

# Autoimmune haemolytic anaemia – a practical guide to cope with a diagnostic and therapeutic challenge

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## ABSTRACT

Autoimmune haemolytic anaemia (AIHA) is a rare disease. In clinical practice, diagnosis and treatment of AIHA turns out to be troublesome. Correct diagnosis is dependent on proper comprehension of the pathophysiology and the laboratory tests performed by the transfusion laboratory. The present review provides a short overview on the pathogenesis of autoimmune haemolytic anaemia. The diagnostic pitfalls will be discussed and a diagnostic algorithm for proper diagnosis of AIHA will be given. Moreover, a brief overview on the treatment of different forms of AIHA is given.

## KEYWORDS

Autoimmune hemolytic anemia, hemolysis, cold-autoantibodies, warm-autoantibodies, complement, autoantibodies

## INTRODUCTION

The diagnosis of autoimmune haemolytic anaemia (AIHA) is a challenge for both the immunohaematology laboratory and the clinician as the laboratory investigation can be troublesome and often requires extensive time-consuming serological testing, especially when a blood transfusion is needed. Frequently, there is a need to start therapy rapidly. Therefore, close collaboration and a good communication between laboratory and clinician is a 'sine qua non'. The aim of the present review is to give an overview of the laboratory techniques used for the diagnosis of AIHA. Moreover, a short overview on therapeutic options in AIHA will be provided.

## OVERVIEW

AIHA is characterised by an increased breakdown of red blood cells (RBC) due to autoantibodies (auto-Ab's) with or without complement activation. The diagnostic features of AIHA include the combination of clinical and laboratory signs of RBC haemolysis together with the detection of auto-Ab's and/or complement deposition on RBC as mostly evidenced by a positive direct antiglobulin test (DAT) also known as direct Coombs test. A negative direct Coombs test using standard techniques does not exclude the diagnosis of AIHA.<sup>1</sup>

In more than 50% of the patients the development of AIHA is associated with an underlying disease (*secondary AIHA*), but can occur without any evidence of an underlying disorder (*idiopathic or primary AIHA, table 1*).<sup>2</sup> Based on the optimal temperature for autoantibody binding to RBC, AIHA is divided into a warm antibody AIHA (WA-AIHA), cold antibody AIHA (CA-AIHA) or AIHA due to biphasic auto-Ab (paroxysmal cold haemoglobinuria, PCH). With an incidence of 1:100,000 WA-AIHA is a rare disease, the incidence of CA-AIHA is even lower (1:1,000,000).<sup>1</sup> In contrast, 10% of patients suffering from lupus erythematosus develop an AIHA.<sup>3,4</sup> Occasionally, lymphoma is complicated by AIHA, but it can also be a herald of a lymphoma that has not yet been diagnosed. This is evidenced by the fact that 18% of patients with primary AIHA develop overt lymphoma at a later date.<sup>5</sup>

## PATHOGENESIS

Autoantibodies directed to epitopes on RBC consisting in sugar and/or protein structures are crucial in the pathogenesis of AIHA. The *isotype* is important for the clinical significance of an autoantibody. Immunoglobulins

**Table 1. Aetiologies of autoimmune haemolytic anaemia**

<b>Autoantibody (incidence)</b>
Warm antibody AIHA (1:100000)
Primary (idiopathic)
Secondary
<i>Lymphoproliferative disease (lymphoma)</i>
<i>Autoimmune diseases (SLE, colitis ulcerosa)</i>
<i>Acute leukaemia</i>
<i>Solid malignancy (ovarian carcinoma)</i>
Cold antibody AIHA (1:100000)
Primary (idiopathic): frequently herald of occult lymphoma
Secondary
<i>Lymphoproliferative disease (M. Waldenstrom, lymphoma)</i>
<i>Infection (mycoplasma, EBV)</i>
<b>Biphasic haemolysins (rare)</b>
Idiopathic
Secondary
<i>Postviral, siphilis</i>
<b>Mixed forms with warm and cold antibodies</b>
Idiopathic
Secondary
<i>Autoimmune diseases (SLE)</i>
EBV: Epstein-Barr virus, SLE: systemic lupus erythematosus

