Guidelines for the investigation and management of autoimmune haemolytic anaemia in adults (age 16 years and above)

Definition

Autoimmune haemolytic anaemia (AIHA) is an acquired haemolysis caused by the host's immune system acting against its own red cell antigens.

Serologically cases are divided into warm type (65%), cold type (29% cold agglutinin disease (CAD), 1% paroxysmal cold haemoglobinuria (PCH; rare in adults so not included in this guideline) or mixed AIHA (5%). Approximately half are primary (idiopathic) AIHA and half are secondary to associated disorders such as an underlying lymphoproliferative disorder.

Diagnosis

When assessing possible AIHA ask the following questions:
1. Is there evidence of haemolysis?
2. Is the haemolysis caused by autoantibodies?
3. What is the type of AIHA to help guide the most appropriate treatment?

History

The history of a patient who may have AIHA should include questions pertaining to:

- Symptoms of anaemia (breathlessness, fatigue, chest pain)
- Symptoms suggestive of intravascular haemolysis (dark urine, loin pain, jaundice)
- Recent infection, particularly if a paediatric patient (as PCH often occurs 1-2 weeks post upper respiratory tract infection)
- Symptoms of cold-induced acrocyanosis (dusky blue tips of fingers, toes, nose or
- ears/ Raynaud's syndrome)
- Constitutional symptoms suggestive of underlying lymphoproliferative disorder (weight loss, night sweats, lymphadenopathy)
- If any recent transfusions, to exclude delayed haemolytic reactions
- Past medical history (including if a solid organ or stem cell transplant recipient)
- Detailed drug history (including herbal medicines and illicit drugs)

Examination

The physical examination of a patient who may have AIHA should include:

- General findings: e.g. pallor, signs of weight loss.
- Chest examination: to exclude lower respiratory tract infection/pulmonary embolism as cause of breathlessness and to assess for signs of heart failure
- Lymphadenopathy / hepatomegaly / splenomegaly which may suggest a lymphoproliferative disorder

Investigations

First line tests:

- Blood tests for FBC, reticulocytes, blood film, LFT, LDH, haptoglobin, ANA, HIV antibody/antigen, HBsAg, HBcAb, immunoglobulins, serum electrophoresis, direct

antiglobulin test (DAT), blood group and antibody screen.
- Consider red cell genotyping for all confirmed cases to facilitate blood transfusion

Additional tests for underlying causes of AIHA (not required for all cases)
- **Cold agglutinins screen (direct agglutination test) and cold antibody titres**. For CAD. A 1:64 titre or greater is considered clinically significant.
- **Donath-Landsteiner Test:** if PCH suspected because DAT is positive for C3 and IgG and direct agglutination test negative or insignificant cold agglutinins and either age <18 years or haemoglobinuria or cold associated symptoms or atypical serology (discussion with transfusion laboratory/NHSBT consultant so samples can be referred to NHSBT)
- **Bone marrow:** consider if high suspicion of AIHA secondary to an underlying lymphoproliferative disorder. Consider for all cases of CAD.
- **CT chest, abdomen and pelvis** (screening for occult malignancy).
- **Drug induced autoantibodies (**discuss with transfusion laboratory/NHSBT consultant)
- **Peripheral T cell subsets.** Only for patients with combined AIHA and immune thrombocytopenia (ITP)

Additional tests to consider for unexplained DAT negative haemolysis
- **Extended DAT screening**. If negative DAT but strong suspicion of Autoimmune haemolysis (discuss with blood bank)
- **PNH (Paroxysmal Nocturnal Haemoglobinuria) Screen**
  - Requested on EPR as PNH cell marker analysis, Blood
- **EMA Binding.** For suspected inherited haemolytic anaemia (discuss with red cell team)
- **Red cell genomics panel (R91 and R92)**. This should only be considered in cases of suspected inherited haemolytic anaemia (discuss with the red cell team). Formal consent must be recorded including discussion about the risks including:
  - Finding out about non-paternity
  - Variants of unknown significance
  - Implications for other family members
- **Infection screen and screen for heavy metals.**

Treatment
General measures for all types of AIHA
- Folic acid (5mg once a day in all cases)
- Patients should contact haematology triage if they develop any new symptoms of acute haemolysis

