Supplementary appendix

Defining autoimmune hemolytic anemia: a systematic review of the terminology used for diagnosis and treatment.

Figure 1. Medline search strategy

Subject heading: Anemia, Hemolytic, Autoimmune

Or autoimmune hemolytic anemia.mp. search as Keyword.

Explode function, all subheadings included.

Limited to years 2006-2015

1317 articles identified.

Combined (or) above with additional key works (limited to years 2006-2015):

Evans syndrome.mp - 177

Cold agglutinin disease.mp - 159

Cold hemagglutinin disease.mp - 8

Paroxysmal cold hemoglobinuria - 23

1371 articles identified.

Table 1. Criteria for the diagnosis of AIHA

Paper	Diagnostic criteria for AIHA	Criteria for DAT negative AIHA if included
(1)	HA (lab and clinical evidence including increased reticulocyte count, elevated indirect bilirubin, increased LDH, decreased haptoglobin and increased transfusion requirement) and a positive DAT with non-specific antibody elution	
(2)	Clinical features of hemolysis and serological positivity for RBC-directed antibodies and/or complement fractions	See main criteria.
(3)	HA with positive DAT	HA, a negative DAT, exclusion of alternative causes of HA and a response to corticosteroids.
(4)	HA (Hb <120 g/L, evidence of hemolysis e.g. low haptoglobin), a positive DAT and no other cause of HA identified	
(5)	HA, a positive DAT and the absence of other hereditary or acquired cause of hemolysis.	(recognized that DAT negative cases can occur but no definition)
(6)	Marked signs of hemolysis and a positive DAT	
(7)	Biochemical evidence of HA (raised LDH, reduced haptoglobin or spherocytes on the blood film), a positive DAT and exclusion of alternative causes of HA (e.g. alloimmune, MAHA). Clinically significant hemolysis was defined by a drop in hemoglobin of 20 g/L or more.	
(8)	HA with a positive DAT. Drug induced HA was excluded.	HA with a negative DAT after extensive laboratory workup and exclusion of alternative causes for HA
(9)	The exclusion of alternative causes of anemia AND all of 1) Hb less than or equal to 110 g/L, in the absence of any cytotoxic treatment in the last month 2) one or more signs of laboratory hemolysis (increased unconjugated bilirubin, raised LDH, reduced haptoglobin 3) either reticulocytosis or positive DAT.	Included in main criteria (point 3)
(10)	HA (Hb <120 g/L, corrected reticulocytes >2%, LDH >220 U/l, and total bilirubin >1.5 mg/dl with the majority in the unconjugated form) and a positive DAT (all cases in the study had a positive DAT).	
(11)	HA (Hb less than or equal to 110 g/L with features of hemolysis [low haptoglobin and/or elevated LDH and/or elevated bilirubin]), a positive DAT and absence of any other hereditary or acquired HA	
(12)	All of: clinical and lab evidence of HA (increased LDH & bilirubin, decreased Hb & haptoglobin and increased transfusion requirements), positive DAT, positive IAT (with broad reactivity to RBC in the serum and eluate) and exclusion of other causes of hemolysis.	
(13)	All of: HA (Hb less than or equal to 100 g/L, one or more lab signs of hemolysis [increased bilirubin, elevated LDH, reticulocytosis]), positive DAT and absence of chemotherapy in the preceding month.	
(14)	HA, a positive DAT and the absence of an alternative cause of hereditary or acquired hemolysis	
(15)	All of: HA (decreased hemoglobin, reticulocytosis, elevated LDH and increased indirect bilirubin), positive DAT, no cause of blood loss.	

(16)	Positive DAT and non-ABO autoantibodies detected by the indirect antiglobulin test	
(17)	Positive DAT and symptomatic anemia.	
(18)	HA (symptomatic) associated with a positive DAT	
(19)	HA (Hb <100 g/L at time of initial diagnosis and evidence of red cell breakdown [elevated bilirubin and/or LDH]) and positive DAT	
(20)	HA (Hb <120 g/L, corrected reticulocyte count >2%, LDH >220 U/L and total bilirubin >1.5 mg/dL with the majority of bilirubin unconjugated]) and positive DAT.	
(21)	HA (elevated LDH and unconjugated bilirubin, increased reticulocytes, decreased hemoglobin), positive DAT and exclusion of other causes of hemolysis e.g. TTP and medication induced hemolysis.	
(22)	HA (in vivo hemolysis [low Hb, high reticulocyte %, high indirect bilirubin, high LDH, low haptoglobin, and/or erythropoiesis in bone marrow]), and exclusion of other anemic icteric diseases without hemolysis (e.g. megaloblastic anemia, MDS, erythroid leukemia, CDA, hepatobiliary disease or constitutional jaundice). Diagnosis of AIHA "by means" of the DAT, steroid-reactivity and exclusion of alloimmune and drug induced hemolytic anemia.	(Study compared DAT negative and DAT positive AIHA cases, but it is unclear how this clinical definition was applied, since some patients were both DAT negative and steroid unresponsive)
(23)	The diagnosis of AIHA required the presence of all the following criteria, provided no other identified cause of anemia: (i) Hb levels lower than or equal to 110 g/L in the absence of any cytotoxic treatment in the preceding month; (ii) one or more laboratory signs of hemolysis (increased bilirubin, elevated lactic dehydrogenase, and reduced haptoglobin); and (iii) positive direct antiglobulin test (DAT) and/or reticulocytosis. Moreover, it was required that bone marrow specimens were evaluated in all DAT negative cases, in order to rule out aplastic anemia and/or anemia related to CLL progression.	See main criteria. Increased reticulocyte count can replace positive DAT but bone marrow required to help with exclusion of alternatives.
(24)	Serological evidence of a red blood cell autoantibody and laboratory and/or clinical evidence of hemolysis	See main criteria
(25)	HA (anemia, high LDH and indirect bilirubin, and reticulocytosis) and a positive DAT	
(26)	Symptomatic anemia with a positive DAT	
(27)	HA, positive DAT, exclusion of other causes of HA	(DAT negative AIHA can also be made but truly a diagnosis of exclusion)
(28)	Evidence of hemolysis, Hb less than or equal to 100 g/L and a positive DAT	
(29)	HA (low haptoglobin, increased LDH, increased bilirubin and reticulocytes) and a positive polyspecific DAT	
(30)	HA (Hb <110 g/L and at least one of: reticulocytes >120x10^9/L, haptoglobin <10 mg/dL, total bilirubin >1 mg/dL). A positive DAT and exclusion if a hereditary hemolytic anemia and maternal alloimmunisation (if <6 months old).	
(31)	HA (Hb <100 g/L, low haptoglobin <0.3 g/l, raised reticulocyte count >100 x 10^9/L), positive DAT and the absence of obvious bleeding.	
(32)	HA (Hb <100 g/L or hematocrit <30% and 1 or more indirect markers of hemolysis [high reticulocytes, low haptoglobin, increased LDH or bilirubin] a positive DAT	DAT negative AIHA could be diagnosed if 2 or more indirect signs of hemolysis were present

