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PEARLS OF LABORATORY MEDICINE

Blood Bank Evaluation of Autoimmune Hemolytic Anemia

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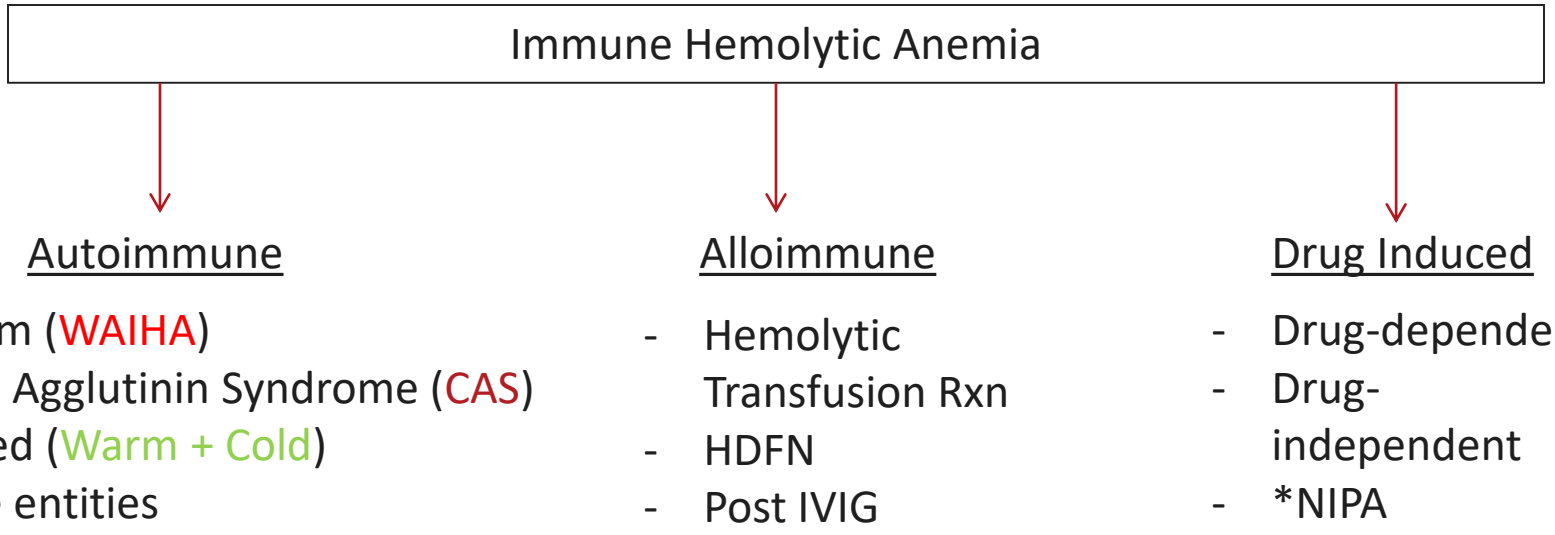
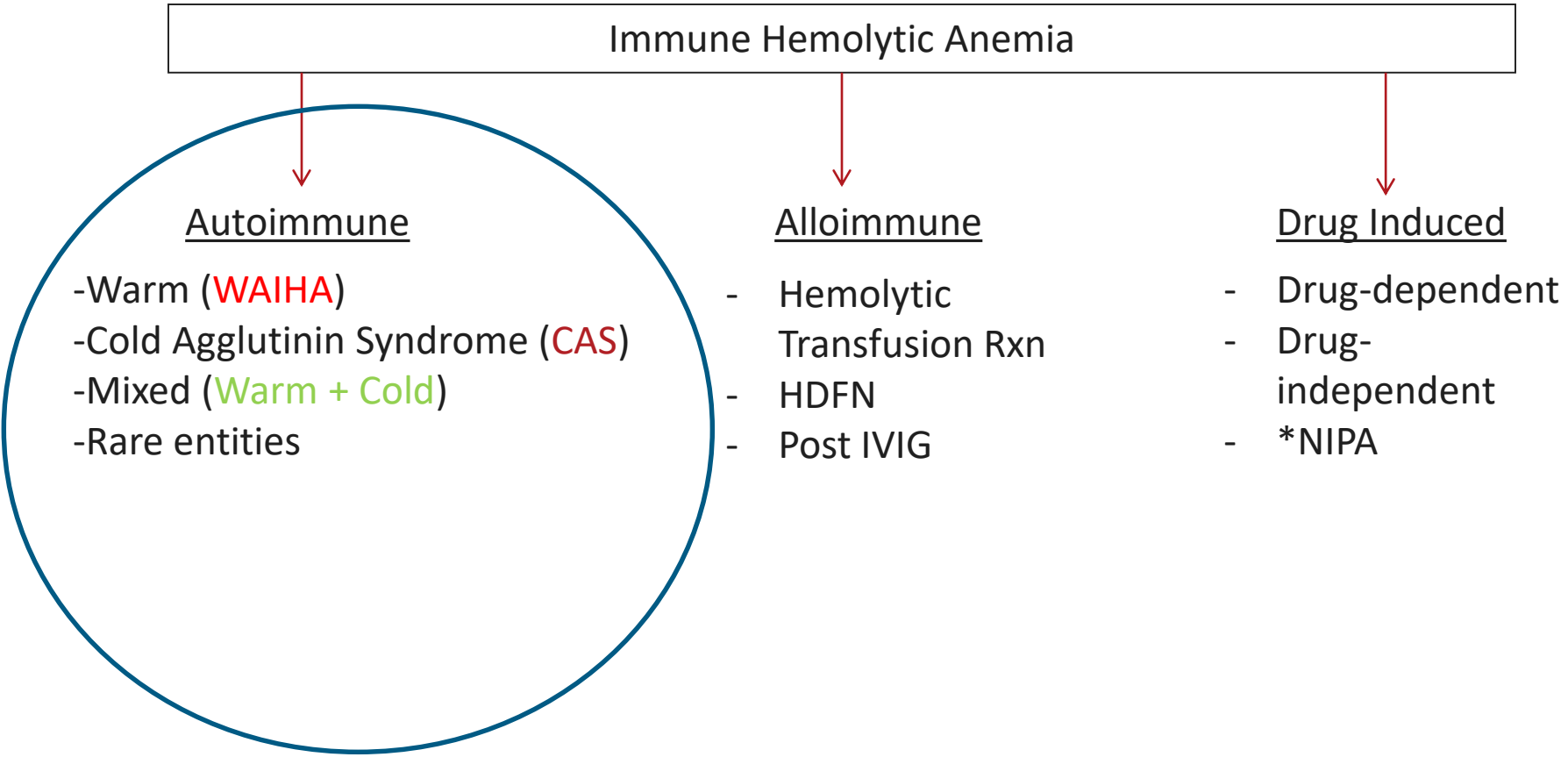
Background



