Guidelines for

Diagnosis and Management of Autoimmune Hemolytic Anemia

Presented by:

Maj Hammad

Armed Forces Bone Marrow Transplant Center Rawalpindi

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DEFINITION (1)**:**

Autoimmune hemolytic anemia is defined by the presence of following three criteria:

1. Hemolytic anemia
2. Positive DAT
3. Exclusion of alternate diagnosis

TYPES OF AIHA (2)

1. Warm AIHA (70-80%)
   - Primary
   - Secondary (infections, lymphoma, autoimmune)
2. Cold AIHA 20-30%)
   a. Cold Hemagglutinin disease CHAD
      - Primary
      - Secondary (malignancy, infection, AI Disease, Post HSCT)

   b. Paroxysmal cold hemoglobinuria PCH
      - Primary
      - Secondary (post-ifectious, mycoplasma, influenza virus)
3. Mixed type AIHA (6-8%)
4. Drug Induced AIHA

STEPWISE APPROACH TO DIAGNOSIS (3):

1. **Evidence of hemolysis:**
2. **Is hemolysis immune-mediated**
3. **What is the type of AIHA? Warm or Cold?**
4. **Primary or secondary AIHA**
5. **Ruling out alternative diagnosis**

   Before diagnosing AIHA, following 5 questions should be answered:

   a. Is there a history of **blood transfusion** in the last 3 months?
      Consider a delayed haemolytic transfusion reaction (HTR)

   b. Has the patient received a solid organ or allogeneic haematopoietic stem cell **transplant** (HSCT)?
      Consider alloimmune haemolysis caused by major ABO mismatch (HSCT) or passenger lymphocyte syndrome (PLS) (solid organ or HSCT).

   c. Has the patient received any relevant **drugs**?
      Consider drug-induced immune haemolytic anaemia (DIIHA).

   d. Is there **another known cause** of haemolysis?
      Given the high prevalence of an incidental positive DAT within the hospital population, consider whether there is an alternative cause of haemolysis or abnormal laboratory values

   e. In infants, could this be haemolytic disease of the newborn **(HDN)**?

Investigation of AIHA	
Tests for Hemolysis	CBC, LDH, Bilirubin (indirect), Haptoglobin, Retic count, Peripheral Film
Test for evidence of immune mediated hemolytic	DAT (Monospecific, IgG and C3d both) Antibody specifity Cold antibody titer (if CAD suspected)
Bone Marrow Examination	In all cases age >15 years In selected cases younger than 15 years
Autoimmune screen	ANA, ENA, Anti CCP, Complement levels, APLAS,
Infection Screen	Hepatitis B and C, HIV
Imaging	CECT Neck Chest Abdomen Pelvis (for cases suspected of having LPD)
Immunoglobulin levels, Lymphocyte subset	In selected cases

DAT Negative AIHA:

DAT negative AIHA is seen in <5% cases. Mostly due to low affinity antibody, low titer of antibody bound to red cells or poor technique. This can be diagnosed by more sensitive methods including gel method and use of monospecific reagents. In rare cases, red cell elution technique can be employed. In children, Donath-Landsteiner antibody test should be considered.

MANAGEMENT:

The treatment of AIHA is still not evidence-based(4) as there are only 2 randomized studies and few prospective phase II trials(5, 6).

A. General considerations:

- Patients with atypical presentation or resistant to the first line therapy shall be discussed in departmental meeting.
- Establish early liaison with blood bank to ensure timely availability of least incompatible blood.
- Multidisciplinary approach to be considered in special situations like pregnancy and patients with co morbidities.
- Every patient with severe disease (Hb < 6 g/dl, hemodynamic instability, rapid hemolysis, clinically unwell) will be admitted and managed as indoor case.

B. Supportive care:

- Supportive care is particularly important for severe disease or hemodynamic instability at presentation.
- If an underlying cause is identified eg infection or CLL, treatment should be directed accordingly.
- If drug-induced hemolysis is suspected, relevant medication should be stopped.
- Transfuse least incompatible, ABO, Rh and K matched blood if Hb <6 gm/dL. In a patient with significant cold-type antibody (CHAD, PCH, mixed AIHA) blood warmer should be used for transfusion.
- VTE prophylxis should be considered in all patients with active hemolysis. LMWH is the drug of choice.
- Folic acid supplementation should be given to all patients with AIHA

C. Specific therapy

Specific therapy includes a stepwise approach in those with non-severe and hemodynamically stable disease:

1. **First line therapy: Corticosteroids** are the most commonly used upfront therapy for AIHA(7).
    a. Prednisolone should be started at a dose of 1-2 mg/kg.
    b. Methylprednisolone 0.8 to 1.6 mg/kg IV is an alternate if patient cannot take orally.
    c. Continue full-dose steroids till Hb is >10 gm/dL which usually takes 2-3 weeks
    d. Start steroid taper once Hb is stable and markers of hemolysis normalize/reduced
    e. Steroid taper should be gradual over 2-3 months with 10 mg reduction in dose every week till 20 mg od, then reduce 5 mg/week to complete withdrawl.
    f. In case of relapse start steroids alongwith 2nd line therapy
    g. In cases with severe AIHA, Rituximab may be used alongwith steroids as frontline therapy (5).
    h. During taper, monitor with CBC, LDH and retic count.
    i. For patients receiving corticosteroids who are at increased risk of PUD eg concomitant thrombocytopenia, use of NSAID, antiplatelet or anticoagulant agent or age >60 should receive a PPI.
    j. All patients receiving corticosteroids for more than 3 months should receive calcium (1000 to 1200 mg per day) and vitamin D (600-800 IU per day) supplementation.
    k. Postmenopausal women and men age >50 years commencing steroids should receive a bisphosphanate (3).