	for either IgG or C3 and no alternative explanation for anemia.	
(33)	(AIHA secondary to lupus) Anemia (Hb <130 g/L in men, <110 g/L in women) and reticulocytosis (corrected reticulocyte count >2.5%). Exclusion of alternative causes of HA	
(34)	HA (corrected reticulocyte count >2%, elevated indirect bilirubin, elevated LDH and low haptoglobin) and positive DAT.	
(35)	HA (normocytic or macrocytic anemia, reticulocytosis, low haptoglobin, raised LDH and indirect bilirubin) and a positive DAT. Typical laboratory findings are not all, always present, especially in secondary AIHA	
(36)	Laboratory evidence of hemolysis (increased reticulocyte count with increased indirect bilirubin, LDH or absent haptoglobin levels) and a positive DAT	
(37)	A fall in Hb of at least 20 g/L, a rise in indirect bilirubin, a positive DAT and/or increased reticulocyte count with no other cause of anemia identified.	See main criteria. Increased reticulocyte count can replace positive DAT.
(38)	Hb <100 g/L, one or more marker of hemolysis (increased indirect bilirubin and/or LDH, decreased haptoglobin, increased absolute reticulocyte count), positive DAT for IgG or C3d and no other cause for anemia identified.	
(39)	HA (anemia and laboratory evidence of hemolysis such as elevated reticulocytes, LDH and reduced haptoglobin), a positive DAT or a direct detection of anti-erythrocyte antibodies.	See main criteria. Direct detection of RBC antibodies can replace positive DAT.
(40)	HA (Hb <100 g/L, at least one marker of hemolysis [increased indirect bilirubin and LDH, low haptoglobin]), increased reticulocyte count and positive DAT. Exclusions - no clinical evidence of bleeding, palpable splenomegaly, BM failure or inflammation and no recent myelosuppressive chemotherapy.	
(41)	HA (Hb less than or equal to 110 g/L and features of hemolysis [low haptoglobin and/or elevated LDH and/or bilirubin]) and a positive DAT	HA as defined with a negative DAT, after exclusion of any other cause of acquired or hereditary hemolytic anemia.
(42)	HA (clinical features of hemolysis, laboratory evidence of hemolysis [3 or more of: Hb <90 g/L, reticulocytes >2%, total serum bilirubin >2 mg/dl and LDH >500 IU/ml]) and a positive DAT	
(43)	HA (rising LDH and bilirubin, low haptoglobin) and a positive DAT	
(44)	HA (anemia with evidence of hemolysis e.g. elevated reticulocytes, elevated LDH), positive DAT and exclusion of alternative causes (e.g. bleeding, congenital hemolysis, alloimmune and drug induced hemolysis).	
(45)	HA (Hb 100 g/L or less with features of hemolysis), a positive DAT and no other causes of anemia.	
(46)		HA (low Hb, raised reticulocyte %, indirect bilirubin and LDH, low haptoglobin level and/or high erythropoiesis level in bone marrow), steroid reactivity, measurement of RBC-IgG and exclusion of other causes of anemia.

(47)	HA (anemia, clinical and biochemical evidence of hemolysis), a positive DAT and exclusion of other causes of HA	(DAT negative AIHA described but diagnostic criteria not defined)
(48)	HA (anemia, spherocytes or fragments on blood film and raised reticulocytes, erythroid hyperplasia in the bone marrow, raised unconjugated bilirubin), a positive DAT and exclusion of other causes of hemolysis.	
(49)	HA (Hb <90 g/L or 30 g/L drop in Hb since last test, features of hemolysis), a positive DAT and exclusion of other causes of anemia and of hemolytic anemia.	
(50)	HA (drop in hemoglobin, rise in indirect bilirubin), positive DAT and/or increased reticulocyte count, and no other cause of anemia identified.	See main criteria. Raised reticulocyte count can replace positive DAT.
(51)	HA (anemia, hyperbilirubinemia, low haptoglobin, and/or elevated reticulocytes) and positive DAT or presence of cold agglutinins.	See main criteria. Presence of cold agglutinins can replace positive DAT.
(52)	HA (clinically significant anemia, increased LDH, low haptoglobin) and a positive DAT	
(53)	HA (peripheral blood spherocytosis and fragmented cells, elevated reticulocyte count, unconjugated hyperbilirubinemia), positive DAT and exclusion of other causes.	HA, exclusion of other causes and responsive to a steroid trial
(54)	HA (clinical and laboratory evidence of hemolysis [increased LDH and bilirubin, decreased Hb and haptoglobin or increase in transfusion requirements]), positive DAT, positive IAT with broad reactivity to RBC in serum and eluate, and exclusion of other causes of immune hemolysis.	
(55)	Hb <100 g/l, positive DAT (to IgG or C3d) in the absence of bleeding.	Hb <100 g/L, at least 2 indicators of hemolysis (increased indirect bilirubin >17.1 micromol/L, absolute reticulocyte count >50 x 10^9/L, LDH >618 U/l or low haptoglobin <0.3 g/L) and no evidence of bleeding.
(56)	Anemia in the presence of antibodies directed against RBCs, evidenced by either direct or indirect Coombs tests.	See main criteria.
(57)	HA (Hemoglobin <120 g/L and one or more laboratory signs of hemolysis [reticulocytosis, decreased haptoglobin, increased bilirubin, or LDH]) and a positive DAT.	
(58)	Severe AIHA: Hb <80 g/L and drop in Hb of 30 g/L since the last reading, reticulocytosis, positive DAT and exclusion of other causes of anemia (e.g. bleeding) and hemolysis.	
(59)	Acquired hemolysis with a positive DAT	
(60)	Evidence of hemolysis (spherocytes and fragmented cells, raised reticulocytes, marrow erythroid hyperplasia and raised unconjugated bilirubin), positive DAT and exclusion of other causes of hemolysis.	
(61)	a) Hb <100 g/L, b) at least one marker of hemolysis (increased indirect bilirubin without liver disease, increased LDH without alternative cause, increased absolute reticulocyte count or increased BM hematopoiesis without bleeding) and c) direct or indirect evidence of an autoimmune mechanism (positive DAT, cold agglutinins or at least two markers of hemolysis without evidence of bleeding or hypersplenism)	See main criteria. Positive DAT can be replaced by cold agglutinins or 2 vs. 1 marker of hemolysis when no bleeding or hypersplenism

AIHA, autoimmune hemolytic anemia; BM, bone marrow; DAT, direct antiglobulin test; HA, hemolytic anemia; IAT, indirect antiglobulin test; LDH, lactate dehydrogenase; RBCs, red blood cells; TTP, thrombotic thrombocytopenic purpura.