of IgM isotype form a pentameric structure and are therefore very efficient in complement activation. IgG1 and IgG3 are efficient complement activators as well, whereas IgG2 and IgA have only a weak capacity to activate complement. IgG4 does not activate complement. Generally, the complement system is not completely activated and complement degradation products (C3c, C3d) can be detected as traces on RBC's ('Complement footprints'). However, complement activation may proceed until the formation and introduction of the membrane attack complex C6-9 (MAC) leading to RBC lysis. The optimal temperature of auto-Ab's to bind to RBC is of clinical relevance as well. Cold autoantibodies (CA-Ab) show optimal binding to RBC below 30 °C and are mostly of IgM isotype. CA-Ab having an optimal binding around 30 °C are clinically relevant since they may induce complement activation *in-vivo*.<sup>6</sup> Warm autoantibodies (WA-Ab) show optimal binding at 37 °C and are mostly IgG, less commonly IgM and rarely IgA.<sup>1</sup> Biphasic auto-Ab's are IgG which show optimal binding below 30 °C and induce complement activation at 37 °C.<sup>6</sup> RBC coated with IgG with/without C3c/C3d are preferentially removed by via Fc-gamma receptor mediated phagocytosis in the spleen, whereas RBC coated with C3c/C3d in the absence of IgG are destroyed via complement-receptor mediated phagocytosis in the liver (*extravascular haemolysis*). In the presence of IgM which is reactive above 30 °C, complement activation may proceed till the insertion of MAC leading to intravascular RBC destruction (*intravascular haemolysis*).

## DIAGNOSIS

### Clinical considerations

The clinical presentation of AIHA is not different from other forms of acute haemolytic anaemia or acute crisis of a chronic haemolytic anaemia. Frequently, patients are icteric and suffer from clinical signs of anaemia, such as pallor, fatigue, shortness of breath and palpitations. In contrast, haemoglobinuria as a sign of intravascular haemolysis is rare, but the patient must explicitly be asked for that symptom. In case of cold agglutinins, cold exposure may lead to agglutination of RBC in the circulation as reflected by cyanotic discolouring of the acra, such as toes, fingers, ears and nose. After warming up, the cyanotic discolouring disappears quickly and in contrast to a Raynaud phenomenon, no reactive hyperaemia occurs. The presence of a disease frequently reported to be associated with AIHA supports the suspected diagnosis. Since many of these diseases are accompanied by anaemia, the diagnosis of a mild AIHA can easily be missed. An overview on the different forms and aetiologies of AIHA is shown in *table 1*.

### General laboratory findings

Besides a careful evaluation of the clinical history, laboratory diagnostics play a central role in the diagnosis of AIHA in order to detect both haemolysis and auto-Ab's to RBC. Increased levels of lactate dehydrogenase (LDH), indirect hyperbilirubinaemia, decreased haptoglobin and reticulocytosis reflect increased RBC breakdown either due to intra- or extravascular haemolysis. Normal levels of LDH do not exclude the presence of haemolysis! Reticulocytosis might be absent in the beginning of AIHA and/or in case of decreased functional capacity of the bone marrow, as seen after chemotherapy. Frequently, microspherocytes can be detected in the peripheral blood smear. Microspherocytes are autoantibody-coated RBC, which have lost their biconcave shape due to loss of part of their membrane upon passage through the spleen.<sup>7</sup> In case of intravascular haemolysis, haemoglobin is released by destructed RBC and cleared by the kidney leading to a brownish discolouring of the urine (haemoglobinuria). Even days after the haemolytic episodes haemosiderin can be detected in the urine.

