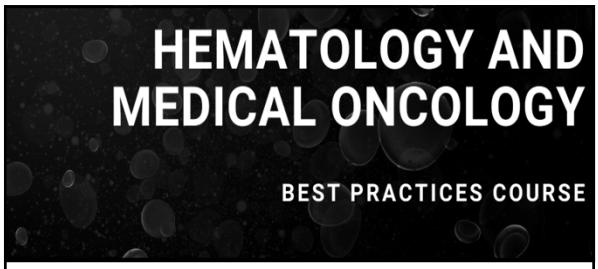


7 - Hemolytic Anemias

Imad A. Tabbara, MD, FACP

1

**Disclosures**

Disclosures of Financial Relationships with Relevant Commercial Interests

2

## 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)

3

## CLASSIFICATION

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

4

## CLASSIFICATION

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

5

## IMMUNE HEMOLYTIC ANEMIAS

- Caused by:
  – ***WARM ANTIBODY***
  – OR
  – ***COLD ANTIBODY***

6

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## IMMUNE HEMOLYTIC ANEMIA

- Rare & Heterogeneous disease
- Incidence: 1 to 3 /100,000 cases per year
- Warm reactive : most common type & accounts for 70-80% of adult cases and 50 % of pediatric cases

7

## 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)

8

## 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

9

## IMMUNE HEMOLYTIC ANEMIAS Diagnosis

- **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*

10

## 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

11

## 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

12

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## DAT-negative Hemolysis

- 3-11% of cases
- Mild to severe life threatening
- Can be primary or secondary similar to DAT-positive disease
- Delay in diagnosis & initiation of treatment may be fatal
- Same management as DAT-positive disease

13

## IMMUNE HEMOLYTIC ANEMIAS Diagnosis

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

14

## IMMUNE HEMOLYTIC ANAMIAS 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)*

15

## 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

16

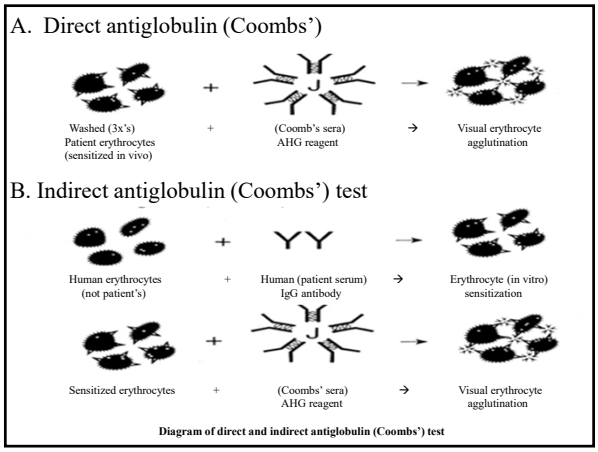

Diagram of direct and indirect antiglobulin (Coombs') test

17

## IMMUNE HEMOLYTIC ANEMIAS Diagnosis

- **Cold Agglutinin Assay**
  - Detects serum Abs which induce clumping of O ⊕ RBCs in the cold
  - Typically, it detects IgM cold reactive Abs

18

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## IMMUNE HEMOLYTIC ANEMIAS
### Diagnosis

- **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 ⊕ Coombs test)

