How I treat autoimmune hemolytic anemias in adults

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Abstract

Autoimmune hemolytic anemia is a heterogeneous disease regarding the type of the antibody involved and the absence or presence of an underlying condition. Treatment decisions should be based on careful diagnostic evaluation. Primary warm antibody autoimmune hemolytic anemias respond well to steroids, but most patients remain steroid dependent and many require second line treatment. Currently, splenectomy can be regarded as the most effective and best evaluated second line therapy, but there are still only limited data on long term efficacy and adverse effects. The monoclonal anti-CD20 antibody rituximab is another second line therapy with documented short term efficacy, but there is limited information on long term efficacy and side effects. The efficacy of immunosuppressants is poorly evaluated. Primary cold antibody autoimmune hemolytic anemias respond well to rituximab but are resistant to steroids and splenectomy. The most common causes of secondary autoimmune hemolytic anemias are malignancies, immune diseases or drugs. They may be treated in a way similar to primary autoimmune hemolytic anemias, by immunosuppressants, or by treatment of the underlying disease.
Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disease. In a recent population based study\(^1\) the incidence was 0.8/100.000/year, but the prevalence is 17/100.000.\(^2\) Primary (idiopathic) AIHA is less frequent than secondary AIHA. Secondary cases are often challenging since not only AIHA, but also the underlying disease(s) must be diagnosed and treated. AIHA is essentially diagnosed in the laboratory and considerable improvement has been made in this field. However, progress in treatment has been much slower.\(^3\)-\(^8\) Therapy has been reviewed by several authors\(^8\)-\(^15\) but no treatment guidelines have been published as yet.

Diagnosis

The diagnosis of AIHA is usually straightforward and made on the basis of the following laboratory findings: Normocytic or macrocytic anemia, reticulocytosis, low serum haptoglobin, elevated LDH, increased indirect bilirubin and a positive direct antiglobulin test (DAT) with a broad spectrum antibody against immunoglobulin and complement (Figure 1). However, there are pitfalls, in particular in secondary cases because not always are all of the typical laboratory findings of AIHA present.\(^15\) Two pieces of information are of utmost importance for the clinician to make an appropriate treatment decision: (1) What type of the antibody is involved? (2) Is the AIHA primary or secondary? The type of antibody can be identified by using monospecific antibodies to IgG and C3d. When the red cells are coated with IgG or IgG + C3d the antibody is usually a warm antibody (warm antibody AIHA, WAIHA). When the red cells are coated with C3d only, the antibody is often but not always a cold antibody. For definite diagnosis of a cold antibody AIHA (CAIHA) the cold agglutinin titre should be markedly elevated (> 1:512). In some cases (DAT negativity, IgM warm antibodies, cold antibodies with low titres or Donath-Landsteiner antibodies) diagnosis may be difficult and the expertise of an immune-hematological laboratory is required. For the diagnosis of secondary AIHA a careful history including information on the onset (acute or insidious), history of infections, information on recent transfusions, exposure to drugs or vaccination, signs of immune disease (arthritis) and general clinical condition are helpful. The exclusion of a drug-induced hemolytic anemia is particularly important since stopping the drug is the most
effective therapeutic measure in this situation. A clinical examination (lymphadenopathy, splenomegaly?) is obligatory. The need for additional investigations must be determined by history, clinical findings and the type of antibody. Routine work-up relevant for treatment decisions may include abdominal examination by CT scan (splenomegaly, abdominal lymphomas, ovarian dermoid cysts, renal cell carcinoma?), quantitative determination of immunoglobulins, a search for a lupus anticoagulant in case of warm antibodies or a bone marrow examination and a search for clonal immunoglobulins (immune fixation) in case of cold antibodies.

The list of underlying diseases in which AIHA can occur is long. The most common underlying diseases are lymphoproliferative disorders and immune diseases. Among others the type of AIHA is the most important clue to the most likely underlying disease (Table 1).

## Treatment of AIHA

### General remarks

This review will deal only with the treatment of adult AIHA.