### Immunohaematological diagnostics

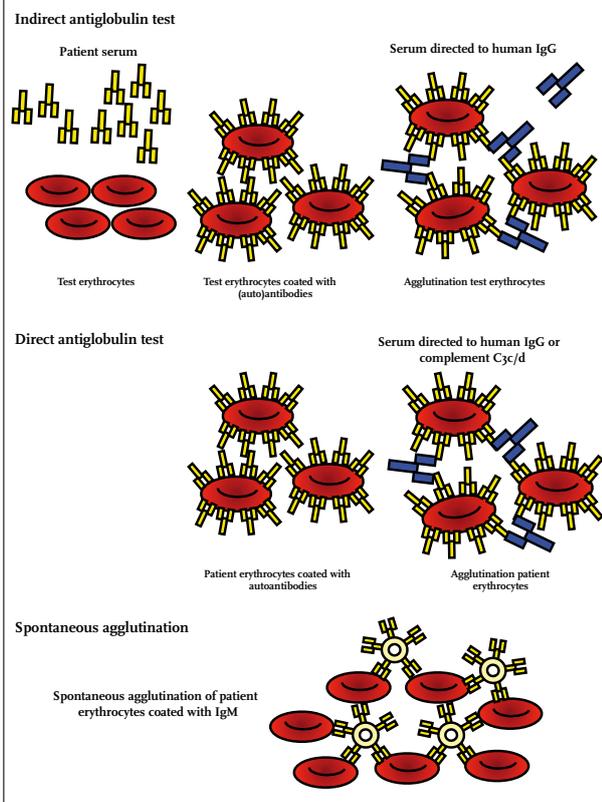
The immunohaematological diagnosis in AIHA aims to detect auto-Ab's to RBC. In a first approach the indirect antiglobulin test (IAT) and the DAT are performed. In the IAT, auto-Ab's to RBCs present in patient's serum are detected. In a first step, standardised test RBC (test panel) are incubated with the patient's serum. In a second step, after removing the unbound immunoglobulins by washing polyspecific antihuman globulin reagent directed to both,

human IgG and complement (complement component C<sub>3</sub>) are added. If RBCs have been coated by auto-Ab's present in the patient serum, the RBC will agglutinate indicating a positive result (positive IAT, *figure 1*, above). In contrast, by means of the direct Coombs test, auto-Ab's bound *in-vivo* to patients RBC are directly detected by adding polyspecific antihuman globulin reagent (*figure 1*, middle). In rare situations the clinical picture is highly suggestive for an AIHA, but the direct Coombs is negative. As a polyspecific anti-human globulin reagent does not contain anti-IgA it is important to repeat the DAT with anti-IgG, anti-IgA, anti-IgM, anti-C<sub>3c</sub> and anti-C<sub>3d</sub> to confirm the DAT to be negative. In the situation the DAT remains negative the presence of microspherocytes in the peripheral blood

smear may help to support the suspected diagnosis AIHA without detectable antibodies.

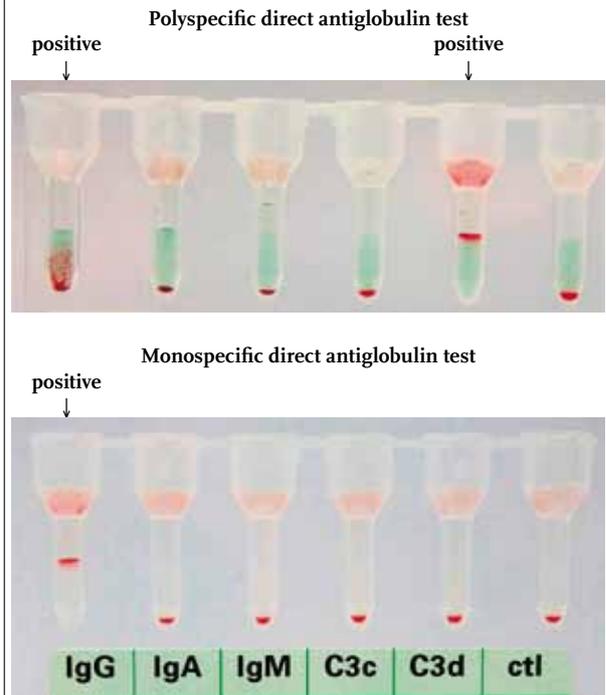
In daily practice fully automated laboratory analysing systems are used to perform DAT and IAT. All these systems are based on the detection of agglutination of RBC. Frequently, column tests with gel-containing microtubes are used. RBC and antiserum are incubated in a reaction chamber followed by a controlled centrifugation of the microtube containing anti human globulin. If agglutination occurred in the reaction chamber, the RBC-antiserum complexes will be trapped in the column upon centrifugation and the test is positive. If no agglutination occurred, the RBC pass the column upon centrifugation resulting in a pellet on the bottom of the microtube, the test is negative (*figure 2*). In some laboratories flow cytometry is used to detect RBC coated with either auto-Ab's or complement, respectively. However, in special situations RBC agglutination is still performed visually in glass tubes by an analyst.

