SPECIFICATION SPN220/2.1

Investigation and Clinical Management of Patients with a positive DAT with and without Haemolysis

Summary of Significant Changes


Purpose

To ensure that a uniform RCI Clinical Policy for the investigation and clinical management of patients with a positive DAT with and without haemolysis is implemented throughout the NHSBT.

Definitions

Not applicable

Applicable Documents

See References
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Significance of a Positive DAT

The direct antiglobulin test (DAT) is generally used to determine whether red cells have been coated, in vivo, with immunoglobulin, complement, or both. A positive DAT, with or without shortened red cell survival, may result from:

1. Autoantibodies to intrinsic red cell antigens, e.g. Autoimmune Haemolytic Anaemia

2. Alloantibodies in a recipient’s circulation, reacting with antigens on recently transfused donor red cells

3. Alloantibodies in donor plasma / derivatives that react with recipients’ red cells
   a) Transfusion of Group O platelets with high titre anti- A,B to Group A/B recipient
   b) Intravenous Immunoglobulin (IVlg) may contain ABO antibodies / anti-D

4. Alloantibodies in maternal circulation that cross the placenta and coat fetal red cells.
   Haemolytic disease of the newborn.

5. Antibodies produced by passenger lymphocytes in transplanted organs.
   Passenger lymphocytes of donor origin produce antibodies directed against ABO or other antigens on the recipient’s cells, causing a positive DAT

6. Complement components only
   a) About 10% of patients with warm AIHA have red cells with a positive DAT due to C3 coating alone.
   b) Cold haemagglutinin disease / Paroxysmal Cold Haemoglobinuria
   c) Drug Induced (Drug-dependent-Immune complex type)

   Multiple Myeloma or recipients of antilymphocyte globulin (ALG) or antithymocyte globulin (ATG)

8. Elevated levels of IgG or complement have been noted on the red cells of patients with sickle cell disease, β-thalassemia, renal disease, autoimmune disorders (including systemic lupus erythematosus), AIDS, and other diseases with elevated serum globulin or blood urea nitrogen (BUN) levels.

9. The incidence of positive DAT among healthy blood donors without clinical manifestation of immune mediated red cell destruction, have been reported 1 : 7000 donors.

10. Positive DAT due to drugs.

Clinical Management of Patients with Positive DAT in warm antibody induced Autoimmune Haemolytic Anaemia (WAIHA).

WAIHA may occur as idiopathic or secondary to other diseases (lymphoproliferative disorders, chronic lymphocytic leukaemia lymphoma, systemic lupus erythematosus, ulcerative colitis, myelodysplastic syndromes).
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1. **Determine ABO, Rh and Kell phenotype.** If the patient’s RBC are heavily coated with antibodies (strong positive DAT): try warm saline wash or use chloroquine diphosphate treatment. Alternatively, Rh DCcEe, M N S s, K, k, Fy\textsuperscript{a}, Fy\textsuperscript{b}, Jk\textsuperscript{a}, Jk\textsuperscript{b} can be predicted with a high level of accuracy by molecular testing.

2. **Direct antiglobulin test:** Use Column Agglutination technique/Gel DAT cards (e.g., Bio-Rad/DiaMed) for all first time investigations. This might detect IgA only AIH or AIHA due to low affinity autoantibodies.

3. **Antibody identification:** by standard methods + auto control. Take special note of any variation in strength of reactions, which may indicate the presence of both allo and autoantibodies. If DAT positive, there is no history of transfusion during the previous 3 months, no evidence of AIHA and no free antibody is present, no other tests required.

4. **Autoadsorption technique:** if reactions obtained by IAT are uniformly weak with all panel cells it is unlikely that there is a significant underlying alloantibody and adsorptions are unnecessary. Autoadsorptions are performed with ZZAP treated patient rbc, but not if the patient has been transfused within the past 3 months. Extended blood group molecular typing will provide valuable information to assist in the identification of alloantibodies.

5. **Differential adsorption technique:** the red cells employed in the differential adsorption technique must be carefully selected to include all clinically significant blood groups and generally performed only in the following circumstances:
   - pan-reacting antibodies are detected and the patient has been transfused within the last three months
   - if there are insufficient red cells (due to a low hct and urgent transfusion requirement) to perform auto-adsorption
   - if auto-adsorption fails to remove (or weaken significantly) pan-reactive antibodies.