In the era of evidence-based medicine it is surprising and regrettable that treatment of AIHA is still not evidence-, but essentially experience-based. There are no randomised studies and only a few prospective phase II trials. Otherwise only retrospective studies, small series of (probably selected) patients or single cases have been reported (evidence level V). There is no formal consensus on the definition of complete (CR) or partial (PR) hematological remission and refractoriness. We found more than 10 different definitions of complete and partial remission in various studies. In this review we have used the definitions of CR and PR as defined by the individual authors. There are only a few long term follow up studies. With a few exceptions no Kaplan Meier analyses were performed (this method was published after the publication of most larger treatment series of AIHA). Therefore, all statements on treatment recommendations in the literature, including this review, have to be regarded with caution. In practice, most treatment decisions must be made individually. In our department treatment decisions are always made
on an individual basis after discussion of experienced hematologists and then with the patient.

AIHA frequently has an acute onset but in most cases must be considered as a chronic disease with few exceptions. In primary WAIHA, there is only a low chance of spontaneous or drug induced long term remission or cure. Thus, the primary goal of treatment is to keep the patient clinically comfortable and to prevent “hemolytic crises” using medical interventions with the lowest possible short and long term side effects.

The patient with acute, newly diagnosed or recurrent AIHA

The onset of AIHA is frequently acute, sometimes life-threatening with weakness and shortness of breath. Hospitalisation is often required. The first decision to be made is whether the patient immediately needs transfusions. This is an individual decision and depends on the speed of development and severity of anemia, the type and cause of hemolytic anemia (the highest acute death rates were observed in patients with fludarabine associated AIHA \(^{31}\) and IgM WAIHA \(^{32}\)), the age and clinical condition of the patient. Since in WAIHA the antibody is directed against blood group antigens no truly matched blood transfusions are possible, but red cells can be safely given if alloantibodies are excluded. In our university hospital the following rules are established: In women without history of pregnancy and/or previous transfusions and in non-transfused males the risk of alloantibody is considered as almost absent, allowing for transfusion of only ABO- and RhD-matched red cells in urgent cases. In other patients an extended phenotyping with respect to Rh subgroups (C,c,E,e), Kell, Kidd and S/s using monoclonal IgM antibodies is performed and compatible red cell concentrates are selected for transfusion. Warm autoadsorption or allogeneic adsorption procedures for detection of alloantibodies \(^{33}\) are used only in exceptional cases. In any case a biological in vivo compatibility test is done at the ward: Rapid infusion of 20 ml blood, 20 minutes observation and, if there is no reaction, further transfusion at the usual speed. In critical cases transfusions should not be avoided or delayed because of uncertainty in matching. Even a small amount of transfused blood can be life-saving. The value of plasmapheresis to reduce antibody titres is unproven. \(^{34}\) In WAIHA treatment with steroids should begin immediately. In patients with CAIHA transfused blood must be prewarmed using commercial warming coils.
Treatment of (primary) idiopathic WAIHA

First line treatment. The mainstay of treatment of newly diagnosed primary WAIHA is glucocorticoids (steroids). According to accepted recommendations we start treatment immediately with an initial dose of 1 mg/kg/day prednisone (PDN) orally or methylprednisolone intravenously. This initial dose is administered until a hematocrit of >30% or a hemoglobin > 10 g/dl (thus not necessarily a complete normalisation of hemoglobin) is reached. If this goal is not achieved within three weeks second line treatment is started since further improvement with steroid treatment is unlikely.9 Once the treatment goal is achieved the dose of PDN is reduced to 20-30 mg/day within a few weeks. Thereafter, the PDN dose is tapered slowly (2.5 – 5 mg/day per month) under careful monitoring of hemoglobin and reticulocyte counts. An alternate day regimen (reducing the dose gradually to nil on alternate days) may reduce the side-effects of steroids. If the patient is still in remission after 3-4 months at a dose of 5 mg PDN/day, an attempt to withdraw steroids is made. All patients on steroid therapy will receive biphosphonates, vitamin D and calcium from the beginning according to the recommendation of the American College of Rheumatology. Supplementation with folic acid is recommended. We carefully monitor blood sugar and treat diabetic patients aggressively since diabetes is a major risk factor for treatment-related deaths from infections.35 We don’t treat patients with acute hemolysis routinely with heparin36 but we always consider the possibility of pulmonary embolism, because symptoms could wrongly be ascribed solely to acute anemia. At particular high risk of thromboembolism are patients with AIHA and lupus anticoagulant97 or recurrent AIHA after splenectomy38.