**Figure 1. Direct and indirect antiglobulin test**



By means of the indirect antiglobulin test (IAT, indirect Coombs test) circulating allo- and autoantibodies present in patient serum are detected. In a first step treated or untreated test erythrocytes are incubated with patient serum. Allo- and autoantibodies present in the patient serum will bind to the test erythrocytes. In case of IgM present in patient serum, test erythrocytes may agglutinate directly, the test is positive. Antibodies type IgG are incomplete antibodies which do not lead to direct agglutination of test erythrocytes. In a second step test erythrocytes coated with IgG are incubated with antiserum against human IgG. In case of agglutination, the test is positive. By means of the direct antiglobulin test (DAT, direct Coombs test) patient erythrocytes coated with either auto- or alloantibodies and/or complement are detected. Patient erythrocytes are incubated with a polyspecific serum directed to human IgG and complement (C<sub>3d</sub>). If there is an agglutination, the test is considered to be positive indicating patient erythrocytes to be coated with IgG and/or C<sub>3d</sub>.

**Figure 2. Direct antiglobulin test**



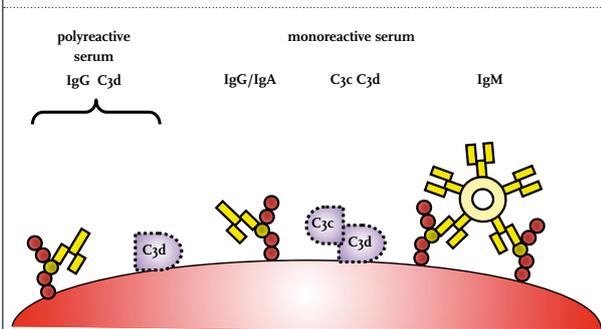
The gel system consists in a microtube containing a reaction chamber (R) and a gelmatrix (G). The reaction chamber either contains a polyspecific (top) or monospecific (bottom) human antiserum directed to immunoglobulins or complement (C<sub>3c</sub>/C<sub>3d</sub>). Patient erythrocytes are added to the reaction chamber and after a short incubation the microtube is centrifuged. If agglutination in the reaction chamber occurred, patient erythrocytes will be trapped in the gel matrix upon centrifugation, the test is positive (arrow). If no agglutination occurred, the erythrocytes pass the gel matrix forming a pellet at the bottom of the microtube, the test is negative. (Figure kindly provided by E. Schaeffer and G.J. van den Akker, AMC.)

### Positive direct Coombs: what to do next?

If the DAT proves to be positive when using a polyspecific antihuman globulin reagent, further specification with a monospecific reagent is needed in order to detect whether RBC are coated with IgG, IgA, IgM and C<sub>3</sub>C or/and C<sub>3</sub>d, respectively (figure 3). If complement deposition (C<sub>3</sub>c/C<sub>3</sub>d) can be detected in the absence of an autoantibody, the presence of CA-Ab (IgM), WA-Ab (IgM, IgA) or biphasic antibodies must be considered. In that situation further laboratory diagnostics are also mandatory, to investigate the presence of either IgM or IgA. IgA auto-Ab's without IgG auto-Ab's are very rare. However they show an optimal binding at 37 °C and can lead to fulminant and fatal haemolysis.<sup>8,9</sup> Due to their size (pentamer) IgM auto-Ab's are difficult to detect because they are removed by the washing procedures while performing the DAT. In addition, the optimal temperature for IgM binding and the temperature at which the DAT is performed are crucial.