Important to get the right diagnosis, because treatments and prognosis can be very different!

Background


Immune Hemolytic Anemia
Autoimmune
-Warm (WAIHA)
-Cold Agglutinin Syndrome (CAS)
-Mixed (Warm + Cold)
-Rare entities
Alloimmune
- Hemolytic Transfusion Rxn
- HDFN
- Post IVIG
Drug Induced
- Drug-dependent
- Drug-independent
- *NIPA

Patient Presents

Initial Work-up & Physical Exam

- Anemia → Otherwise unexplained drop in Hgb or hematocrit, tachycardia, dyspnea
- Jaundice, dark urine → Due to elevated bilirubin from RBC destruction
- Splenomegaly → Due to immune mediated destruction of cells
- Deranged "Hemolysis Labs" → LDH, Haptoglobin, indirect bilirubin, reticulocytosis
- Peripheral smear → Spherocytes, sometimes agglutination

Assume: no evidence of blood loss, no schistocytes or evidence of mechanical destruction of cells

Possible Immune Mediated Hemolysis

Differential Diagnosis

Warm (WAIHA)

Cold

Mixed

Rare Entities

Warm Autoimmune Hemolytic Anemia

- Most Common (70-80% of total AIHA cases)
  - Overall incidence low, perhaps ~1:75-80,000
- Usually IgG mediated
- Antibody involved reacts with patient's own cells optimally at a warm temperature (37°C)
- All ages, with peak incidence between age 70 and 80
- Highly variable disease severity
- Can be idiopathic, or secondary to underlying condition etc.
- Usually treated with steroids
- Remember – most patients with warm autoantibodies do not have warm autoimmune hemolytic anemia!