Second line treatment (When? what? and who decides?). About 80% of patients achieve a CR or PR with initial PDN treatment.9 However, the majority of responders require maintenance steroids to maintain an acceptable hemoglobin value (>9-10g/dl). About 40–50% of patients need 15 mg or less PND/day (15 mg/day is regarded by many as the highest tolerable dose for long term treatment), but 15–20% need higher maintenance PDN doses. It is not exactly known how many patients will remain in remission after withdrawal of steroids and are possibly cured. It is estimated that this occurs in less than 20% of patients.9,10,38
If a patient is refractory to the initial corticosteroid treatment a diagnostic reevaluation with regard to a possible underlying disease should be made. Patients with malignant tumors, benign ovarian teratomas or with warm IgM antibodies are often steroid refractory.

With regard to the decision for a second line treatment we classify patients in three categories. (1) Patients who are refractory to initial steroids and those who need more than 15 mg/d PDN as maintenance dose are absolute candidates for a second line therapy. (2) Patients who need between 15 mg to 0.1 mg/kg/PDN per day should be encouraged to proceed to a second line treatment, (3) while patients with PDN requirement of ≤0.1 mg/kg/day may do well with long term low dose PDN.

Patients who are refractory to initial steroid therapy are easily convinced for the need of a second line therapy, because they usually have severe side effects of steroid therapy, patients of the second category are often subjectively satisfied with corticosteroid therapy and often want to proceed with this treatment. However, they are usually not aware of the risks of long term corticosteroid treatment. They probably hope for a late remission which may occur but is not very likely (in contrast to autoimmune thrombocytopenia).

If the decision for a second line treatment has been made, there are several options. For each option the benefit/risk ratio should be individually assessed.

Splenectomy and rituximab are the only second line treatments with a proven short term efficacy. We recommend splenectomy to all patients without contraindications as the best second line therapy for the following reasons. (1) The short term efficacy is high. Following splenectomy short term CR or PR can be expected in two thirds of patients with a range of 38–82% depending on the percentage of secondary cases. Although, no high quality data on long term success are available (a Kaplan Meier analysis of disease and drug free survival after splenectomy has never been done in AIHA), there is good evidence that a substantial number of patients will remain in remission without need of medical intervention for years. Chertkov and Dacie were the first to describe the effects of splenectomy in WAIHA in a series of 28 patients. Half of the patients had a CR or PR. Only two patients were in remission for more than 5 years, but six patients remained in a stable PR for up to 7 years. The best data on follow up were provided by Coon. In 52 splenectomized patients (percentage of primary AIHA unknown) they found that 63% of patients had a hematocrit > 30% without steroids after a mean follow up of 33
months and 21% had a hematocrit ≥ 30% with a PDN requirement of ≤15 mg/day after a mean follow up of 73 months. In the study of Allgood38 44 % of patients were in CR after more than one year after splenectomy. It is also the experience of many hematologists that patients with recurrence after splenectomy require lower doses of steroids to maintain acceptable hemoglobin levels41. (3) The perioperative risk of splenectomy is low. Splenectomy can safely be performed laparoscopically in almost all cases of primary AIHA, since the spleen is usually normal-sized. The mortality of laparoscopic splenectomy (all indications) was 0.5% in a large national study.44 All patients should receive postoperative thromboprophylaxis with low molecular weight heparin, probably even beyond hospital discharge. The withdrawal of steroids after splenectomy should be done slowly (as described for primary treatment) to prevent hemolytic crises in case of recurrence. (4) The only relevant long-term risk is a lifelong persisting higher rate of infections (the most feared is overwhelming pneumococcal septicaemia). The infection risk is probably overstated for adult AIHA patients, since the highest risk is in children and patients with hematological malignancies. In AIHA the risk must be balanced against the risk of other second line treatments. In a recent large population based study45 an increased risk for infections in splenectomised (vaccination rate approximately 60%) patients has been confirmed. Although data were not provided for AIHA but rather for idiopathic autoimmune thrombocytopenia (ITP), they may be relevant for AIHA. The adjusted relative risk in the matched-indication comparison (= comparison of splenectomized vs. non-splenectomized patients with the same disease) of hospital contacts for infections was 1.4 beyond 365 days after splenectomy but mortality was not increased.46 There is good, but not definite evidence that preoperative vaccination reduces the risk of severe infections.47 Other long term risks are an increased risk of venous thromboembolism48 and a (very small) risk of pulmonary hypertension.