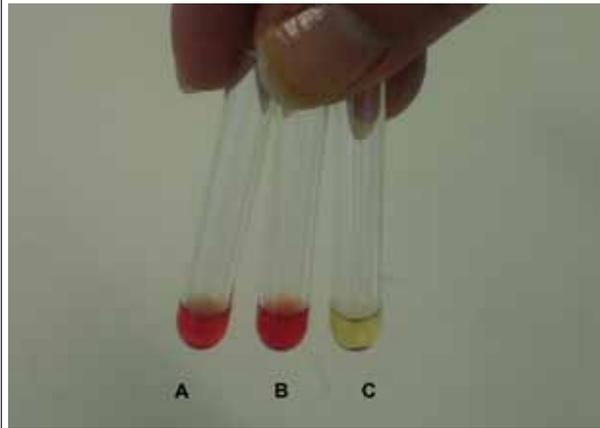
In a next step, the properties of IgM to directly agglutinate RBC due to its size (pentamer) can be utilised (complete antibody). If there is spontaneous agglutination after incubation of patient serum with test RBC at 16 °C, a CA-Ab IgM must be suspected. A potentially clinically relevant cold antibody must be considered if agglutination occurs at 30 °C. Another useful test to detect complement binding antibodies in serum is a haemolysis test using RBC pretreated with enzymes (being much more sensitive for complement-mediated lysis as compared with normal RBC) incubated with patient serum at both 16 °C and 37 °C. Thereafter, standard serum with a lower pH after adding acid is added as complement source and incubation is performed (figure 4). If lysis occurs a clinically relevant antibody which can potentially cause haemolysis or shortening of the life span of the RBC

**Figure 3.** Monospecific direct antiglobulin test (Coombs test)



In case of a positive polyspecific antiglobulin test the components on the patient erythrocytes need further specification. Patient erythrocytes are incubated with monospecific serum directed to human IgG, IgA, IGM or complement components (C<sub>3</sub>c, C<sub>3</sub>d). If there is agglutination with one of the antisera, the test is positive indicating the presence of the respective immunoglobulin or complement component on the patient erythrocytes.

**Figure 4.** Detection of autoantibodies potentially able to induce haemolysis



Pretreated test erythrocytes, which are more sensitive for haemolysis than normal test erythrocytes are incubated with patient serum first at 16 °C (A) and 37 °C (B) (control: C). After addition of standard serum as source of fresh complement, the sensibilised test erythrocytes are incubated at 37 °C. If haemolysis occurs, the autoantibody may potentially induce haemolysis in vivo. Rarely, an autoantibody may induce haemolysis in non-pretreated test erythrocytes (figure kindly provided by P. Ligthart, Sanquin).

must be considered. In case of fulminant intravascular haemolysis auto-Ab's frequently have the potential to induce lysis even in non-pretreated RBC *in-vitro*. If a CA-Ab is suspected, the pre-analytical handling of the patient samples is crucial. After venipuncture the blood sample must immediately be put on 37 °C, since the auto-Ab's will bind to RBC at room temperature thereby decreasing the auto-Ab's concentration in the serum, bearing the risk of a false-negative result.