Table 2. Criteria for the diagnosis of cold agglutinin disease

Paper	Diagnostic criteria - CAD
(62)	Primary CAD: chronic hemolysis, polyspecific DAT strongly positive, monospecific DAT strongly positive for C3d, CA titer greater or equal to 64 at 4°C (sample at 37-38°C until serum removed from clot), no overt malignant disease (clinical assessment, radiology as required). Secondary CAS: CA-mediated syndrome complicating a well-defined clinical disease (aggressive lymphoma, specific infections)
(8)	CAD: DAT positive for C3d only with a cold agglutinin of I specificity at a titer of 64 or higher
(63)	Cold antibody hemolytic anemia: AIHA with a C3d positive DAT and a cold agglutinin titer >1:500
(64)	CAD: chronic hemolysis, positive CA titers and characteristic findings on the DAT. If DAT not available, diagnosis was verified by CA titers and a clinical picture consistent with CAD. In patients without a CA titer, diagnosis was made based on the DAT and clinical picture.
(65)	Primary CAD: chronic hemolysis, positive polyspecific DAT, monospecific DAT strongly positive for C3d, CA titer of 64 or greater at 4°C. No overt malignant disease
(66)	Primary CAD: chronic hemolysis, CA titer 64 or greater at 4°C, typical DAT (positive polyclonal test, positive monoclonal test with C3d, and negative or weakly positive with IgG). CAD is primary if no malignant disease can be found by clinical or radiological assessment
(67)	Primary CAD: chronic hemolysis, a CA titer of 64 or greater at 4°C, typical DAT (positive polyspecific DAT, positive monospecific DAT with C3d and negative or weakly positive for IgG). Trial inclusion also required demonstration of a clonal B cell proliferation described by a monoclonal Ig band and a bone marrow clonal expansion of lymphocytes of the corresponding phenotype demonstrated by immune histochemistry or flow cytometry. Secondary CAD (excluded from study) was CAD associated with an apparent or aggressive lymphoma
(68)	Primary CAD: chronic hemolysis, CA titer of 64 or more, positive DAT, specific DAT positive for C3d and no clinical or radiological signs of lymphoma
(69)	CAS: 1) clinical evidence of acquired hemolytic anemia, 2) positive DAT with C3, 3) negative DAT with IgG, 4) a CA with reactivity up to at least 30 degrees Celsius in saline or albumin and 5) a CA titer at 4°C of 256 or more except in exceptional cases.
(70)	CAD: chronic hemolysis, a CA titer at 4°C of 64 or higher and a typical DAT (positive polyspecific DAT with a monospecific DAT positive to C3d and negative or weakly positive for IgG). Trial inclusion also required demonstration of a clonal B cell proliferation described by a monoclonal Ig band and a bone marrow clonal expansion of lymphocytes of the corresponding phenotype demonstrated by immune histochemistry or flow cytometry
(71)	Primary CAD: chronic hemolysis, CA titer at 4°C of 64 or more and typical DAT (polyspecific DAT positive, specific DAT positive for C3d), no malignant disease by clinical or radiological assessment.
(72)	CAD: chronic hemolysis, CA titer at 4°C or more and typical DAT (polyspecific DAT positive, specific DAT strongly positive for C3d)
(73)	CAD: HA (clinical and biochemical signs), a DAT strongly positive to C3d but negative with IgG, and a CA titer of 64 or more

HA, hemolytic anemia; CA, cold agglutinin; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; DAT, direct antiglobulin test; Ig, immunoglobulins.

Table 3. Criteria for the diagnosis of warm AIHA

Paper	Diagnostic criteria - warm AIHA
(3)	AIHA (hemolytic anemia with positive DAT) with a DAT positive for IgG +/- C3d (review also recognizes the occurrence of warm-IgM mediated AIHA)
(4)	AIHA (HA [Hb <120 g/L, evidence of hemolysis e.g. low haptoglobin], a positive DAT and no other cause of HA identified) with DAT positive to IgG only or IgG + C3d. Patients were excluded if they had CAD (not defined) or C3d only DAT
(8)	AIHA (HA and a positive DAT) with a DAT positive for IgG only or IgG + C3d
(11)	AIHA (Hb less than or equal to 110 g/L with features of hemolysis [low haptoglobin and/or elevated LDH and/or elevated bilirubin] and a positive DAT and absence of any other hereditary or acquired HA) with a DAT positive to IgG only or IgG and C3d. Also DAT positive to C3d only if CAS excluded.
(18)	AIHA (symptomatic hemolytic anemia associated with a positive DAT), with the DAT positive with anti-IgG alone or a combination of anti-IgG and anti-C3d.
(19)	AIHA (positive DAT, Hb <100 g/L at time of initial diagnosis and evidence of red cell breakdown [elevated bilirubin and/or LDH]) with a DAT positive for IgG only or IgG and C3d
(74)	Patients with AIHA and 2 out of 3 of 1) DAT positive to IgG +/- IgA or IgM, 2) Eluate IAT positive (with warmed washed RBCs at 37-40°C) 3) Serum IAT positive (warmed to 37-40°C)

AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; DAT, direct antiglobulin test; HA, hemolytic anemia; IAT, indirect antiglobulin test.

Table 4. Criteria for the diagnosis of paroxysmal cold hemoglobinuria

Paper	Diagnostic criteria - paroxysmal cold hemoglobinuria
None	

Table 5. Criteria for the diagnosis of mixed AIHA

Paper	Diagnostic criteria - mixed AIHA
(3)	AIHA (HA with positive DAT), DAT positive for both IgG and C3d; with co-existence of both warm autoantibodies and high-titer cold agglutinins
(8)	AIHA (HA with positive DAT), DAT positive for both IgG and C3d; with co-existence of both warm autoantibodies and high-titer cold agglutinins
(74)	Evidence for cold AIHA: DAT positive for C3d, agglutinin strongest at 0-10°C and reactive at ≥30°C. Evidence for warm AIHA: 2 out of 3 of 1) DAT positive to IgG +/- IgA or IgM, 2) Eluate IAT positive (with warmed washed RBCs at 37-40°C) 3) Serum IAT positive (warmed to 37-40°C)

AIHA, autoimmune hemolytic anemia; DAT, direct antiglobulin test; HA, hemolytic anemia; IAT, indirect antiglobulin test.

Table 6. Criteria for the severity of AIHA

Paper	Disease severity
(75)	Severe AIHA: Hb ≤ 60 g/L and not maintained by daily transfusion. Extremely severe AIHA: Hb <30 g/L
(8)	Anemia at onset classified as very severe (Hb ≤60 g/L), severe (Hb 61-80 g/L), moderate (Hb 81-100 g/L) or mild (Hb >100 g/L).