If splenectomy is performed all measures must be taken to prevent complications. We recommend that all our patients have preoperative vaccination against pneumococci, meningococci and hemophilus and that vaccination for pneumococci should then be repeated every 5 years. Patients must be informed about the risk of infections and should be advised to take antibiotics in case of fever. They should also be informed about the higher risk of venous thromboembolism.
Unfortunately, a prediction for response to splenectomy is not possible in an individual patient. Neither response to steroids, duration of disease, nor predominant red cell sequestration in the spleen is predictive.

So far splenectomy is the only treatment which may provide freedom from treatment in a substantial number of patients for more than two years and possibly cure in about 20%. We believe that splenectomy is underused and should be offered as the preferred second line treatment. In rituximab-studies only one third of patients had been splenectomized before administration of this off-label drug.

The other reasonable option for second line treatment is the anti-CD20 antibody rituximab. The discovery that this drug is effective in AIHA and ITP was a breakthrough in the treatment of these diseases after almost 50 years with very little progress. Rituximab has a well documented short–term efficacy but can currently be prescribed only off-label in this indication. The standard regimen is 375 mg/m²/week for four doses. Patients on steroids prior to initiation of rituximab therapy should continue steroids until the first signs of response to rituximab. In a retrospective study, rituximab in standard dose was given to 11 patients with refractory primary WAIHA. Four patients received additional therapies. Eight patients achieved a CR and 3 a PR, but 6 patients still had discrete laboratory signs of hemolysis. At a mean follow-up of 604 days all patients were still in CR/PR. The longest remission duration was 2884 days. The efficacy and toxicity of rituximab monotherapy was tested in five additional retrospective studies in a mixed population of refractory primary or secondary AIHA. Overall response rate was 82% (half CR and PR). Safety data were available in three studies. In one study two patients had severe infections and one a myocardial infarction, otherwise there were no major safety problems. The most severe potential long term complication of rituximab treatment is progressive multifocal leukencephalopathy (PML), which, however, has been observed so far in only two patients with AIHA. There is no doubt that the short term benefit/risk ratio for rituximab is high and rituximab is certainly the best option for patients who are not eligible for or refuse splenectomy. The problem is the small number of selected patients, the heterogeneity of patient population and the lack of systematic long term data on efficacy and safety in the published reports. In ITP it has been shown that patients with a CR after rituximab can have long remission durations and splenectomy can be avoided or postponed. Such data are not available for rituximab in AIHA. It appears that rituximab therapy has to be repeated every 1-3
years and this may increase the risk of infections including PML. We also don’t know whether patients will become refractory after repeated treatments.

In practice, it is frequently the informed patient who decides on the second line treatment modality. After consulting the internet (which usually promotes the most recent, but not the best established treatments) patients often refuse splenectomy (they often do not understand why a healthy organ should be removed) and request treatment with the newest drug - which is currently rituximab.

Medical reasons in favour of rituximab are relative contraindications for splenectomy such as massive obesity, technical problems, and a high risk of venous thromboembolism. A contraindication to rituximab treatment is an untreated hepatitis B virus infection.

High dose immunoglobulin has often been used as second line therapy after or concurrent with PDN because of the presumed efficacy and low risk of side effects. However, efficacy is low. We have used high dose immunoglobulin very rarely for treatment of AIHA. In a recent guideline high dose immunoglobulin was not recommended for routine use in AIHA. A potentially interesting second line (or even first line) treatment may be danazol, a synthetic anabolic steroid with pleiotropic effects. A success rate of 60-77% has been reported with danazol concurrent or after steroids, but these data have not been confirmed. We have used danazol only in few instances in the past, albeit without effect.