In order to identify the specificity, the warm auto-Ab's can be separated from the RBC by means of laborious elution techniques. In analogy to the IAT the eluate (containing the auto-Ab's which were bound to RBC) is tested in a standard panel of RBC. If a specificity of the eluted antibody can be identified, this will be indicated in the diagnostic rapport (e.g. specific autoantibody, anti-C). However, in many cases no specificity can be identified (non-specific antibody). Specific WA-Ab's are frequently directed to parts or to the entire Rhesus system, rarely to the Kell system.<sup>1</sup> CA-Ab are frequently directed to I-antigen or H antigen, whereas biphasic auto-Ab's have anti-P specificity.<sup>6</sup>

### Type and screen: remains challenge in AIHA

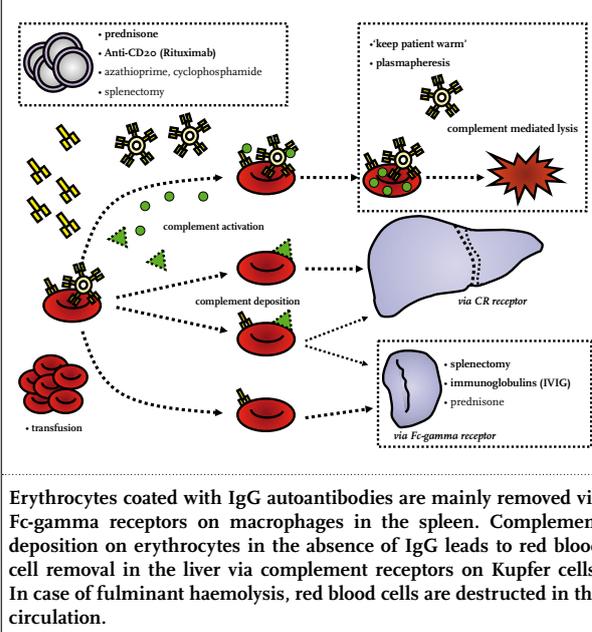
In case of a planned transfusion, type and screen has to be performed. Besides the characterisation of the auto-Ab's, detection of alloantibodies is of outstanding importance. Literature suggests that alloantibodies can be detected in 15 to 43% of patients suffering from AIHA, mostly after receiving transfusions.<sup>10</sup> Moreover,

patients with one alloantibody have a significantly increased risk to develop additional alloantibodies.<sup>10,11</sup> The presence of auto-Ab's in serum complicates the type and screen procedure. The determination of the patient's blood group (*Type*) by serological methods remains difficult, especially in patients with CA-Ab, and requires time-consuming washing steps (extensive washing to get rid of the RBC-bound auto-Ab's). Sometimes, serological blood group determination is not possible. Genotyping for the most important blood groups (Rhesus, Kell, Duffy, Kidd, SS's) may offer a solution. In case of WA-Ab bound to the RBC typing with monoclonal reagents is a possibility to avoid genotyping. The detection of alloantibodies remains difficult, since patient auto-Ab's react with test RBCs. This is also illustrated by the fact that in some cases crossmatching is positive for all selected RBC concentrates. With different absorption techniques (auto- and alloabsorption) auto-Ab's can be removed from patient serum in order to perform a proper screening for alloantibodies. However, these techniques are time-consuming, require abundant patient material and can only be performed by specialised reference laboratories.

## THERAPY

If possible, transfusion should be avoided! There is a significant risk for alloantibody formation upon transfusion in that situation. Moreover, ongoing haemolysis can be exacerbated by transfusion, since auto-Abs also react with transfused red blood cells. Anaemia should only be corrected in case of clinical symptoms. Transfusion must be performed under control of vital parameters, such as cardiac function (ECG), renal function and diuresis. If there is no vital indication for a transfusion it is prudent to wait for the results of the immunohaematological tests and the ensuing transfusion advice based on this. In a second approach the process of haemolysis must be stopped or at least be attenuated via an inhibition of autoantibody production and/or inhibition of premature RBC destruction. Successful treatment of secondary AIHA is only possible when the underlying disease is treated. *Figure 5* provides an overview on the different therapeutic approaches in AIHA. Due to the availability of a therapy efficiently targeting autoantibody-producing B-cells (anti-CD20 antibody therapy), the significance of splenectomy is a matter of debate. Prospective randomised trials evaluating the efficacy of different treatment modalities are not widely available since AIHA is a rare disease and affects a heterogeneous patient population. Moreover, the interpretation of the efficacy of the treatment effects in these studies is difficult since there are no uniform definitions for response to therapy, complete and

**Figure 5.** Mechanisms of red blood cell removal in autoimmune haemolytic anaemia



partial remission, respectively. In the following section, therapeutic approaches for WA-AIHA and CA-AIHA will be discussed. The definitions partial and complete response are adopted from the publication cited in the text.

