 37 C since autoAb does not react at this temperature but an alloAb, if present, will react

• Transfusion of warm blood is advisable despite lack of proven efficacy of this approach
IMMUNE HEMOLYTIC ANEMIAS
Cold- Reactive

- **Paroxysmal Cold Hemoglobinuria (PCH)**
  - Rare disorder
  - Used to be seen in association with tertiary syphilis
  - In children, it follows a viral infection. Ab appears 7-10 days after onset of illness and persists for 6-12 weeks
  - May follow other infections (Mycoplasma & Klebsiella pneumonias) and vaccination for measles
Paroxysmal Cold Hemoglobinuria (PCH)

- Antibody is a polyclonal cold reactive IgG (Donath-Landsteiner) directed against the P antigen
- P antigen is also the receptor for parvovirus B19 suggesting a relationship
- Ab does not cause much agglutination but can fix complement
- Red cell destruction is by complement-mediated lysis upon cold exposure
Cold-Reactive

- **Paroxysmal Cold Hemoglobinuria (PCH)**
  - Adult form is usually chronic lasting several years
  - May occur in association with other immune disorders
  - Rarely associated with lymphoproliferative disorders
IMMUNE HEMOLYTIC ANEMIAS
Cold-Reactive

• **Paroxysmal Cold Hemoglobinuria (PCH)**
  – **Treatment:**
    • Usually self-limited in children
    • Maintain warm environment
    • Prednisone, cyclophosphamide, azathioprine in chronic PCH
    • Splenectomy & IVIG of no value
    • Rituximab has been used
<table>
<thead>
<tr>
<th>Underlying disease or condition</th>
<th>Prevalence of AIHA, %</th>
<th>WAIHA</th>
<th>CAIHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>2.3 - 4.3</td>
<td>87%</td>
<td>7%</td>
</tr>
<tr>
<td>NHL (except CLL)</td>
<td>2.6</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>IgM gammopathy</td>
<td>1.1</td>
<td>No</td>
<td>All</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0.19 - 1.7</td>
<td>Almost all</td>
<td>Rare</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Very rare</td>
<td>2/3</td>
<td>1/3</td>
</tr>
<tr>
<td>Ovarian dermoid cyst</td>
<td>Very rare</td>
<td>All</td>
<td>No</td>
</tr>
<tr>
<td>SLE</td>
<td>6.1</td>
<td>Almost all</td>
<td>Rare</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>1.7</td>
<td>All</td>
<td>No</td>
</tr>
<tr>
<td>CVID</td>
<td>5.5</td>
<td>All</td>
<td>No</td>
</tr>
<tr>
<td>ALPD</td>
<td>50</td>
<td>All</td>
<td>No</td>
</tr>
<tr>
<td>After allogeneic SCT</td>
<td>4.4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>After organ transplantation</td>
<td>5.6 (pancreas)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug-induced in CLL</td>
<td>2.9 - 10.5</td>
<td>Almost all</td>
<td>Rare</td>
</tr>
<tr>
<td>Interferon α</td>
<td>Incidence: 11.5/100,000 patient-years</td>
<td>All</td>
<td>0</td>
</tr>
</tbody>
</table>

* NHL, non-Hodgkin lymphoma; SLE, systemic lupus erythematosus; CVID, common variable immune deficiency; ALPD, autoimmune lymphoproliferative disease; and SCT, stem cell transplantation.
## Treatment of WAIHA and CAIHA

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>First-line</th>
<th>Second-line</th>
<th>Third-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary AIHA</td>
<td>Steroids</td>
<td>Splenectomy rituximab</td>
<td>Azathioprine, MMF, cyclosporin, cyclophosphamide</td>
</tr>
<tr>
<td>B- and T-cell NHL</td>
<td>Steroids</td>
<td>Chemotherapy ± rituximab (splenectomy in SMZL)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Steroids</td>
<td>Chemotherapy (radiotherapy)</td>
<td></td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Steroids, surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian dermoid cyst</td>
<td>Oophorectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>Steroids</td>
<td>Azathioprine</td>
<td>MMF</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Steroids</td>
<td>Azathioprine</td>
<td></td>
</tr>
<tr>
<td>CVID</td>
<td>Steroids + IgG</td>
<td>Splenectomy</td>
<td></td>
</tr>
<tr>
<td>ALPD</td>
<td>Steroids</td>
<td>MMF</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Allogeneic SCT</td>
<td>Steroids</td>
<td>Rituximab</td>
<td>Splenectomy, T-cell infusion</td>
</tr>
<tr>
<td>Organ transplantation (pancreas)</td>
<td>Discontinuation of immune suppression, steroids</td>
<td>Splenectomy</td>
<td></td>
</tr>
<tr>
<td>Interferon α</td>
<td>Withdrawal</td>
<td>Steroids</td>
<td></td>
</tr>
<tr>
<td>Primary CAD</td>
<td>Protection from cold exposure</td>
<td>Rituximab, chlorambucil</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal cold hemoglobinuria</td>
<td>Supportive treatment</td>
<td>Rituximab</td>
<td></td>
</tr>
</tbody>
</table>