**Treatment of patients with refractory or recurrent disease after splenectomy or rituximab.** For patients who are refractory to splenectomy or those with recurrence after splenectomy (after exclusion of an accessory spleen) there are two options (Figure 2): Retreatment with steroids with the hope that the disease is now more responsive to steroids (which sometimes happens). We would try this in patients who had a relatively low pre-splenectomy steroid requirement (≤ 15 mg prednisone/day). Otherwise we would proceed directly to rituximab.

Patients who do not respond to rituximab should urgently be advised to undergo splenectomy. In patients who relapse after an initial response to rituximab and who had an initial response duration of less than one year, we recommend splenectomy and reserve retreatment with rituximab for progression after splenectomy. For patients with long remission durations after first rituximab treatment, retreatment with rituximab may be a reasonable option. Data in a few
patients indicate\cite{51,52} that a good response to retreatment with rituximab can be expected, but there are no data on the duration of a second remission.

**Treatment options beyond second line.** Immunosuppressive treatment was often recommended as preferred second line treatment because response rates of 40 - 60\% have been claimed in earlier reviews.\cite{9,10,62} There is no doubt that immunosuppressive treatment is effective in some cases, but there is doubt on the overall efficacy. The opinion that cyclophosphamide is highly effective appears to be based on data from two earlier articles.\cite{63,64} These studies provided overall results but no specific patient details. A critical analysis of other published cases of patients treated with azathioprine or cyclophosphamide\cite{39,41,65} reveals that probably less than one third had any “response”. Many patients received concomitant treatment with steroids. The durability of responses is unknown in most studies. Dosing of azathioprine is difficult because of the narrow therapeutic window, hypersensitivity due to genetic defects, and interaction with other drugs. Cyclophosphamide has a substantial mutagenic potential on long term treatment. We regard the benefit/risk of azathioprine/cyclophosphamide only moderate at best. Skinner\cite{66} wrote on immunosuppressive drugs in AIHA in his review 1972: “Unfortunately, all that is known now is merely that immunosuppressive therapy of this condition is feasible.” This is still true today.

All other immunosuppressive treatments (mycophenolate mofetil, cyclosporine) have in common that only very few patients were treated, but surprisingly in almost all cases favourable responses were achieved.\cite{67,68} This probably indicates that there was a strong selection bias. From the pre-treatment data in rituximab trials it appears that in the pre-rituximab era azathioprine and cyclophosphamide were very popular as second line therapy but we have used immunosuppressants very rarely because of doubts on efficacy and the fear of side effects.

**Treatment of last resort (severe anemia and none of the known drugs had worked).** High dose cyclophosphamide has been used as treatment for selected highly refractory patients. In the study of Moyo\cite{69} nine patients received several cycles of cyclophosphamide (50 mg/kg/d for 4 days) and six out of nine patients achieved a CR with a median duration of 15 months at the time of publication (2002). All these patients are still in CR in 2010.\cite{70} The results of autologous stem cell transplantation
were disappointing.\textsuperscript{71} Alemtuzumab has been effective in a few patients, but toxicity is high.\textsuperscript{72}

On the basis of published data on benefits and risks (independent of individual factors) in our opinion the sequence of second line treatments in primary WAIHA should be splenectomy, rituximab and thereafter any of the immunosuppressive drugs (Figure 2). In practice the choice of the sequence mainly depends on the personal experience of the physician, patient factors such as age and comorbidity, the availability and cost of drugs and the preference of the patient. The main factor for the selection of any drug should be safety, since the curative potential of all these drugs is low and treatment may be more dangerous for the patient than the disease to be treated.

**Treatment of secondary AIHA**

**WAIHA associated with systemic lupus erythematosus (SLE).** SLE is a most common cause of secondary AIHA (Table 2). The preferred first line therapies are steroids used in the same manner as in primary AIHA. The response rate is high. On a maintenance treatment of 5 – 20 mg PDN (in some patients with additional azathioprine or cyclophosphamide) the recurrence rate was low (3-4/100 patient years).\textsuperscript{83} The same second line treatments as in primary AIHA have been effective in some cases.\textsuperscript{83} Rituximab has been effective in single cases, but there is a concern of an increased risk of PML in this particular disease. Splenectomy seems to have an only low long-term efficacy.