AIHA, autoimmune hemolytic anemia; Hb, hemoglobin

Table 7. Criteria for the disease phase of AIHA

Paper	Disease phase (e.g. acute/chronic)
(76)	Disease phase was defined by analogy to standard definitions used for ITP. Hence newly diagnosed (within 3 months from diagnosis), persistent (3-12 months from diagnosis) and chronic (lasting more than 12 months).
(48)	AIHA considered chronic if the symptoms persisted for more than 6 months.

AIHA, autoimmune hemolytic anemia

Table 8. Criteria to define "refractory" AIHA

Paper	Diagnostic criteria for "refractory" AIHA
(77)	HA, positive DAT and steroid inefficacy or dependence
(7)	Failure to respond after 4 or more treatment modalities including steroids, rituximab, other immune suppression or surgical splenectomy.
(36)	1) Hb <110 g/L despite receiving at least 2 treatment lines, 2) Hb >110 g/L after at least 3 treatment lines and treatment dependence to maintain this level of Hb

DAT, direct antiglobulin test; HA, hemolytic anemia; Hb, hemoglobin

Table 9. Treatment response criteria

Paper	Treatment response criteria
(76)	CR (to splenectomy): increased in Hb above 120 g/L in absence of further therapy and/or recent transfusion
(75)	Improvement (response to whole blood exchange transfusion): transfusion free, Hb increased up to 60 g/L, symptoms resolved, reduced strength or negative DAT. Stable: minimal or no transfusion required, laboratory hemolytic variables normalized, symptoms improved but not resolved. Ineffective: Hb not improved, still requiring daily transfusion.
(6)	CR: recovery of Hb to ≥120 g/L without transfusion and disappearance of hemolysis signs (reticulocyte count <100 x 10^9/L and normal LDH). A negative DAT is not required. PR: Hb < 120 g/L but with a gain of at least 20 g/L from baseline with or without persistent hemolysis signs
(7)	CR: normal Hb and biochemical markers of hemolysis with independence from additional treatment. PR: improvement in markers of hemolysis but requirement for maintenance treatment.
(8)	CR: Hb ≥120 g/L and normalization of all hemolytic markers. PR: Hb ≥100 g/L or at least 20 g/L increase in Hb and no transfusion requirement.
(11)	CR: Hb ≥120 g/L without recent transfusion and without features of hemolysis (normal LDH, haptoglobin, and bilirubin if performed). PR: Hb ≥100 g/L with at least an increase of 20 g/L from base line and persistent hemolysis. Patients were considered to have achieved a partial remission if they required a daily dose of prednisolone <10mg to maintain that response. NR: if not fulfilling CR or PR.
(12)	CR: resolution of all clinical and laboratory evidence of hemolysis and no detectable antibody in serum, eluate or on the RBC surface. PR: persistence of detectable antibody with improvement of laboratory data or a decrease in transfusion requirements. NR: if not fulfilling CR or PR.
(78)	Criteria were for all autoimmune disease. CR: normalization of clinical signs and laboratory tests. PR: improvement in clinical symptoms or laboratory analysis and/or steroid dependence was observed despite the presence of autoantibodies. NR: when clinical signs/symptoms and laboratory findings were unchanged or worsened despite therapy
(17)	CR: Hb >120 g/L and normalization of hemolytic markers. PR: Hb ≥100 g/L or at least 20 g/L increase in Hb in the absence of any treatment
(18)	CR: normalization of Hb without biochemical evidence of hemolysis and without on-going immunosuppressive therapy. PR: CR but requiring on going prednisolone (<10mg/day), or a compensated stable HA with acceptable Hb without treatment except prednisolone at <10mg/day.
(19)	CR: normalization of Hb, bilirubin and/or LDH sustained for at least 6 months. PR: an increase in Hb of 20 g/L from baseline or maintenance of Hb above 100 g/L for at least 6 months post treatment.
(64)	Response was defined as an improvement in clinical symptoms
(22)	Response: improvement in anemia (Hb >100 g/L) and hemolysis after treatment
(24)	Initial response (to splenectomy): rise or maintenance of laboratory values concurrent with taper or discontinuation of medical therapy. CR: no need for additional medical therapy (with or without normalization of laboratory values) at ≥2 weeks post-operatively. NR: the continued requirement for medical therapy.
(26)	CR: Hb >120 g/L and normalization of all hemolytic markers (reticulocytes, LDH, bilirubin, haptoglobin). PR: Hb 100 - 120 g/L or at least 20 g/L increase in Hb and no transfusion required. Sustained response (used to evaluate duration of response): Hb > 100 g/L in the absence of any treatment.
(65)	CR (primary CAD): Absence of anemia, no signs of hemolysis and disappearance of clinical symptoms of CAD. No monoclonal serum protein and no signs of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry. PR: a stable increase in hemoglobin levels by at least 20 g/L or to the normal range. A reduction of serum IgM levels by at least 50% of the initial level or to the normal range. Improvement of clinical symptoms and transfusion independence. NR:

	any outcome not meeting the criteria for CR or PR.
(28)	CR (in CVID patients): Hb ≥ 120 g/L in the absence of transfusion and without persistent features of hemolysis. Response (R): Hb ≥100 g/L with an increase of at least 20 g/L from baseline (can be persistent hemolysis if Hb is stable). R and CR only if no other medication used to treat the AIHA except CVID directed IVIg and/or steroids at a stable or decreasing dose.
(30)	CR: hemoglobin ≥110 g/L and reticulocytes ≤ 120 x 10^9/L, irrespective of the DAT and treatment. PR: hemoglobin 70 - 110 g/L and/or reticulocytosis >120 x 10^9/L. NR: hemoglobin <70 g/L,
(66)	CR (primary CAD): Absence of anemia, no signs of hemolysis and disappearance of clinical symptoms of CAD. No monoclonal serum protein and no signs of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry. PR: a stable increase in hemoglobin levels by at least 20 g/L or to the normal range. A reduction of serum IgM levels by at least 50% of the initial level or to the normal range. Improvement of clinical symptoms and transfusion independence. NR: any outcome not meeting the criteria for CR or PR.
(31)	CR: Hb >120 g/L without transfusion. Normalization of LDH and reticulocyte count. PR: Hb rise of at least 20 g/L but with final Hb <120 g/L, along with improved LDH/reticulocyte count and reduced transfusion requirement.
(67)	CR (primary CAD): Absence of anemia, no signs of hemolysis and disappearance of clinical symptoms of CAD. No monoclonal serum protein and no signs of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry. PR: a stable increase in hemoglobin levels by at least 20 g/L or to the normal range. A reduction of serum IgM levels by at least 50% of the initial level or to the normal range. Improvement of clinical symptoms and transfusion independence. NR: any outcome not meeting the criteria for CR or PR.
(34)	Response: Hb reached 100 g/L in the absence of hemolysis (normal corrected reticulocyte count, LDH and haptoglobin)
(36)	CR: non-transfused Hb >120 g/L and Hb increase of at least 20 g/L above pre-treatment Hb with discontinuation of concomitant immunosuppressive therapies. PR: non-transfused Hb >100 g/L and Hb increase of at least 20 g/L above pre-treatment Hb. Maintained response: response maintained for greater than 6 months after the beginning of treatment with discontinuation of concomitant therapy
(79)	Remission: Hb greater than 100 g/L, without evidence of hemolysis for more than 3 months and while receiving less than 10 mg prednisolone/day
(80)	CR: normal hemoglobin without immunosuppressive therapy and no hemolysis. PR: transfusion independence in a previously dependent patient and/or a 20 g/L increase in Hb. NR: no CR or PR.
(41)	CR: Hb of 120 g/L or more in the absence of transfusion without features of hemolysis (normal bilirubin and LDH +/- normal haptoglobin if performed). PR: Hb of at least 100 g/L with an increase of at least 20 g/L from baseline and persistent hemolysis
(43)	Response: Hb >120 g/L or increase in Hb of >20 g/L
(45)	CR: Hb greater than 110 g/L in women or 120 g/L in men without hemolysis (i.e. normal haptoglobin and LDH) off treatment. PR: Hb greater than 100 g/L with at least a 20 g/L increase from the pre-treatment level (with no transfusion in the last 2 weeks) with persistent hemolysis (i.e. low haptoglobin and/or high LDH) off treatment or on a stable dose of prednisolone of 10 mg/day or less
(48)	Response (to steroids): stable or rising Hb with fall in reticulocyte count within 14 days of starting steroids.
(49)	CR: Hb increased to above 110 g/L. PR: Hb between 90 and 110 g/L. NR if no CR or PR.
(81)	CR: sustained increase of Hb >110 g/L and reticulocytes <120 x10^9/L during 4 consecutive weeks. PR: sustained hemoglobin of 70 - 110 g/L or Hb >110 and reticulocyte count >120 during 4 consecutive weeks. Responses had to be independent of rescue or supportive care regimens between measurements.

(70)	CR (primary CAD): Absence of anemia, no signs of hemolysis and disappearance of clinical symptoms of CAD. No monoclonal serum protein and no signs of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry. PR: a stable increase in hemoglobin levels by at least 20 g/L or to the normal range. A reduction of serum IgM levels by at least 50% of the initial level or to the normal range. Improvement of clinical symptoms and transfusion independence. NR: any outcome not meeting the criteria for CR or PR.
(71)	CR (primary CAD): Absence of anemia, no signs of hemolysis and disappearance of clinical symptoms of CAD. No monoclonal serum protein and no signs of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry. PR: a stable increase in hemoglobin levels by at least 20 g/L or to the normal range. A reduction of serum IgM levels by at least 50% of the initial level or to the normal range. Improvement of clinical symptoms and transfusion independence. NR: any outcome not meeting the criteria for CR or PR.
(82)	CR: Hb (blood routine test) was normal. PR: Hb was more than 80 g/L but below normal.
(52)	Recovery: a non-transfusional increase in Hb of > 20 g/L, accompanied by a decrease in LDH, with or without resolution of the positive DAT.
(53)	Response: transfusion independence with Hb >20 g/L above baseline and absolute value more than 80 g/L.
(83)	CR: stable Hb levels >120 g⁄L, transfusion-free and absence of clinical and laboratory signs of hemolysis (no jaundice, normalization of LDH, haptoglobin and indirect bilirubin serum levels, normal reticulocyte count) irrespective of DAT. PR: rise in Hb levels more than 20 g⁄L, transfusion-free either without or reduced transfusion requirement, and improvement of clinical and laboratory signs of hemolysis.
(54)	CR: normalization of all clinical and laboratory signs of hemolysis and no detectable antibody in serum, eluate or on the red cell surface. PR: presence of autoantibody with improvement of laboratory data or decrease in transfusion requirements.
(84)	CR: normalization of hemoglobin, transfusion free and absence of clinical and laboratory signs of hemolysis. PR: rise in Hb ≥20 g/L, transfusion free either without or reduced transfusion requirement, and improvement of clinical and laboratory signs of hemolysis.
(58)	CR: Hb increased above 110 g/L. PR: - Hb increased to 80 - 110 g/L. In patients with Hb over 80 g/L, PR was defined as an increase in Hb was more than 15 g/L. NR: no CR or PR.
(72)	CR (primary CAD): Absence of anemia, no signs of hemolysis and disappearance of clinical symptoms of CAD. No monoclonal serum protein and no signs of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry. PR: a stable increase in hemoglobin levels by at least 20 g/L or to the normal range. A reduction of serum IgM levels by at least 50% of the initial level or to the normal range. Improvement of clinical symptoms and transfusion independence. NR: any outcome not meeting the criteria for CR or PR.
(60)	Response: transfusion independence associated with an increased Hb of >20 g/L over baseline and an absolute value more than 80 g/L.
(73)	CR (CAD): normalization of Hb, absence of hemolysis (including monoclonal IgM) and disappearance of clinical symptoms of CAD. PR: increase in Hb by 10 g/L or more for at least 1 month, no need for red cell transfusion, improvement in CAD clinical symptoms and if elevated IgM, at least a 50% reduction. NR was no CR/PR

CAD, cold agglutinin disease; CR, complete response; DAT, direct antiglobulin test; HA, hemolytic anemia; Hb, hemoglobin; LDH, lactate dehydrogenase; NR, no response; PR, partial response