   Remember rare cases of anti-k (Cellano) and other antibodies directed against high incidence antigens.

6. **Red cell eluate study to be undertaken:**
   a) If there is history of transfusion during past 1 month whatever the serology
   b) Evidence of haemolysis with no demonstrable allo or autoantibody in the serum
   c) When adsorption studies are inconclusive, especially in patient transfused within the past 3 months.
   d) Patients with a diagnosis other than AIHA, e.g. patients with chronic renal failure and HIV infection, do not require an eluate to be tested each time pre-transfusion tests are undertaken, unless the patient has an increased transfusion requirement or fails to maintain expected increment in Hb.
   e) Post BMT case, if there is ABO mismatch transplant tested with A1, A2 and B cells.
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Examples of positive DAT and no elutable antibody are seen in cases with:

1) penicillin type induced haemolysis
2) patients with increased amounts of immune complexes
3) patients with high paraprotein / gammaglobulins

If a specific antibody is eluted, the patient’s red cells should be checked if possible for the antigens concerned. The presence of alloantibodies in an eluate suggests:

1) delayed transfusion reaction (or haemolytic disease of the newborn)
2) “mimicking” autoantibodies\(^8,9\) and
3) Matuhasi-Ogata phenomenon.\(^10\)

Policy for selection/provision of Cross-Matched Blood in WAIHA cases

Involves a risk benefit judgement. The chief value of transfusion is to gain time for other therapies (e.g. Corticosteroids) to work. Blood must be transfused cautiously and for appropriate indications. Rapid haemolysis e.g. Hb <5g/dL or life threatening symptomatic anaemia (angina, respiratory distress, cerebral ischaemia, progressive cardiac decompensation associated with reticulocytopenia constitutes a medical emergency).

1. Blood selected for patients with clinically significant allo-antibodies must lack the corresponding antigens.

2. Select K negative blood of the same ABO group and of Rh type compatible with that of the patient eg:\(^11\)

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<td>R2R2</td>
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This will avoid stimulating the production of Rh/K alloantibodies and will prevent transfusion reactions from such antibodies already present but masked by the autoantibodies.

It is preferable to select blood using this principle even if the patient’s autoantibody shows specificity within the Rh system.\(^11,12\) The only exception would be if there was active ongoing haemolysis with clear-cut single Rh specificity (e.g. anti-e), in which case it might be considered that the advantage of possible increased red cell survival would outweigh the potential for stimulating alloantibody production.\(^13\)

3. Crossmatched units that are serologically incompatible but considered appropriate for the patient should be issued as “SUITABLE FOR”.

This copy is uncontrolled unless printed on ‘Controlled’ paper
4. If transfusion of ABO Rh, K compatible red cells does not result in expected rise in Hb, extend the phenotype (or predicted phenotype if molecular methods are being employed) to include Ss, Kidd and Duffy and contact the NHSBT consultant to consider/discuss with hospital clinician the option of further transfusion, with IVIg / steroid cover.14

5. In the situation where the need for blood is urgent and there is insufficient time to perform autoadsorption/differential adsorption test, select ABO, Rh phenotype compatible, K negative blood. These are the most common specificities of alloantibodies found in AIHA.15 In extreme circumstances, transfusion under IVIg / steroid cover should be considered.14

If time permits, testing of a 1 in 3 dilution of the patient's serum may be helpful to exclude the presence of strong alloantibodies.

The decision to transfuse these units in life threatening emergency requires adequate consultation between hospital clinician and NHSBT consultant.

Comment. No critically ill patient with autoimmune haemolytic anaemia should die through lack of blood.

6. Once alloantibodies are excluded after adsorption studies at a reference laboratory, the hospital may select the same ABO, Rh and K phenotype units and use an immediate spin cross match technique for compatibility testing prior to issue of blood.16 The laboratory results and the advice provided to the hospital by the reference laboratory should be well documented.

7. Frequency of Laboratory investigation: rarely patients with severe WAIHA haemolysis briskly and may need frequent transfusions until immunosuppressive drugs become effective.