**AIHA associated with malignancies**

**CLL-associated WAIHA.** For the treatment of patients with CLL-associated WAIHA several aspects are important: Compared to patients with primary AIHA they are at a higher risk of infections, they are older and have higher comorbidity. CLL-associated AIHA may be either “spontaneous” or drug induced. For treatment decisions not only the AIHA but also stage and progression of CLL have to be taken into consideration. A number of relatively small studies in different populations of patients with various drugs have been performed. The type of patients and pretreatment was not uniform in these studies.
Our strategy for treatment of CLL associated AIHA is shown in Table 3. It is based on published data\textsuperscript{92} and our practical experience.

It seems reasonable to use steroids as first line therapy in the same manner as in primary AIHA in patients with non-progressive early CLL. However, there are no data on the efficacy and adverse effects of steroid monotherapy. In fludarabine induced AIHA, CLL steroid monotherapy is the best choice and often successful.\textsuperscript{84} In AIHA associated with untreated “active” CLL, long term steroid treatment (combined with chlorambucil) seems to be very successful (84% CR/PR, 54% of the CR patients relapse-free after 5 years) with an acceptable toxicity.\textsuperscript{16} In steroid refractory AIHA in CLL, more aggressive treatments are indicated. A very effective and surprisingly well tolerated second line treatment is the combination of rituximab, cyclophosphamide and dexamethasone (RCD).\textsuperscript{86} Favourable results in AIHA associated with progressive CLL were also obtained with R-CVP.\textsuperscript{87} Other treatment options are cyclosporin which has relative good activity\textsuperscript{89} and rituximab. Rituximab monotherapy is less active than in primary AIHA and has a higher toxicity.\textsuperscript{88}

**WAIHA in Non-Hodgkin’s lymphomas.** The treatment of AIHA in NHL depends on the type of lymphoma. Generally, the AIHA of patients with NHL has a poor response to steroids. Splenectomy is effective only in splenic marginal zone lymphoma. The best responses in high grade B-cell lymphomas, follicular lymphomas, angioimmunoblastic T-cell lymphoma (AILT) and other T-cell lymphomas have been obtained with intensive anti-lymphoma chemotherapy with or without rituximab.\textsuperscript{73} Most of the chemotherapy induced complete remissions of AIHA were sustained.

**Drug related WAIHA.** Currently, the most important drug related AIHAs are due to drugs which are used for treatment of CLL, in particular fludarabine but also after other antileukemic drugs. AIHA may occur during or after drug exposure. Fludarabine triggered AIHA may be life-threatening. It responds to steroids, but only half of the patients are in remission off steroids.\textsuperscript{84} Another important cause of WAIHA is interferon alpha treatment, in particular in hepatitis C.\textsuperscript{30} These patients recover usually after cessation of interferon.

**Treatment of cold antibody AIHA (CAIHA)**
Almost all CAIHA seem to be secondary. The underlying conditions in most cases are lymphoproliferative diseases (including IgM-MGUS), less commonly autoimmune diseases or infections, and rarely drugs.8,93

**Primary chronic cold agglutinin disease (CAD).** Primary CAD is defined as a CAIHA in patients with IgM-MGUS or in lymphoma without overt clinical signs but with bone marrow infiltration.94 The anemia is rarely acute, often mild and drug treatment is required in only half of the patients. All patients should be advised to avoid cold exposure. In contrast to WAIHA CAIHA does not respond to steroids and/or splenectomy. In patients with evidence of lymphoma who are not severely anemic, therapy with chlorambucil may be tried,65,95 but the efficacy in terms of hemoglobin increase is rather small. The most effective and best evaluated treatment is rituximab in standard lymphoma dose. Berentsen et al.81 performed an open, uncontrolled prospective phase II study of rituximab in CAD. Twenty out of 27 patients responded, but almost all responses (n=19) were partial remissions. The median duration of response was 11 months, and most of the relapsed patients responded to retreatment with rituximab. Very similar results were obtained by Schöllkopf et al.96 We treat all our patients with symptomatic CAD (hemoglobin below 9 – 10 g/dl and/or vascular symptoms) with rituximab. Remarkable responses have recently been obtained with eczuzulimab79 and bortezomib80 in rituximab refractory patients.