19

## 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

20

## IMMUNE HEMOLYTIC ANEMIAS
### Warm Antibody

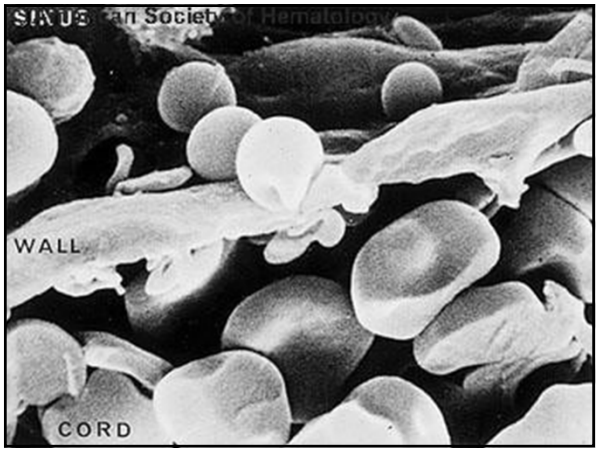
- Mediated by IgG Abs that react with RBCs at body temperature (37 degree C)
- These Abs do not cause lysis or agglutination of RBCs
- Ab-coated RBCs are removed from circulation by Fc receptor-expressing macrophages in the spleen

21

## 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

22




23

## 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

24

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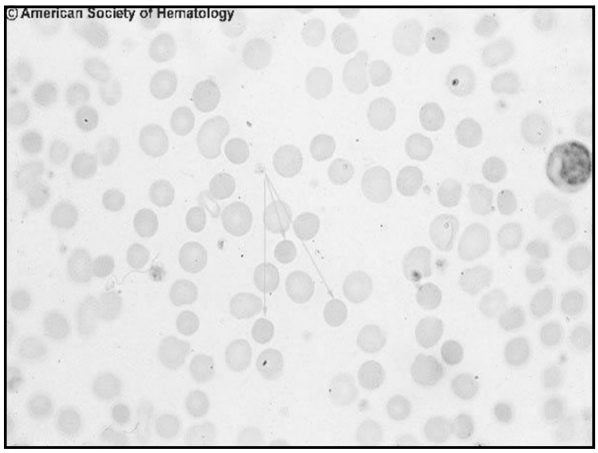


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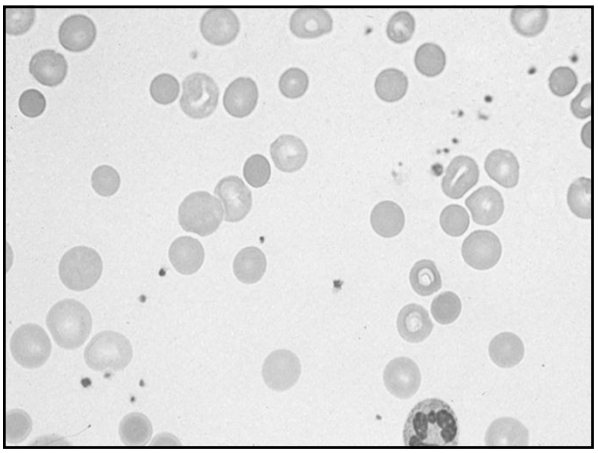

26

## IMMUNE HEMOLYTIC ANEMIAS
## Warm-Reactive

- Idiopathic or primary in 50% of cases
- 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**
  - **Penicillins/cephalosporins**

27

## 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

28

## AIHA
## Allogeneic Blood Transfusion

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

29

## 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

30

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## 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

31

## AHIA
## Lymphoproliferative Disorders

- 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***

32

## IMMUNE HEMOLYTIC ANEMIAS
## Infections

- **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

33

## 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)

34

## AIHA
## EVANS Syndrome

- Immune thrombocytopenia with acquired hemolytic anemia
- Can be a combination of any 2 or 3 autoimmune cytopenias
- Autoantibody formation due to defective B cell selection and maturation

35

## AIHA
## EVANS Syndrome

- Can be a manifestation of:
  - Autoimmune lymphoproliferative syndrome ( ALPS)
  - Classic primary immunodeficiency (PID)
  - Other novel immune dysregulation syndrome

*Diagnosis of Evans syndrome: initiate basic immunologic workup & screening for common variable immunodeficiency & ALPS

36

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## AIHA/ALPS

- ALPS is caused by germline or occasionally somatic mutations in FAS, FASL or CASP10
- Impaired FAS mediated apoptosis of activated autoreactive lymphocytes
- In childhood, chronic ITP , AHIA
- Lymphadenopathy, splenomegaly plus other autoimmune manifestations
- Increased risk for malignancy (lymphoma)