Table 10 Assessment of response duration

Paper	Durability of response
(4)	Relapse: reappearance of hemolytic anemia <100 g/L leading to a therapeutic intervention. Assessment: documents number of relapses but duration of response not assessed
(6)	Relapse: reported but not defined. Assessment: treatment free survival (the interval between the initiation of treatment and the next line of therapy)
(7)	Relapse: reported but not defined. Assessment: response duration not assessed
(8)	Relapse: Hb ≤100 g/L or at least 20 g/L decrease in Hb with or without increased LDH. Assessments: time to relapse (median and range), time to next treatment due to relapse or lack of response, risk of relapse based on cumulative incidence and adjusted hazard ratios.
(11)	Relapse: reported but not specifically defined. Remission was defined: complete remission if a lasting complete response without treatment. Partial remission was when the patient required a dose of prednisolone <10 mg/day to maintain at least a long term response. Assessment: relapse free survival
(12)	Relapse: reported but not defined. Assessment: number of relapses but duration of response not reported
(63)	Relapse: reported but not defined. Assessment: duration of response not reported.
(17)	Relapse: reported but not defined. Assessment: relapse free survival
(18)	Relapse: reported but not defined. Assessment: relapse free survival
(19)	Relapse: a fall in Hb below 100 g/L and the requirement for new treatment. Assessment: relapse rate (%) with median duration of follow up and median time to next treatment.
(64)	Relapse: not specifically defined. Assessment: response duration was from time of response to start of alternative therapy or censoring of data. Median response duration (splenectomy).
(24)	Relapse: the recurrence of disease requiring additional medical therapy after a complete response. Assessment: relapse rate (%) with median time of follow up and median time to relapse
(26)	Relapse: reported but not defined. However sustained response was defined as Hb >100 g/L in the absence of treatment. Assessment: duration of response and relapse free survival.
(28)	Relapse: reported but not defined. A response was considered durable if it lasted more than 12 months. Assessment: durable response rate (%) with median follow up, relapse free survival.
(30)	Relapse: not specifically defined. Assessment: estimated probability of surviving in continuous complete remission (a stable complete remission without specific treatment for more than 1 year) at 2 and 5 years after diagnosis (%).
(31)	Relapse: HA (Hb <100 g/L, low haptoglobin <0.3 g/L, raised reticulocyte count >100 x 10^9/L), positive DAT and the absence of obvious bleeding. Assessment: duration of response calculated from treatment end to time of relapse by Kaplan-Meier
(67)	Relapse (CAD): a decrease in Hb below 100 g/L or by at least 20 g/L from the highest level achieved, and/or recurrence of clinical symptoms. Assessment: median response duration (time from achieving response to relapse or death).
(34)	Relapse: a failure to maintain a response to treatment. Assessment: number of relapses reported but not duration of response.
(36)	Relapse: not defined. Assessment: median duration of response, Kaplan–Meier estimated median and mean of maintained response (response maintained for greater than 6 months after the beginning of treatment with discontinuation of concomitant therapy).
(79)	Relapse: a fall in Hb to less than 100 g/L. Assessment: median duration of remission, incidence of relapse (episodes/person/year).
(80)	Relapse: loss of CR or PR in patients achieving CR or PR respectively. Assessment: progression free survival measured by Kaplan-Meier method.

(41)	Relapse: reported but not defined. Assessment: number of relapses with range of follow up (splenectomy), number of relapses with mean follow up (rituximab).
(43)	Relapse: DAT positive and evidence of hemolytic anemia (rising LDH and bilirubin, low haptoglobin). Assessment: duration of response was the time until additional treatment was required for AIHA. Median response duration (months) was estimated using Kaplan-Meier product-limit method.
(45)	Relapse: reported but not defined. Assessment: number of responding patients who relapsed.
(48)	Relapse (after a response to steroids): a fall in Hb on tapering steroids or within four weeks of stopping steroids. Assessment: number of responding patients who relapsed.
(49)	Relapse: reported but not defined. Assessment: number of relapses, median time to first relapse, recurrence rate per 100 person-years.
(81)	Relapse: reported but not defined. Assessment: duration of response (to relapse or time of last review)
(52)	Relapse: reported but not defined. Assessment: occurrence of relapse and duration of response (months)
(53)	Relapse: reported but not defined. Assessment: number of relapses, median duration of response in relapsing patients.
(83)	Relapse: reported but not defined. Assessment: mean time of follow up since treatment (since all patients remained in remission)
(58)	Relapse: reported but not defined. Assessment: number of relapses. Recurrence rate per 100 person years. Expected recurrence free proportion (%) at a median follow up of 180 months.
(60)	Relapse: reported but not defined. Assessment: number of relapses and median time to relapse.
(73)	Relapse: when the criteria for the maximal obtained response was no longer fulfilled. Assessment: median duration of response.

CAD, cold agglutinin disease; CR, complete response; DAT, direct antiglobulin test; HA, hemolytic anemia; Hb, hemoglobin; LDH, lactate dehydrogenase; PR, partial response

Table 11 Definitions of primary and secondary AIHA

Paper	Primary vs. secondary AIHA
(76)	Primary (warm): AIHA with the exclusion of underlying autoimmune diseases, primary immunodeficiency, infection, drug intake or lymphoproliferative disorder.
(62)	Primary CAD: a clonal lymphoproliferative disorder but with no overt malignant disease. Secondary CAS: a secondary cold agglutinin mediated syndrome complicating a well-defined clinical disease (aggressive lymphoma, specific infections).
(2)	Warm AIHA may be secondary to diverse causes including malignancy, autoimmune disease, infection, immunodeficiency and medication.
(3)	It can be primary or secondary to lymphoproliferative syndromes, infections, immunodeficiency and tumors
(4)	warm AIHA may be primary (idiopathic) or secondary to various conditions such as lymphoproliferative diseases, autoimmune disorders (mainly systemic lupus erythematosus),primary immunodeficiencies, chronic viral infections, solid tumors or drugs.
(75)	Primary (idiopathic): no secondary cause identified. Secondary: to various origins both hereditary and acquired (lists most common associations).
(5)	Primary: no underlying or associated disease. Secondary: cases with an underlying or associated disease (particularly lymphoproliferative disorders, autoimmune, infection or tumor)
(77)	AIHA was primary (idiopathic) or secondary when patients had a suspected secondary cause to their disorder (mostly lymphoproliferative disorders, autoimmune disorders and infections
(8)	Primary: AIHA in the absence of underlying lymphoproliferative syndrome, infection, autoimmune disease, neoplastic disease or drug induced AIHA
(11)	AIHA is subdivided into primary (idiopathic) or secondary depending on the presence or not of an associated and potentially causative disorder.
(14)	Primary (idiopathic) or secondary when associated with an underlying disease.
(17)	Primary: AIHA in the absence of lymphoproliferative, infectious or neoplastic disease
(18)	Warm AIHA can be primary or secondary to another disease (e.g. CLL, SLE or ulcerative colitis).
(19)	Warm AIHA can be primary or secondary to lymphoproliferative disorders, infections, immunodeficiency and primary autoimmune disorders.
(64)	AIHA may be primary (idiopathic) or secondary to an underlying condition such as infection, malignancy or immune disease.
(26)	Primary: absence of underlying lymphoproliferative, infectious or neoplastic disease.
(65)	Primary (CAD): a clonal lymphoproliferative disease but without overt malignant disease. Secondary CAS: cold antibody mediated HA complicating an overt and well defined malignant disease different from LPL and MZL
(27)	Primary (idiopathic): the absence of an underlying disease or condition promoting immune dysregulation. Secondary: the presence of an underlying disease or condition promoting underlying immune dysregulation.
(29)	Primary (idiopathic): if no known or suspected autoimmune disease, lymphoproliferative or other neoplastic diseases, infections or immune deficiency syndrome. Patients were observed for 6 months to exclude primary malignancy.
(30)	Secondary causes listed and discussed.
(66)	Primary (CAD): if no malignant disease can be found by clinical or radiological assessment. Secondary (CAD): occurrence as a complication to aggressive or overt extramedullary lymphoma or other cancers. Secondary CAD distinguished from cold antibody AIHA secondary to *Mycoplasma* or viral infections.