**Secondary CAIHA.** Chronic cold agglutinin AIHA also occurs in indolent and aggressive B and T-cell lymphomas. The CAIHA of these patients responds well to anti-lymphoma chemotherapy.73 In rare cases a CAIHA associated with a solid tumor was controlled by curative resection of the primary tumor.21

**Infection-related AIHA**

WAIHA may occur after a variety of viral infections such as hepatitis C, A, E and CMV. CAIHA is a rare, but typical complication of mycoplasma infection which resolves spontaneously, although resolution is probably accelerated by antibiotic treatment.

A special problem is the preparation of patients with high titre cold antibodies for surgery. Cryofiltration apheresis was successful in some patients in this situation.97
Future directions

There is an urgent need for better data and new treatments for WAIHA. Before new or old drugs or procedures are evaluated retrospectively or prospectively a consensus on the definitions of responses is required. This could be achieved by an expert panel of hematologists as it has been done for ITP. For first line therapy steroids will remain the preferred treatment. In the era of comparative-effectiveness research we need to determine whether splenectomy or rituximab is the best second line therapy in terms of efficacy, adverse events and cost efficiency. Any potential new drugs which will emerge must then be compared with the established best current second line therapy. Scientifically, the best way would be to do a randomized study comparing the best second line treatments - splenectomy and rituximab - after a standardized first line treatment. It is however doubtful, whether such as study will recruit enough patients. A solution could be a cooperative worldwide effort of hematologists to set up a registry of patients with AIHA who had undergone splenectomy or rituximab treatment for retrospective analysis of these cases. The results would of course not be evidence based medicine of highest standard, but certainly much better than the current state of knowledge. These data could be the basis for future prospective comparative studies with known or new drugs.

Acknowledgement

The authors wish to express their sincere thanks to Clive Zent (Mayo Clinic, Rochester, MN), Simon Panzer, G. Körmöczi and Sabine Eichinger (Medical University of Vienna) for critical reading of the manuscript and their suggestions. We also thank RA Brodsky, CL Bennett and RW Thomsen for providing additional information on their patients (studies). We thank Hanna Obermeier and Michaela Bronhagl for secretarial assistance.

Authorship

Contribution: K.L. and U.J. retrieved data and wrote the paper.
Conflict-of-interest disclosure: K.L. has received a lecture fee from Hoffmann-La Roche. U.J has received research support and lecture fees from Hoffmann-La Roche.

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Table 1. Prevalence and type of antibodies in secondary AIHA in adults