37

## AHIA/ALPS

- **Treatment**
  - First Line: Steroids & IVIG
    - Splenectomy: last resort because of increased risk of fatal pneumococcal sepsis
    - Rituximab: prolonged & severe hypogammaglobulinemia
  - Second Line: Mycophenolate Mofetil (MMF) & Sirolimus

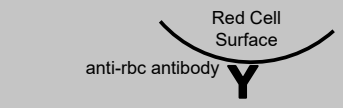
38

## 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

39

## 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

40

## 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

41

## 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

42

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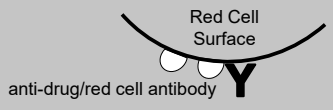
## DRUG-INDUCED FORMATION OF ABS AGAINST THE RBC –Hapten COMPLEX




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

Examples
- Quinine/Quinidine
- Stibophen
- Chlorpropamide
- Amphotericin

43

## 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

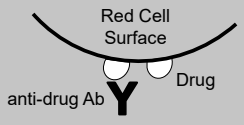
44

## 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

45

## 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

46

## 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

47

## AIHA /Warm-Reactive Treatment

- Treatment of underlying condition
- Removal of drug
- Folic acid

48

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## AIHA/ Warm-Reactive Treatment

- **First line**
  - Prednisone: 1-2 mg/kg Q8-12 hours for 72 hours then decrease to 1-2 mg/kg/d
    - 60%-70% sustained response (20% CR)
    - Relapse occurs in 50% of responders either during steroid tapering or after discontinuation
  - IVIG: 1g/kg/d for 2 days

49

## AIHA/ Warm-Reactive Treatment

- **Second line**
  - **Rituximab: 375 mg/m2 weekly for 4 weeks**
  - **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

50

## AIHA/Warm-Reactive Treatment

- **Second line**
  - MMF: 600 mg/m2 BID
  - Sirolimus: 2 mg/m2 daily
  - Danazol: 600-800 mg/d in 3-4 divided doses followed by maintenance 200-600 mg/d

51

## AIHA/Warm-Reactive Treatment

- **Third Line**
  - Azathioprine: 1-2 mg/kg/d
  - 6-Mercaptopurine: 50-75 mg/m2/d
  - Cyclophosphamide: 1-2 mg/kg/d PO or 300/1000mg/m2 IV every 2-4 weeks
  - Cyclosporine: 5mg/kg/d

52

## AIHA/Warm-Reactive Treatment

- **Fourth Line**
  - High Dose Cyclophosphamide: 50 mg/kg/d for 4 consecutive days followed by G-CSF
  - Alemtuzumab: 3 mg IV or SC on d1, 10 mg on d2, 30 mg on d3, maintenance 10-30 mg 3 X weekly for up to 12 weeks
  - Autologous or allogeneic HSCT

53

## 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 that auto- Abs, may cause increased hemolysis after transfusion

54

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## 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

55

## 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

56

## AIHA/ Warm-Reactive

- TRANSFUSION RX
  - No patients should die because of inability to find blood for transfusion
  - Most patients tolerate serologically incompatible blood

57

## AIHA/ Warm-Reactive

- 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

58

## 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

59

## Posttransfusion Hemogloninemia & Hemoglobinuria

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

60

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## Cold Agglutinin disease (CAD)

- **Primary CAD**
  - clonal B cell lymphoproliferative disorder called primary cold agglutinin-associated lymphoproliferative disease
  - Distinct from lymphoplasmacytic lymphoma, marginal zone lymphoma, and other low grade lymhoproliferative disorders
- **Secondary CAD**
  - Aggressive lymphomas
  - Hodgkin's lymphoma
  - Carcinomas
  - Infectious conditions

61

## Cold Agglutinin Disease

- 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)