(67)	Primary CAD: evidence of a clonal B-cell lymphoproliferative disorder but no apparent or aggressive lymphoma. Secondary (CAD): CAD associated with an apparent or aggressive lymphoma
(35)	Secondary causes listed
(36)	AIHA can be idiopathic or have a suspected secondary cause (causes listed)
(79)	Primary (idiopathic): AIHA without associated diseases
(39)	AIHA is either idiopathic or secondary to malignancy, infection, connective tissue disease or drug administration.
(42)	AIHA was "primary" or secondary to some underlying diseases (listed).
(68)	Primary (CAD): no malignancy by clinical or radiological assessment (but an underlying clonal B-cell disorder is usually detected). Secondary (CAD): associated with malignant disease.
(47)	Primary (idiopathic): no apparent association with an underlying disease. Secondary: associated disease or conditions are listed. Primary (CAS): Idiopathic (most exhibit evidence of monoclonal B-lymphoproliferation). Secondary CAS: associated with infection or clinically evident malignant B-cell LPD.
(48)	Primary (idiopathic): no underlying pathology could be detected. Secondary: not specifically defined. Children in series with tuberculosis and chronic liver disease were ladled secondary.
(69)	Primary (idiopathic): no association with underlying disease. Secondary: associated with an additional disorder. Notes that some disorders are more frequently associated with AIHA than by chance alone. In other cases, AIHA resolves with treatment of the associated disorder. Others have an immune aberration but whether truly associated is not always clear. CAS may be primary (idiopathic) or secondary to infections and malignant disorders.
(70)	Primary (CAD): unrelated to lymphoma or other underlying disorders (except that an underlying clonal B-cell disorder can usually be detected). Secondary (CAD): accompanied by malignancy, most often lymphoma.
(71)	Primary (CAD): no malignancy by clinical or radiological assessment (but an underlying clonal B-cell disorder). Secondary (CAD): accompanied by malignancy, most often lymphoma.
(83)	Primary: not associated with an underlying disease. Secondary: a close relationship with other autoimmune or neoplastic diseases.
(72)	Primary (CAD): not associated with lymphoma or other diseases (but an underlying clonal B-cell disorder). Secondary (CAD): accompanied by malignancy, most often lymphoma.
(59)	Primary: no underlying systemic disease. Secondary: AIHA occurs against the background of a systemic disease such as autoimmune diseases (e.g. SLE), autoimmune inflammatory disease (e.g. ulcerative colitis), neoplasms (e.g. lymphoma, leukemia), immunodeficiency, infection or drug usage.
(73)	Primary (CAD): lacking any sign of underlying disease. Secondary (CAD): when associated with a B-cell lymphoproliferative disorder.

AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; CLL, chronic lymphocytic leukemia; LPL, lymphoplasmacytic lymphoma ; MZL, marginal zone lymphoma; SLE, systemic lupus erythematosus.

References

1. Ahmed I, Teruya J, Murray-Krezan C, Krance R. The incidence of autoimmune hemolytic anemia in pediatric hematopoietic stem cell recipients post-first and post-second hematopoietic stem cell transplant. Pediatr Transplant. 2015;19(4):391-8.
2. Naik R. Warm autoimmune hemolytic anemia. Hematology - Oncology Clinics of North America. 2015;29(3):445-53.
3. Barcellini W. Immune Hemolysis: Diagnosis and Treatment Recommendations. Seminars in Hematology. 2015;52(4):304-12.
4. Lecouffe-Desprets M, Neel A, Graveleau J, Leux C, Perrin F, Visomblain B, et al. Venous thromboembolism related to warm autoimmune hemolytic anemia: a case-control study. Autoimmun Rev. 2015;14(11):1023-8.
5. Dierickx D, Kentos A, Delannoy A. The role of rituximab in adults with warm antibody autoimmune hemolytic anemia. Blood. 2015;125(21):3223-9.
6. Quinquenel A, Willekens C, Dupuis J, Royer B, Ysebaert L, De GS, et al. Bendamustine and rituximab combination in the management of chronic lymphocytic leukemia-associated autoimmune hemolytic anemia: a multicentric retrospective study of the French CLL intergroup (GCFLLC/MW and GOELAMS). Am J Hematol. 2015;90(3):204-7.
7. Wang M, Wang W, Abeywardane A, Adikarama M, McLornan D, Raj K, et al. Autoimmune hemolytic anemia after allogeneic hematopoietic stem cell transplantation: analysis of 533 adult patients who underwent transplantation at King's College Hospital. Biol Blood Marrow Transplant. 2015;21(1):60-6.
8. Barcellini W, Fattizzo B, Zaninoni A, Radice T, Nichele I, Di BE, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood. 2014;124(19):2930-6.
9. Visco C, Barcellini W, Maura F, Neri A, Cortelezzi A, Rodeghiero F. Autoimmune cytopenias in chronic lymphocytic leukemia. Am J Hematol. 2014;89(11):1055-62.
10. Lai M, De Stefano V, Landolfi R. Haemoglobin levels in autoimmune haemolytic anaemias at diagnosis: relationship with immunoproteins on red blood cells. Immunol Res. 2014;60(1):127-31.
11. Roumier M, Loustau V, Guillaud C, Languille L, Mahevas M, Khellaf M, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: New insights based on a single-center experience with 60 patients. Am J Hematol. 2014;89(9):E150-E5.
12. Sanz J, Arango M, Carpio N, Montesinos P, Moscardo F, Martin G, et al. Autoimmune cytopenias after umbilical cord blood transplantation in adults with hematological malignancies: a single-center experience. Bone Marrow Transplant. 2014;49(8):1084-8.
13. Visco C, Cortelezzi A, Moretta F, Falisi E, Maura F, Finotto S, et al. Autoimmune cytopenias in chronic lymphocytic leukemia at disease presentation in the modern treatment era: is stage C always stage C? Leuk Lymphoma. 2014;55(6):1261-5.
14. Michel M. Warm autoimmune hemolytic anemia: advances in pathophysiology and treatment. Presse Med. 2014;43(4 Pt 2):e97-e104.
15. Yang Z, Wu B, Zhou Y, Wang W, Chen S, Sun A, et al. Clinical and serological characterization of autoimmune hemolytic anemia after allogeneic hematopoietic stem cell transplantation. Chin Med J (Engl). 2014;127(7):1235-8.
16. Watz E, Remberger M, Ringden O, Lundahl J, Ljungman P, Mattsson J, et al. Analysis of donor and recipient ABO incompatibility and antibody-associated complications after allogeneic stem cell transplantation with reduced-intensity conditioning. Biol Blood Marrow Transplant. 2014;20(2):264-71.
17. Barcellini W, Zaja F, Zaninoni A, Imperiali FG, Di Bona E, Fattizzo B, et al. Sustained response to low-dose rituximab in idiopathic autoimmune hemolytic anemia. Eur J Haematol. 2013;91(6):546-51.