<table>
<thead>
<tr>
<th>Underlying disease or condition</th>
<th>Prevalence* of AIHA</th>
<th>WAIHA</th>
<th>CAIHA</th>
<th>References</th>
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<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>2.3 – 4.3%</td>
<td>87%</td>
<td>7%</td>
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<tr>
<td>Non-Hodgkin lymphoma (NHL) (except CLL)</td>
<td>2.6%</td>
<td>More common</td>
<td>Less common</td>
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<td>1.1%</td>
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<td>Hodgkins lymphoma</td>
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<td>Almost all</td>
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<td>Solid tumors</td>
<td>Very rare</td>
<td>2/3</td>
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<td>Autoimmune lymphoproliferative disease (ALPD)</td>
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<td>Post-allogeneic stem-cell transplantation (SCT)</td>
<td>4.4%</td>
<td>Yes</td>
<td>Yes</td>
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<td>Post-organ transplantation</td>
<td>5.6% (pancreas)</td>
<td>Yes</td>
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<td>Drug induced in CLL</td>
<td>2.9 – 10-5%</td>
<td>Almost all</td>
<td>Rare</td>
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<td>Interferon alpha</td>
<td>Incidence: 11,5/100,000/patients years</td>
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*Data from recent and/or larger studies
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<th>First line</th>
<th>Second line</th>
<th>Beyond second line</th>
<th>Last resort</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary AIHA</td>
<td>Steroids</td>
<td>Splenectomy</td>
<td>Rituximab</td>
<td>Azathioprine, MMF, cyclosporin, cyclophosphamide</td>
<td>See text</td>
</tr>
<tr>
<td>B and T cell NHL</td>
<td>Steroids</td>
<td>Chemotherapy +/-rituximab (splenectomy in SMZL*)</td>
<td>High dose cyclophosphamide</td>
<td></td>
<td>73, 74</td>
</tr>
<tr>
<td>Hodgkins lymphoma</td>
<td>Steroids</td>
<td>Chemotherapy</td>
<td></td>
<td></td>
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<tr>
<td>Solid tumors</td>
<td>Steroids</td>
<td>Surgery</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ovarian dermoid cyst**</td>
<td>Ovarectomy</td>
<td></td>
<td></td>
<td></td>
<td>22</td>
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<tr>
<td>SLE</td>
<td>Steroids</td>
<td>Azathioprine</td>
<td>MMF</td>
<td>Rituximab autologous SCT</td>
<td>See text</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Steroids</td>
<td>Azathioprine</td>
<td>Total colectomy</td>
<td></td>
<td>24, 75</td>
</tr>
<tr>
<td>CVID</td>
<td>Steroids + IgG</td>
<td>Splenectomy</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>ALPD**</td>
<td>Steroids</td>
<td>MMF</td>
<td>Sirolimus</td>
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<td>76, 77</td>
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<td>Allogeneic SCT</td>
<td>Steroids</td>
<td>Rituximab</td>
<td>Splenectomy T-cells infusion</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Organ transplantation (pancreas)**</td>
<td>Discontinuation of immune suppression steroids</td>
<td>Splenectomy</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>Withdrawal</td>
<td>Steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cold agglutinin disease (CAD)</td>
<td>Protection from cold exposure</td>
<td>Rituximab Chlorambucil</td>
<td></td>
<td>Eczulimab***, Bortezomid***</td>
<td>65,73-81</td>
</tr>
<tr>
<td>Paroxysmal cold hemoglobinuria (PCH)</td>
<td>Supportive treatment</td>
<td>Rituximab</td>
<td></td>
<td></td>
<td>82</td>
</tr>
</tbody>
</table>

*Splenic marginal zone lymphoma, ** No personal experience, *** Off-label
Table 3. Suggested treatments of CLL-associated AIHA

<table>
<thead>
<tr>
<th>Condition</th>
<th>First line treatments</th>
<th>Second line treatments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated drug-related AIHA, Untreated AIHA in early stage CLL</td>
<td>Steroids</td>
<td>RCD</td>
<td>84,85</td>
</tr>
<tr>
<td>Untreated AIHA in active CLL</td>
<td>Steroids + Chlorambucil</td>
<td>RCD, R-CVP</td>
<td>16,86,87</td>
</tr>
<tr>
<td>Steroid refractory, non-progressive CLL</td>
<td>Rituximab, cyclosporin, splenectomy</td>
<td>RCD, R-CVP</td>
<td>88-90</td>
</tr>
<tr>
<td>Multiply refractory AIHA, advanced or progressive CLL</td>
<td>Alemtuzumab</td>
<td></td>
<td>91</td>
</tr>
</tbody>
</table>

* R-CVP rituximab, cyclophosphamide, vincristine, prednisone
Figure 1: Diagnostic algorithm in autoimmune hemolytic anemia

Normocytic (macrocytic) anemia, reticulocytosis, low haptoglobin, increased indirect bilirubin, elevated LDH

Hemolytic anemia

DAT

AIHA

IgG +/- C3d

C3d

WAIHA

CAIHA (PCH)

History, clinical examination, abdominal CT scan, immunoglobulines, lupus anticoagulant

Bone marrow examination, immune fixation, immunoglobulines
Figure 2: Treatment algorithm for steroid refractory WAIHA

Steroid refractory WAIHA

- Splenectomy
  - Refractory or recurrent
    - (Low dose) steroids
    - Rituximab
      - Refractory
        - Retreatment with Rituximab
          - insufficient response
            - Other immunosuppressants or experimental therapy
  - Recurrent
    - Retreatment with Rituximab
      - insufficient response

- Rituximab
  - Refractory or recurrent
    - Splenectomy
      - Refractory
        - Retreatment with Rituximab
          - insufficient response

Less preferred

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How I treat autoimmune hemolytic anemias in adults

Klaus Lechner and Ulrich Jäger