A sample obtained within three days of the previous transfusion is acceptable for serological investigation for AIHA to exclude additional alloantibodies and to select suitable units.17,18

DAT negative AIHA

DAT-negative AIHA has been reported in about 6% of all warm AIHA. There are several possible mechanisms. Low affinity IgG antibodies which may dissociate from the red cells during washing for DAT. There may be few IgG molecules coated on the red cells that falls below the threshold, which can be detected by routine methods DAT may be demonstrable by more sensitive techniques such as solid phase, enzyme-linked anti-globulin test, flow-cytometry.19

Hyperhaemolysis syndrome in SCD

Hyperhaemolysis syndrome is characterised by marked reticulocytopenia (a significant decrease from the patient's usual absolute reticulocyte level) hyperbilirubinemia and haemoglobinuria. Both the transfused and patient's own cells are destroyed. The DAT may be negative. Some patients have multiple RBC alloantibodies or may also have autoantibodies, in other, no alloantibodies are
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...demonstrable. Recovery is manifested by reticulocytosis with gradual improvement in Hb level. The exact etiology is not known. The following are the possible causes: genetic pre-disposition, bystander haemolysis mechanism, suppression of erythropoiesis and hyperactivity of reticuloendothelial cells. Subsequent transfusion may further exacerbate haemolysis, may become life-threatening or even can cause death. Therefore awareness of hyperhaemolysis syndrome is important and further transfusion should be withheld from the patient.

However, in severe life threatening haemolysis, continued transfusion of blood with IVIg, steroids cover may be life saving.

Positive DAT complement only or IgM and complement (cold-reactive autoantibodies in cold Haemagglutin Disease: CHAD)

The acute form of CHAD is usually associated with lymphoproliferative disorder (lymphoma) mycoplasma pneumoniae infection or infectious mononucleosis and the chronic form is often seen in the elderly, which can be idiopathic or associated with lymphoma, Waldenstrom's macroglobulinaemia and chronic lymphocytic leukaemia.

Cold autoantibodies are usually IgM, examples of cold reacting IgA autoantibodies (e.g. anti-Pr) have also been reported. Autoantibody specificity is not diagnostic of the underlying condition of CHAD and clinical relevance depends on the thermal range of the antibody. Cold haemagglutinins of thermal amplitude ≥ 30°C (detected by tube NISS direct agglutination technique) are considered to be a reasonable indicator of clinical significance.

Potent cold reactive antibodies reacting by IAT at 37°C may mask the underlying alloantibodies active at 37°C. The patient sample should be treated with DTT (DTT is used to treat serum to prevent IgM antibodies acting as agglutinins, by disruption of J chains) and post DTT treated sample should be tested at 37C by IAT technique using monospecific anti IgG reagent. Titration/specificity study is not necessary for serological diagnosis of CHAD. Serological investigation should include autoadsorption or Rabbit Erythrocyte Stroma adsorption technique. The need for a blood warmer is controversial in CHAD for transfusion support. Acute forms of CHAD with infections often have a short clinical course. The chronic form may require therapy. Corticosteroids, IVIg and splenectomy are ineffective in CHAD. Rituximab has been tried as 1st line and Fludarabine +/- Rituximab as 2nd line.

Positive DAT by complement/IgG and IgM (mixed-type AIHA)

In approximately 7% of cases with AIHA, both warm IgG autoantibody and cold IgM autoantibody are simultaneously detected in the patient's serum. These cases are referred to as mixed-type AIHA. The diagnosis of mixed-type AIHA requires thorough serologic studies. Demonstration of both warm IgG autoantibody and cold IgM autoantibody reacting at high thermal amplitude (>30C) is essential for diagnosis.

Mixed-type AIHA can be further classified into idiopathic or secondary, the latter often associated with systemic lupus erythematosus or lymphoma.

PAROXYSMAL COLD HAEMOGLOBINURIA (PCH)
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**Pathophysiology**

PCH is caused by an IgG biphasic autoantibody, usually with anti-P specificity and commonly seen as acute condition in children. This antibody binds to the RBC in the cold, but activates complement, and causes haemolysis at 37°C. Cases may be idiopathic or can be secondary to acute viral infection in children. Chronic PCH is a very rare condition affecting adults and may be associated with congenital or tertiary syphilis.