62

## Cold Agglutinin Disease

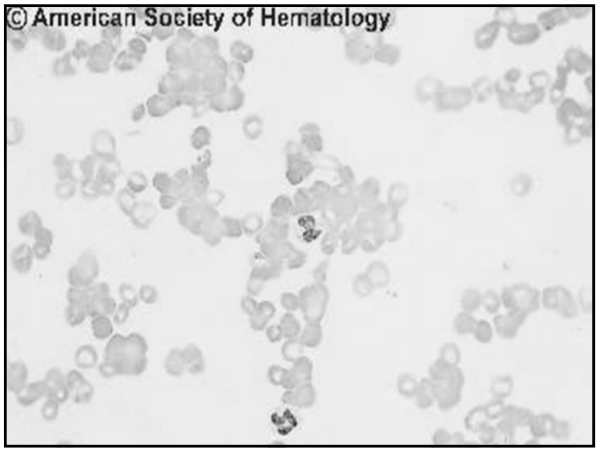
- Warming leads to quick disagglutination
- Low titers (<1:32) of this Ab can be found in normal serum with no clinical consequences
- In patients with disease, Ab titer is >1:1,000 at 4°C and 1:16 at 37°C
- Hemolysis is intravascular

63

## Cold Agglutinin Disease

- 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

64

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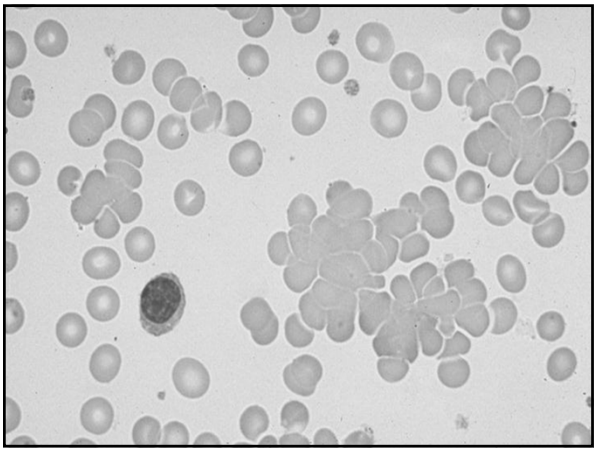

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## Cold Agglutinin Disease

- **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

67

## Cold Agglutinin Disease

- **MYCOPLASMA PNEUMONIA**
- Cold agglutinin titers are usually > 1:256
- Direct Coombs (+) for complement only

68

## Cold Agglutinin Disease

- 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

69

## Cold Agglutinin Disease

- 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

70

## Cold Agglutinin Disease

- 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

71

## Secondary Cold Agglutinin Disease Treatment

**Treat the Underlying disorder**

72

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## Cold Agglutinin Disease

- TREATMENT
  - Avoid cold exposure
  - Folic acid
  - Corticosteroids : not effective except in IgG cold-reactive Ab, or if a concurrent warm reactive IgG is present
  - Splenectomy: not indicated

73

## Primary Cold Agglutinin Disease

- TREATMENT
  - Rituximab : first line treatment with median duration of remission of 1 year in 50% of cases.
  - Alpha-interferon: may play a role . Beneficial in combination with Rituximab
  - Fludarabine + Rituximab : 75% response (median duration 5 years). More toxicity
  - Bendamustine+ Rituximab & Bortezomib-based therapy
  - Plasmapheresis: Effective, but of temporary value
  - IV Ig : Not indicated

74

## Cold Agglutinin Disease

- 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

75

## 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

76

## IMMUNE HEMOLYTIC ANEMIAS Cold-Reactive

- **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

77

## IMMUNE HEMOLYTIC ANEMIAS 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

78

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## 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