Warm AIHA
- First line treatment Prednisolone 1mg/kg per day (continue prednisolone for at least 3 weeks before considering second line treatment)
- Consider rituximab 375mg/m^2 weekly for four weeks as second line treatment for patients with refractory or relapsed warm AIHA
- Further treatment options include steroid-sparing immunosuppressant drugs, such as azathioprine and mycophenolate
- Other immunosuppressants such as daratumumab, bortezomib, ciclosporin and sirolimus have been used but are off-licence
- Splenectomy can be considered in the event of failure of medical treatment
- Thromboprophylaxis with low molecular weight heparin (incidence of venous thromboembolism as high as 21% in AIHA, consider even in ambulatory patients if Hb <85g/l)

In an emergency situation

- Red cell transfusion if life-threatening anaemia and/or if patient is significantly symptomatic
    - Ensure ABO, Rh, Kell matched blood
- Consider prednisolone 1mg/kg once a day (80mg once a day maximum)
- Consider Intravenous immunoglobulin: 1g/kg as a single dose
- Plasma Exchange (limited evidence)
    - only has a role in stabilising severe disease
    - requires discussion with apheresis and haematology consultant on-call
    - In hours: discuss with relevant consultant and transfusion SpR on bleep 6888
    - Out of hours: via Haematology SpR on call (through switchboard). Treatment should be agreed with a haematology consultant.
    - Complete referral form and send to: nhsbt.stsnursesoxford@nhs.net
- Emergency splenectomy, if unfit or too anaemic consider splenic embolization.

CAD

- Patients should be advised to avoid cold exposure where possible
- Indications for treatment: symptomatic anaemia, severe circulatory symptoms or transfusion dependence
- First line treatment: rituximab 375mg/m2 weekly for four weeks. If clonality has been demonstrated, discussion at lymphoma MDT is recommended for directed therapy.
- Consider referral for all patients for clinical trials of complement inhibitors
- Thromboprophylaxis is not needed during acute haemolysis due to CAD unless there is another indication for its use

- ***In an emergency situation:***
- Trial of prednisolone 1 mg/kg/day may be considered as a rescue therapy.
- Red cell transfusion if life-threatening anaemia:
    - ABO, Rh, Kell matched blood
    - Use a blood warming set for transfusions
- Plasma Exchange (limited evidence)
    - only has a role in stabilising severe disease
    - requires discussion with apheresis and haematology consultant on-call
    - In hours: discuss with relevant consultant and transfusion SpR on bleep 6888
    - Out of hours: via Haematology SpR on call (through switchboard)
    - Complete referral form and send to: nhsbt.stsnursesoxford@nhs.net

- For patients with CAD undergoing surgery aim for normothermia
- Educate patient about condition including:
    - Symptoms and signs of low haemoglobin
    - Cold avoidance if CAD and dressing to protect the extremities
    - Emergency contact numbers and when to get help

Mixed warm and cold AIHA

- Treatment should follow the warm AIHA recommendations
- If there is cold haemolysis, patients should be advised to follow the measures for avoiding exposure to the cold following the recommendations in the CAD section

Drug-induced AIHA

- Can present within hours with complement mediated intravascular haemolysis
- Can also see extravascular haemolysis several months after drug exposure.
- Can sometimes present like a haemolytic transfusion reaction or sepsis.
- Less common than AIHA and only needs further investigation if there is haemolysis + good temporal relationship with drug in question.
- **Most common causative agents:** 2nd and 3rd generation cephalosporins, diclofenac, rifampicin, oxaliplatin, fludarabine. Further implicated medications listed at this link.
- **Management:**
    - Stop suspected drug cause; haemolytic parameters would be expected to improve over 1-2 weeks.
    - Steroids are of uncertain benefit but may be considered on an individual basis

British Society for Haematology (BSH) recommendations for secondary AIHA – link.

Diabetes monitoring

HbA1c results may be falsely low for patients with a reticulocytosis. Consider monitoring diabetes with fructosamine tests if required.

Iron leading

Consider iron chelation with deferasirox for patients who have received 20 units red cells or more. Request ferritin, iron studies and T2* MRI to guide chelation therapy.

References

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Name	Revision	Date	Version	Review date
Dr Mike Desborough, Dr Elizabeth Hutchinson, Dr Noémi Roy, Julie Staves, Dr Sue Pavord	New protocol	Feb 2022	V1.0	Feb 2024
NSSG protocol day	Update	Jun 2023	V1.1	Jun 2026
Dr Mike Desborough	Diabetes monitoring and iron chelation	Nov 2023	V1.2	Nov 2026
Dr Mike Desborough	Red cell genotyping	Mar 2024	V1.3	Mar 2017