MMF, mycophenolate mofetil; NHL, non-Hodgkin lymphoma; SMZL, splenic marginal zone lymphoma; SLE, systemic lupus erythematosus; SCT, stem cell transplantation; CVID, common variable immunodeficiency; ALPD, autoimmune lymphoproliferative disease; and CAD, cold agglutinin disease.
# Treatment of CLL-associated AIHA

<table>
<thead>
<tr>
<th>Condition</th>
<th>First-line</th>
<th>Second-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated drug-related AIHA, untreated AIHA in early stage CLL</td>
<td>Steroids</td>
<td>RCD</td>
</tr>
<tr>
<td>Untreated AIHA in active CLL</td>
<td>Steroids + chlorambucil</td>
<td>RCD; R-CVP</td>
</tr>
<tr>
<td>Steroid-refractory AIHA, non-progressive CLL</td>
<td>Rituximab; cyclosporin; splenectomy</td>
<td>RCD; R-CVP</td>
</tr>
<tr>
<td>Refractory AIHA, advanced or progressive CLL</td>
<td>Alemtuzumab</td>
<td></td>
</tr>
</tbody>
</table>

RCD indicates rituximab, cyclophosphamide, and dexamethasone; and R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.
## IMMUNE HEMOLYTIC ANEMIAS

### Mechanisms of Hemolysis

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fc Receptor mediated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Complement mediated</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cold-reaction dependent</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
MECHANISMS OF ACTION OF CORTICOSTEROIDS

- Reduce production of IgG
- May down-regulate Fc receptors (in high doses)
- Do not affect IgM production
# IMMUNE HEMOLYTIC ANEMIAS THERAPY

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in Ab production</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cytotoxic agents</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Reduction in available Ab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Reduction in destruction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>IV Ig</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Warm environment</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Characteristics of Anti-RBC Antibodies

<table>
<thead>
<tr>
<th></th>
<th>Idiopathic AIHA</th>
<th>Chronic cold agglutinin disease</th>
<th>Mycoplasma-associated cold agglutinin disease</th>
<th>EBV-associated cold agglutinin disease</th>
<th>PCH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class of Antibody</strong></td>
<td>IgG most common</td>
<td>IgM</td>
<td>IgM</td>
<td>IgM</td>
<td>IgG</td>
</tr>
<tr>
<td><strong>Temp. for Reactivity</strong></td>
<td>Warm</td>
<td>Cold</td>
<td>Cold</td>
<td>Cold</td>
<td>Cold</td>
</tr>
<tr>
<td><strong>Red Cell Antigen Specificity</strong></td>
<td>Rh-Ag</td>
<td>I-Ag</td>
<td>I-Ag</td>
<td>i-Ag</td>
<td>P-Ag</td>
</tr>
<tr>
<td><strong>Coombs Test for IgG</strong></td>
<td>+ or rarely -</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Coombs Test for C₃</strong></td>
<td>+ or -</td>
<td>Usually +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*
# Intravascular vs. Extravascular Hemolysis

<table>
<thead>
<tr>
<th></th>
<th>Intravascular Hemolysis</th>
<th>Extravascular Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Complement-mediated lysis</td>
<td>Fc or C₃b receptor mediated phagocytosis</td>
</tr>
<tr>
<td><strong>Clinical symptoms of acute hemolysis (fever, backache)</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Spherocytes</strong></td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>Indirect &gt; Direct</td>
<td>Direct &gt; &gt; Indirect</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>(+)</td>
<td>(+)/(-)</td>
</tr>
<tr>
<td><strong>Coombs Test</strong></td>
<td>(+)C3, (+/-) IgG</td>
<td>(+/-) IgG, (+)C3</td>
</tr>
<tr>
<td><strong>Hemoglobinuria and hemosiderinuria</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Clinical Association</strong></td>
<td>D-L Hemolysin Cold Agglutinins Drug-related hemolysis: Quinine</td>
<td>Warm reactive IgG-mediated AIHA, drug-mediated immune hemolysis</td>
</tr>
</tbody>
</table>