79

## 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

80

## Secondary AIHA

| Underlying disease or condition | Prevalence of AIHA, % | WAIHA | CAIHA |
|---|---|---|---|
| CLL | 2.3 - 4.3 | 87% | 7% |
| NHL (except CLL) | 2.6 | More common | Less common |
| IgM gammopathy | 1.1 | No | All |
| Hodgkin lymphoma | 0.19 - 1.7 | Almost all | Rare |
| Solid tumors | Very rare | 2/3 | 1/3 |
| Ovarian dermoid cyst | Very rare | All | No |
| SLE | 6.1 | Almost all | Rare |
| Ulcerative colitis | 1.7 | All | No |
| CVID | 5.5 | All | No |
| ALPD | 50 | All | No |
| After allogeneic SCT | 4.4 | Yes | Yes |
| After organ transplantation | 5.6 (pancreas) | Yes | No |
| Drug-induced in CLL | 2.9 - 10.5 | Almost all | Rare |
| Interferon α | Incidence: 11.5/100,000 patient-years | All | 0 |

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

81

## Treatment of WAIHA and CAIHA

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

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.

82

## Treatment of CLL-associated AIHA

| Condition | First-line | Second-line |
|---|---|---|
| Untreated drug-related AIHA, untreated AIHA in early stage CLL | Steroids | RCD |
| Untreated AIHA in active CLL | Steroids + chlorambucil | RCD; R-CVP |
| Steroid-refractory AIHA, non-progressive CLL | Rituximab; cyclosporin; splenectomy | RCD; R-CVP |
| Refractory AIHA, advanced or progressive CLL | Alemtuzumab | |

RCD indicates rituximab, cyclophosphamide, and dexamethasone; and R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

83

## IMMUNE HEMOLYTIC ANEMIAS Mechanisms of Hemolysis

| | IgG | IgM |
|---|---|---|
| Fc Receptor mediated | Yes | No |
| Complement mediated | Yes | Yes |
| Cold-reaction dependent | No | Yes |

84

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## MECHANISMS OF ACTION OF CORTICOSTEROIDS

- Reduce production of IgG
- May down-regulate Fc receptors (in high doses)
- Do not affect IgM production

85

## IMMUNE HEMOLYTIC ANEMIAS THERAPY

| | IgG | IgM |
|---|---|---|
| **Reduction in Ab production** | | |
| Corticosteroids | Yes | No |
| Cytotoxic agents | Yes | Yes |
| **Reduction in available Ab** | | |
| Plasmapheresis | No | Yes |
| **Reduction in destruction** | | |
| Splenectomy | Yes | No |
| IV Ig | Yes | No |
| Warm environment | No | Yes |

86

## Characteristics of Anti-RBC Antibodies

| | Idiopathic AIHA | Chronic cold agglutinin disease | Mycoplasma-associated cold agglutinin disease | EBV-associated cold agglutinin disease | PCH |
|---|---|---|---|---|---|
| **Class of Antibody** | IgG most common | IgM | IgM | IgM | IgG |
| **Temp. for Reactivity** | Warm | Cold | Cold | Cold | Cold |
| **Red Cell Antigen Specificity** | Rh-Ag | I-Ag | I-Ag | i-Ag | P-Ag |
| **Coombs Test for IgG** | + or rarely - | - | - | - | - |
| **Coombs Test for $C_3$** | + or - | Usually + | + | + | + |

87

## Intravascular vs. Extravascular Hemolysis

| | Intravascular Hemolysis | Extravascular Hemolysis |
|---|---|---|
| **Pathophysiology** | Complement-mediated lysis | Fc or $C_3$b receptor mediated phagocytosis |
| **Clinical symptoms of acute hemolysis (fever, backache)** | YES | NO |
| **Spherocytes** | (-) | (+) |
| **Bilirubin** | Indirect > Direct | Direct > > Indirect |
| **LDH** | (+) | (+)/(-) |
| **Coombs Test** | (+)C3, (+/-) IgG | (+/-) IgG, (+)C3 |
| **Hemoglobinuria and hemosiderinuria** | YES | NO |
| **Clincial Association** | D-L Hemolysin<br>Cold Agglutinins<br>Drug-related hemolysis: Quinine | Warm reactive IgG-mediated AIHA, drug-mediated immune hemolysis |

88

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