## Treatment of WA-AIHA

### Transfusion

The blood product must be compatible with respect to complement-activating alloantibodies present in patient's serum. If possible the selected product must be negative for the antigens, to which alloantibodies have been identified in the antibody screening. In addition, the development of new or additional alloantibodies must be prevented. Therefore, a blood product as compatible as possible with the recipient antigens will be selected. The minimal requirement is that the selected product must be compatible to Rhesus and Kell antigens. In case of severe haemolysis blood product selection may also consider the specificity of auto-Ab's. When there is a conflict making the right choice to select RBC it is important to keep in mind that in case of transfusion alloantibodies are more important than auto-Ab's. If there is no time to wait for the result of the serological investigations, it must be considered to prevent alloantibody formation by matching patient and donor for the most important RBC antigens: Rhesus, Kell, Kidd, Duffy, Ss.

### Steroids

Steroids are effective in the treatment of AIHA and therefore are the treatment of choice. Steroids decrease the production of auto-Ab's by B-cells.<sup>12</sup> Moreover, steroids reduce the density of Fc-gamma receptors on phagocytes

in the spleen.<sup>13,14</sup> Steroids induce a partial remission in 60 to 70% of the patients, in 10 to 15% a complete remission is achieved.<sup>1,15,16</sup> Commonly, prednisolone, 1 mg/kg/day is started, and depending on the clinical response is tapered slowly. After stabilisation of the haemoglobin a scheme frequently used at our department is to taper prednisolone to a dosage to 20 mg/day in two weeks. If the haemoglobin level remains stable, dosage can further be reduced to 10 mg/day after a month. Thereafter, the steroid dosage can further be tapered and be stopped after two weeks. In order to diagnose steroid-induced diabetes mellitus early, blood glucose levels must be monitored regularly. Moreover, osteoporosis prophylaxis must be started since the patients suffering from AIHA receive steroids over a long period of time. The psychological side effects of steroid treatment are frequently underestimated (e.g. agitation, lack of self-control, psychosis) and might become an incriminatory problem for the patient and social environment. Therefore steroid doses have to be reduced often or the therapy has even to be stopped.

#### *Cytotoxic drugs*

Azathioprine and cyclophosphamide are both immune suppressors leading to a decrease of autoantibody production. The addition of these drugs can be considered if steroid therapy does not lead to a sufficient result, when a steroid maintenance dose of more than 20 mg/day is needed or steroid doses must be tapered due to side effects.<sup>17,20</sup> Cyclophosphamide (100 mg/d) or azathioprine (100-150 mg/d) can be administered as monotherapy or in combination with steroids. Due to their myelosuppressive effects peripheral blood cell counts must be controlled regularly and if needed dosage must be adapted. In refractory AIHA pulse therapy with cyclophosphamide (50 mg/kg over 4 days) in combination with mesna and G-CSF might be successful.<sup>21</sup> In desperate cases vincristine might be a valuable alternative bearing the advantage of being less myelotoxic than cyclophosphamide.<sup>22</sup> Immunosuppressive drugs, such as cyclosporine or mycophenolate-mofetil seem to be effective in some case series.<sup>23,24</sup>