**Clinical features**

The most common clinical features include haemoglobinuria, jaundice and pallor preceded by viral infection. Acute, transient PCH is characterised by a sudden onset of acute intravascular haemolysis, most frequently seen in young children, following a viral illness. It has been reported following measles, mumps and chicken pox, but in many cases, no specific viral infection can be identified. Relative reticulocytopenia has been noted in some patients with PCH at the time of presentation. Parvovirus induced PCH has been reported in association with reticulocytopenia. Erythrocyte P antigen is a viral receptor for Parvovirus infection of red cell precursors. Awareness and correct diagnosis of PCH is important, as haemolysis is transient in nature and can be halted by keeping the patient warm.

**Serological investigation and pretransfusion testing**

PCH is caused by an IgG autoantibody, and the biphasic nature of the antibody has been demonstrated by either the Direct or Indirect Donath-Landsteiner Test (DLT). Special attention, therefore, should be given to laboratory investigations, if PCH is suspected.

**Direct Antiglobulin Test**

The DAT is positive for complement only. The biphasic IgG molecules will already have dissociated in vivo.

**Blood Grouping**

In acute PCH, antibody specificities other than anti-P are extremely rare, and the antibody can often be shown to have a thermal activity up to 24°C. In the rare chronic form of PCH, the thermal amplitude rarely exceeds 15°C. Cold autoantibody may, therefore, agglutinate all cells within the reverse ABO group, leading to discrepant ABO typing. If these findings are correctly interpreted as a non-specific cold reaction and the tests are repeated at 37°C, the reactions will disappear.

**Antibody Screening**

BCSH guidelines recommend the use of IAT only at 37°C for pre-transfusion antibody screening, without an additional screening technique, since IAT 37°C methods used alone can detect the majority of clinically significant alloantibodies. Negative antibody screen by the standard IAT at 37°C is a common finding in a suspected case of PCH because of the low thermal amplitude nature of the autoantibody. If the antibody investigation is carried out at a lower temperature (15°C), either with enzymes or treated red cells in a direct agglutination technique or by IAT, in suspected PCH cases, pan reactive cold antibodies may be
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*detected as the majority of autoantibodies show anti-P specificity with thermal amplitude range up to 15-24°C. Usually the antibody titre is low (less than 64) even investigated at 4°C. Anti-P specificity can be confirmed at the reference laboratory.*

Note: A low serum complement level and/or a low antibody level can result in a negative outcome to the tests. Negative results, therefore, do not rule out PCH. *Donath-Landsteiner Test (DLT) is the confirmatory test for PCH.*

**Donath-Landsteiner Test (DLT)**

The nature of the biphasic antibody can be demonstrated by DLT. The DLT can be performed as either a Direct or Indirect procedure. For technical details, see Dacie and Lewis Practical Haematology. False results are not uncommon in the Direct DLT for one or more reasons stated below:

1. Low antibody level
2. Low complement level (complement is consumed during the haemolytic process)
3. Due to the presence of C3dg on the patient’s red cells (resistant to complement-mediated haemolysis).

**Indirect DLT**

As the Indirect DLT is more sensitive than the Direct DLT it should be used in preference.

**One-stage Indirect DLT**

Serum, obtained from the patient’s whole blood that has been allowed to clot at 37°C. One volume of a 50% suspension of washed, group O, P+ red cells is added to 9 volumes of the patient’s serum. The tube is incubated at 0°C in a melting ice bath for 1 hour, and then placed at 37°C for 30 minutes. The tube is then centrifuged at 37°C, and the supernatant is examined for haemolysis.

Three controls should also be set-up in parallel.

1. One of the causes of false negatives with the direct DLT is low complement levels. This can be overcome by adding fresh, ABO compatible serum as a source of complement. One volume of 50% cell suspension is added to 4.5 volumes of patient’s serum, and 4.5 volumes of fresh, ABO compatible serum, and then tested as above.
2. A duplication of the test cell-serum suspension (one volume to nine volumes) kept strictly at 37°C for the duration of the test.
3. A duplicate of the test cell-serum suspension (one volume to nine volumes), except that fresh, normal serum is used in place of the patient’s serum. This control is also chilled and subsequently warmed.

A positive result will be indicated by haemolysis in the test suspension and in control tube 1. If rare P-, Pk-, P1- cells are used in a duplicate set of tubes, a negative result will confirm the specificity of the antibody as anti-P.
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Two-stage Indirect DLT

Globoside is the most abundant red cell membrane glycolipid, and is present in the serum of all P+ individuals to variable amounts. Addition of ABO compatible fresh serum therefore, as a source of complement, could result in cross-reaction with anti-P and can lead to a false negative indirect DLT.37 This can be overcome by the two-stage indirect DLT.