Caution: These patients are known to have an increased rate of thromboembolism, especially if the patient also has a lupus anticoagulant.

Evan's Syndrome: Combination of WAIHA and thrombocytopenia, found in 10-15% of WAIHA patients.

The DAT test in Warm Autoimmune Hemolytic Anemia

- In approximately 75% of cases, the DAT is positive for IgG
  - Either IgG only, or a combination of IgG and C3
  - In these situations, the antibody screen is also generally positive (panagglutinin)
- In about a quarter of cases, the DAT is positive for C3 only.
  - This is reported in the textbooks but practitioners frequently contest this claim

Cold Agglutinin Syndrome (CAS)

- Less common than WAIHA, in total approximately 15% of total cases of AIHA.
- Typically IgM with optimal reactivity below 37°C
- Most patients are in their 60s

Caution: Observation of cold agglutination of a sample is not diagnostic of cold agglutinin syndrome. Many patients with pathologic warm antibodies may also have benign cold antibodies in their serum.

The DAT test in Cold Agglutinin Syndrome

- These cases should essentially all have a DAT which is positive for C3 and negative for IgG
- The 4ºC titer, if measured, should be at least 64 and generally >1000, and should be higher than the room temperature titer
- These cases are associated with significant hemolysis; as such, they generally are associated with agglutination at room temperature and at 30ºC (even rarely at 37ºC).
- The thermal amplitude of the antibody is generally viewed as more significant than the titer at 4ºC.
- Many labs do not perform 4ºC titers due to difficulties with quality control.

Mixed IgG Warm and IgM Cold

- Perhaps 7-8% of total cases of AIHA.
- Rare entity showing characteristics of both warm and cold hemolytic anemia.
- DAT positive for both IgG and complement
- Cold agglutinins are present at 4ºC and react all the way up to 37ºC.
- Clinically, may be misdiagnosed when a patient really just has an aggressive warm autoantibody.
- Clinical outcome in true cases is often poor, despite therapy, which may include whole blood exchange.

Patient Presents

Initial Work-up & Physical Exam

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Possible Immune Mediated Hemolysis

Differential Diagnosis

Warm (WAIHA)

Cold

Mixed

Rare Entities

Rare Varieties of AIHA

- IgM Warm
- IgG Cold
- DAT Negative

IgM Warm AIHA

- Uncommon cause of AIHA
- The DAT is generally only positive for complement, and the antibody screen is usually positive at AHG phase due to carryover.
- Can be difficult to distinguish from other entities serologically.

IgG Cold AIHA:
AKA Paroxysmal Cold Hemoglobinuria (PCH)

- Generally a pediatric, hemolytic syndrome associated with a recent illness.
  - Common presenting symptoms may include fever, pallor, malaise, abdominal pain, dark urine, jaundice, etc., consistent with intravascular hemolysis.
  - Caused by IgG P antibody – a “biphasic hemolysin”- that binds at cold temperatures, then mediates hemolysis when warmed. The “biphasic hemolysin” is confirmed by the Donath-Landsteiner test.
  - DAT is negative for IgG, positive for C3 (presumably due to weak attachment of the IgG antibody to RBCs)
  - Median age: 5 years. M:F ~2:1.
  - Not an uncommon cause of autoimmune hemolysis in children, although autoimmune hemolysis in children is rare overall.
  - Reported to be associated with neutrophilic erythrophagocytosis on the peripheral smear.

DAT Negative AIHA

- Account for perhaps 5% of all AIHA
- By definition, the DAT is negative in these cases, but there is a clinical suspicion for an immune hemolytic anemia.
- Believed to be mediated by an antibody which is below the threshold of sensitivity for the assay.
  - Could also be mediated by IgA, etc.
- Polybrene can be used to detect very low levels of antibody
  - Generally this test (“super-Coombs”) is performed only be reference laboratory due to quality control issues.