#### *Splenectomy*

By means of splenectomy RBC destruction is abated and the production of auto-Ab's is decreased. Two weeks after splenectomy anaemia has stabilised in more than 50% of the patients.<sup>25-27</sup> Approximately 20% of the patients reach long-time remissions or are even cured from the disease. In half of the patients steroids can further be tapered. However, one-third of the patients do not reach a substantial remission. The mortality of splenectomy by laparotomy is around 1%, in laparoscopic splenectomy it is about 0.5%.<sup>28,29</sup> Patients after splenectomy have an increased risk for infections as compared with the normal

population.<sup>30,31</sup> Vaccination against *N. meningitidis*, *Str. pneumoniae*, *H. influenzae*, if possible prior to splenectomy, significantly decreases the risk for infection in these patients.<sup>32</sup>

#### *Anti-C20 antibody*

Rituximab is a chimeric, monoclonal antibody targeting CD20 expressed on all B-cells except plasma cells.<sup>33</sup> Administration of rituximab decreases autoantibody production by targeted destruction of B cells. The efficacy of rituximab in WA-AIHA is difficult to assess due to the presence of a considerable publication bias and the lack of controlled prospective studies. Retrospective studies report a complete remission in 20 to 70% of the patients. In prospective studies, >60% of the patients achieve a complete remission, but most patients will relapse sooner or later (>24 months).<sup>34-38</sup> Rituximab is well tolerated, occasionally allergic reactions with hives, chills and hypotension occur. As a very rare but fatal complication, progressive multifocal leucoencephalopathy after rituximab therapy in patients suffering from systemic lupus erythematosus has been reported.<sup>34,39</sup> Despite the lack of controlled prospective studies rituximab has to be considered to replace splenectomy as therapy of choice in steroid-resistant WA-AIHA. If splenectomy is reconsidered after failure of rituximab therapy, it must be kept in mind that vaccination to encapsulated bacteria might be ineffective after Rituximab therapy.

#### *Immunoglobulins*

In approximately 40% of cases, administration of immunoglobulins improves anaemia temporarily. This is mainly attributed to a reduction of RBC destruction in the spleen.<sup>40</sup> In addition, immunomodulatory effects of gammaglobulins might contribute to the beneficial effect as well. Therapy with immunoglobulins might be considered in acute life-threatening situations in order to reduce breakdown of patients or donor erythrocytes.

#### *Treatment of CA-AIHA*

Fortunately, anaemia in CA-AIHA is usually mild and there is no need for correction. The basic treatment in that situation is quite simple: 'keep it warm'. Patients must protect themselves properly against the cold by wearing gloves, a hat and warm shoes. If necessary, transfusion must be performed under controlled conditions at 37 °C by means of a controlled heating system.<sup>6,34</sup> During surgery, body temperature must be kept at 37 °C. The criteria to choose a blood product are similar to those in WA-AIHA. However, the treatment of CA-AIHA remains a frustrating issue. Moreover, only a modicum of controlled studies are available. Steroids are clearly less effective than in WA-AIHA.<sup>6,41-43</sup> The same holds for cyclophosphamide and azathioprine.<sup>6</sup> In CA-AIHA there is no role for

splenectomy.<sup>6</sup> A couple of studies report some beneficial effects of gammaglobulins. In two controlled trials, rituximab was demonstrated to induce a response in 40 to 50%, but again achievement of complete remission is rare and relapses are common.<sup>44,45</sup> Since IgM are mainly located intravascularly, plasmapheresis induces a quick reduction of IgM levels and may therefore contribute to a short-term stabilisation of an AIHA.<sup>46</sup> Since plasmapheresis has to be performed at 37 °C, the technical procedure remains a challenge.

#### *Treatment options in case of intravascular haemolysis*

The treatment options in case of fulminant intravascular haemolysis are restricted. There are no controlled studies. Therapy focuses on supportive care with a close monitoring of vital functions, renal function and haemolysis parameters. In the literature, gammaglobulins and plasmapheresis have been reported as therapeutic options. In selected cases an inhibitor of the activation of complement component C5 (eculizumab) has been administered thereby attenuating the formation of the membrane attack complex.<sup>47</sup>

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