In the two-stage indirect DLT, ABO compatible, fresh serum is only added to the red cell-serum suspension following the initial 1 hour incubation at 0°C. This prevents antibody inhibition during the cold phase, and allows maximum sensitisation of the red cells.37

In some cases the Donath-Landsteiner antibody is only detectable using enzyme (papain) treated cells in the two stage indirect Donath-Landsteiner test.

Note: Indirect DLT sample handling (collection and separation of serum from whole blood) should be strictly at 37°C to prevent autoadsorption which may cause false negative result.

Transfusion Support

Awareness, a high index of suspicion of PCH and a correct diagnosis are important, as keeping the patient warm at an ambient temperature of 30°C will assist recovery. In rare severe cases, however, when blood transfusion may be required, ABO, Rh and K compatible units should be selected for the crossmatch, and the use of blood warmers may provide some protection against a haemolytic reaction.34 P- (pp or Pk) blood is not readily available, but should be considered if there is no response to transfusion of P+ cross-match compatible blood. In such a case, the reference centre should be contacted to explore the availability of P- units at the National Frozen Blood Bank. Steroids may be helpful.

Paroxysmal nocturnal haemoglobinuria

Patients with paroxysmal nocturnal haemoglobinuria (PNH) have an increased sensitivity to complement mediated lysis. In the past washed cells were thought to be necessary but there is evidence that leucodepleted red cells in SAG-M are suitable and have been shown not to increase haemolysis.39 Therefore washed cells are not required.

Positive DAT / Drug induced Immune Haemolytic Anaemia

It may be evident from the medical history and serological investigation that drug-induced immune haemolytic anaemia should be considered. In cases where drug-induced immune haemolysis is suspected, please refer the case to Sheffield RCI laboratory and proceed investigations accordingly. (See list of drugs implicated in immune haemolytic anaemia).

NB: The presence of free autoantibodies in the serum may interfere with investigations for drug induced haemolysis. Please check with the Sheffield Blood Centre before agreeing to these investigations being undertaken.
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1. Drug Adsorption: Antibodies directed against certain drugs that bind to red cell membranes, (e.g. high dose IV penicillin/some cephalosporins): Positive DAT due to IgG coating. Antibody eluted from the red cells reacts with penicillin-coated red cells but not with uncoated red cells.

2. Non-specific adsorption: First generation cephalosporins alter the red cell membrane, which induces non-specific adsorption of proteins / immunoglobulins. Only positive DAT with no haemolysis.40

3. Drug-dependent Immune-Complex Mechanism
   Complement components due to formation of drug/anti-drug immune complexes (e.g. Quinidine / Phenacetin).41

4. Drug-Independent Autoantibody Production
   Serologically indistinguishable from those of WAIHA. Red cells are coated with IgG, eluate/serum reacts with all cells tested.
   (e.g. L dopa, Procainamide, Mefenamic Acid, Fludarabine).39
   Second and third generation cephalosporins are increasingly associated with severe AIHA.40
   Some of these drugs may induce drug independent autoantibodies and others may also induce drug dependant antibodies through drug adsorption mechanism.

Interpretation of positive DATs must include the patient's history, clinical data, and the results of other laboratory tests.
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<th>Drugs Implicated in Immune Haemolytic Anaemia</th>
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<td>Acetylsalicylic acid 2</td>
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<td>Ajamidine 2</td>
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<td>Aminophylline 2</td>
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1. Documented or possible drug adsorption mechanism
2. Documented or possible immune-complex mechanism
3. Documented or possible autoimmune mechanism.

* Reported to cause a positive DAT without overt haemolysis

Ref: Clinical Practice of Transfusion Medicine, 3rd Ed., Churchill Livingstone
L.D. Petz, Drug Induced Immune Haemolytic Anaemia (Pg 494-496)
REFERENCES


4. Heddle N, Kelton JG, Turchyn KL, Ali MAM. Hypergammaoglobulinemia can be associated with a positive direct antiglobulin test, a non-reactive eluate, and no evidence of haemolysis Transfusion 1988; 28:29-33


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Reviewed and approved by RCI colleagues via e-mail: October 2014