Dr. Gehrie's Screening Algorithm

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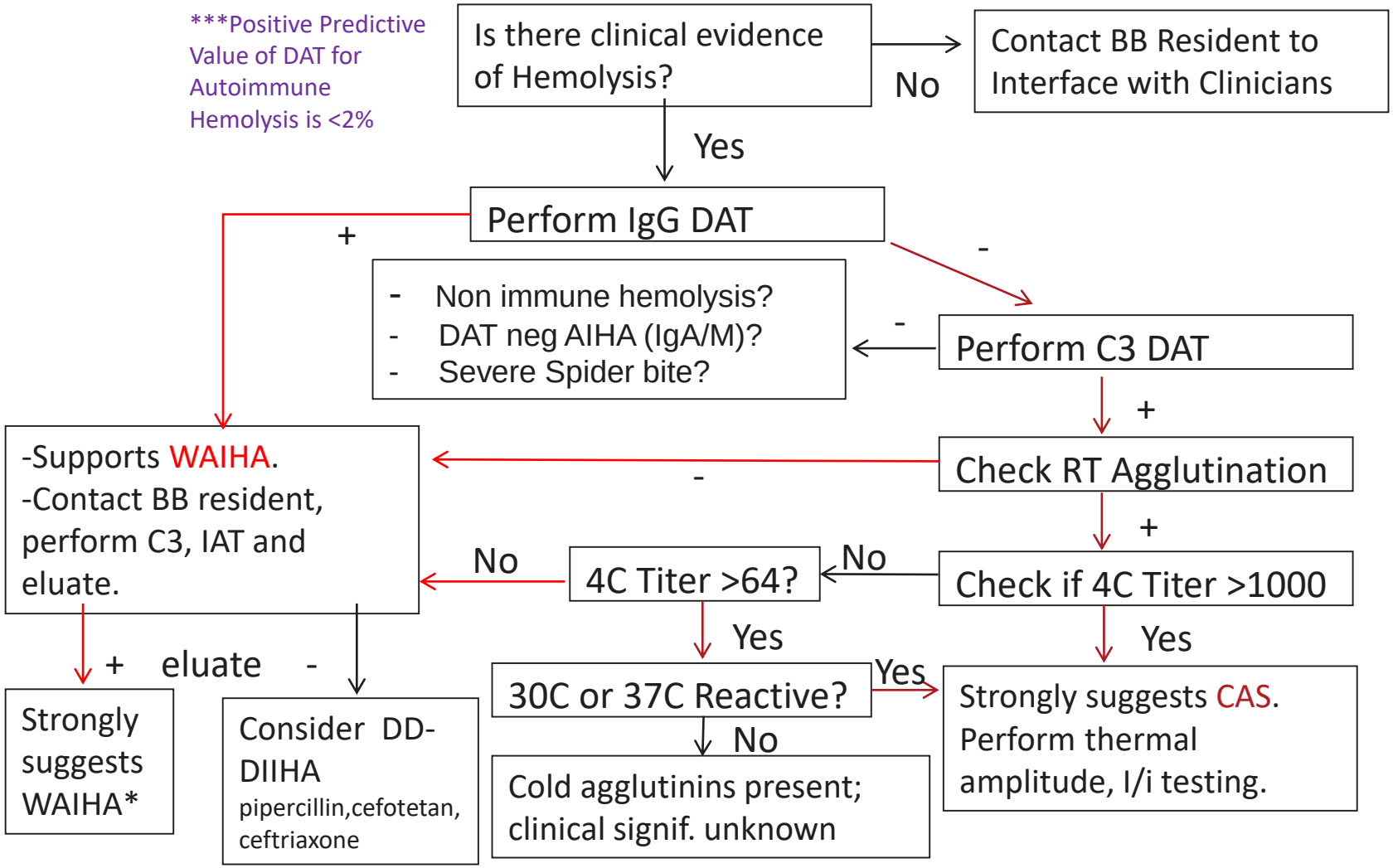

*Please note that Drug Independent DIIHA is indistinguishable from WAIHA based on lab testing. Check medical record for alpha-methyldopa or fludarabine, in particular.

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Summary

- Immune hemolytic anemia is a medically important category of hemolytic anemia.
- Different categories of immune hemolysis have characteristic patterns of DAT reactivity.
  - These patterns can overlap, making at times making the precise diagnosis a challenge.
- Hemolytic anemia should not be diagnosed based on blood bank testing alone
  - There should be other clinical and laboratory data to confirm the diagnosis
- Immune hemolysis should not be excluded based on blood bank testing alone (e.g., “DAT Negative” cases)

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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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