2. 2nd line therapy: Second line therapy should be considered if

a. There is no response to steroids after 3 weeks **or**

b. Relapse occurs during or after steroid taper.

The choice is between splenectomy and rituximab of which latter is preferred. Splenectomy produces response rate of 70% whereas for rituximab, response rate of upto 100% has been reported for primary warm AIHA and upto 80% for primary and secondary warm AIHA combined. Median time to response is 3-6 weeks (range 2-12 weeks) (3).

Recommendations:

a. Rituximab should be used as preferred 2nd line therapy in cases refractory or intolerant to steroid therapy.

b. Rituximab is given at a dose 375 mg/m2 weekly for 4 weeks. Lower dose of 100 mg/week for 4 weeks may also be used.

c. Rituximab can cause severe infusion reactions as well as profound immunosuppression, thus close monitoring for adverse effects is recommended. Every patient must be screened for latent HBV, HIV and tuberculosis infection

3. **Third line therapy:**

A number of immunosuppressive as well as targeted therapies are available for third line treatment of AIHA however there is no clear choice between them due to lack of evidence. Response to immunosuppressive therapies may takes weeks or even months so they are usually employed in combination with steroids and continued after steroid taper. There is no clear

advantage of any one over the others and choice is based on physician's experience and preferences.

Recommendations:

1. Azathioprine: As much as 60% percent of patients may respond to azathioprine given at a dose of 100-200 mg/day.
2. MMF is used at a does of 500 mg twice daily to 1000 mg twice daily. Response take 3-4 months.
3. Cyclophosphamide is the most rapidly acting therapy and is given at a dose of 100 mg daily PO or 500 mg IV every 3-4 weeks. Its adverse affects especially bladder toxicity can be severely debilitating.
4. Danazol at a dose of 200 to 800 mg per day has been used.
5. Ciclosporin 5-10 mg/kg PO in 2 doses has been used in some cases. Sirolimus is especially useful in patients with concomitant ALPS.

Splenectomy in AIHA:

Considering the invasive and permanent nature of splenectomy, coupled with availability of non-invasive options like rituximab, splenectomy will be recommended once patient has failed steroids, rituximab and one of the immunosuppressive therapies splenectomey is indicated after steroid and rituximab failure. It is most useful in patients with secondary AIHA with concurrent SMZL.

1. Patient must be clearly counseled about the permanent nature of splenectomy and antecedent benefits as well as risks.
2. Relevant vaccinations must be done 2 weeks before splenectomy
3. VTE risk associated with AIHA is compounded after splenectomy, thus LMWH prophylaxis should be given to all patients and continued prophylaxis in high risk patients.

Beyond Third Line therapy:

Newer targeted therapies that have been used for AIHA include

- Alemtuzumab(6)
- Vinca alkaloids
- Bortezomib
- Daratumumab
- Eculizumab

AIHA in Pregnancy:

1. A diagnosis of AIHA in pregnancy should be based on positive DAT with evidence of hemolysis as well as ruling out other potential causes
2. Antennal care should involve joint obstetric and hematology care.
3. Risk of neonatal anemia and jaundice should be anticipated and neonatologist informed.
4. First line treatment is prednisolone with dose based on disease severity and keeping to the lowest required
5. During pregnancy, perform ultrasound Doppler of the fetal MCA to detect fetal anemia and treatment of maternal hemolysis should be prompted.

6. Second line treatment include transfusion support to maintain Hb, IVIG in severe cases and azathioprine as steroid sparing agent.
7. Following delivery, DAT should be performed. If DAT positive or neonatal anemia, management should be similar to HDFN.
8. Monitoring should continue for 6 weeks to detect late onset hemolysis.

Treatment of CHAD

1. All patients should be advised to avoid cold exposure
2. Treatment indications include symptomatic anemia, severe circulatory symptoms or transfusion dependence
3. Rituximab is first line of treatmen. If a clonal lymphoproliferative disorder has been identified, Fludaribine may be added.
4. All blood products should be given via blood warmer.
5. For patients with CHAD undergoing surgery, normothermia should be maintained during and after surgery.
6. Splenectomy is not indicated in CHAD.

Treatment of PCH

1. Most patients do not need specific treatment as hemolysis resolves with infection.
2. Treatment with steroids is indicated in severe or persistent disease
3. Encourage cold avoidance and avoid active cooling for fever

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