18. Birgens H, Frederiksen H, Hasselbalch HC, Rasmussen IH, Nielsen OJ, Kjeldsen L, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. Br J Haematol. 2013;163(3):393-9.
19. Maung SW, Leahy M, O'Leary HM, Khan I, Cahill MR, Gilligan O, et al. A multi-centre retrospective study of rituximab use in the treatment of relapsed or resistant warm autoimmune haemolytic anaemia. Br J Haematol. 2013;163(1):118-22.
20. Lai M, Leone G, Landolfi R. Autoimmune hemolytic anemia with gel-based immunohematology tests. Am J Clin Pathol. 2013;139(4):457-63.
21. Daikeler T, Labopin M, Ruggeri A, Crotta A, Abinun M, Hussein AA, et al. New autoimmune diseases after cord blood transplantation: a retrospective study of EUROCORD and the Autoimmune Disease Working Party of the European Group for Blood and Marrow Transplantation. Blood. 2013;121(6):1059-64.
22. Kamesaki T, Toyotsuji T, Kajii E. Characterization of direct antiglobulin test-negative autoimmune hemolytic anemia: a study of 154 cases. Am J Hematol. 2013;88(2):93-6.
23. Maura F, Visco C, Falisi E, Reda G, Fabris S, Agnelli L, et al. B-cell receptor configuration and adverse cytogenetics are associated with autoimmune hemolytic anemia in chronic lymphocytic leukemia. Am J Hematol. 2013;88(1):32-6.
24. Patel NY, Chilsen AM, Mathiason MA, Kallies KJ, Bottner WA. Outcomes and complications after splenectomy for hematologic disorders. Am J Surg. 2012;204(6):1014-9.
25. D'Abronzo LS, Barros MM, Bordin JO, Figueiredo MS. Analysis of polymorphisms of TNF-alpha, LT-alpha, IL-10, IL-12 and CTLA-4 in patients with warm autoimmune haemolytic anaemia. Int J Lab Hematol. 2012;34(4):356-61.
26. Barcellini W, Zaja F, Zaninoni A, Imperiali FG, Battista ML, Di BE, et al. Low-dose rituximab in adult patients with idiopathic autoimmune hemolytic anemia: clinical efficacy and biologic studies. Blood. 2012;119(16):3691-7.
27. Michel M. Classification and therapeutic approaches in autoimmune hemolytic anemia: an update. Expert Rev Hematol. 2011;4(6):607-18.
28. Gobert D, Bussel JB, Cunningham-Rundles C, Galicier L, Dechartres A, Berezne A, et al. Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. Br J Haematol. 2011;155(4):498-508.
29. Ahmad E, Elgohary T, Ibrahim H. Naturally occurring regulatory T cells and interleukins 10 and 12 in the pathogenesis of idiopathic warm autoimmune hemolytic anemia. Journal of Investigational Allergology & Clinical Immunology. 2011;21(4):297-304.
30. Aladjidi N, Leverger G, Leblanc T, Picat MQ, Michel G, Bertrand Y, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. Haematologica. 2011;96(5):655-63.
31. Rossignol J, Michallet AS, Oberic L, Picard M, Garon A, Willekens C, et al. Rituximab-cyclophosphamide-dexamethasone combination in the management of autoimmune cytopenias associated with chronic lymphocytic leukemia. Leukemia. 2011;25(3):473-8.
32. Moreno C, Hodgson K, Ferrer G, Elena M, Filella X, Pereira A, et al. Autoimmune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. Blood. 2010;116(23):4771-6.
33. Domiciano DS, Shinjo SK. Autoimmune hemolytic anemia in systemic lupus erythematosus: association with thrombocytopenia. Clinical rheumatology. 2010;29(12):1427-31.
34. Comellas-Kirkerup L, Hernandez-Molina G, Cabral AR. Antiphospholipid-associated thrombocytopenia or autoimmune hemolytic anemia in patients with or without definite primary antiphospholipid syndrome according to the Sapporo revised classification criteria: a 6-year follow-up study. Blood. 2010;116(16):3058-63.
35. Lechner K, Jager U. How I treat autoimmune hemolytic anemias in adults. [Review]. Blood. 2010;116(11):1831-8.

36. Penalver FJ, varez-Larran A, ez-Martin JL, Gallur L, Jarque I, Caballero D, et al. Rituximab is an effective and safe therapeutic alternative in adults with refractory and severe autoimmune hemolytic anemia. Annals of Hematology. 2010;89(11):1073-80.
37. Visco C, Novella E, Peotta E, Paolini R, Giaretta I, Rodeghiero F. Autoimmune hemolytic anemia in patients with chronic lymphocytic leukemia is associated with IgVH status. Haematologica. 2010;95(7):1230-2.
38. Zanotti R, Frattini F, Ghia P, Visco C, Zamo A, Perbellini O, et al. ZAP-70 expression is associated with increased risk of autoimmune cytopenias in CLL patients. American Journal of Hematology. 2010;85(7):494-8.
39. Nakasone H, Kako S, Endo H, Ito A, Sato M, Terasako K, et al. Diabetes mellitus is associated with high early-mortality and poor prognosis in patients with autoimmune hemolytic anemia. Hematology. 2009;14(6):361-5.
40. Xu W, Li JY, Miao KR, Cao X, Liu Q, Fan L, et al. The negative prognostic significance of positive direct antiglobulin test in Chinese patients with chronic lymphocytic leukemia. Leukemia & lymphoma. 2009;50(9):1482-7.
41. Michel M, Chanet V, Dechartres A, Morin AS, Piette JC, Cirasino L, et al. The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases. Blood. 2009;114(15):3167-72.
42. Das SS, Nityanand S, Chaudhary R. Clinical and serological characterization of autoimmune hemolytic anemia in a tertiary care hospital in North India. Annals of Hematology. 2009;88(8):727-32.
43. Kaufman M, Limaye SA, Driscoll N, Johnson C, Caramanica A, Lebowicz Y, et al. A combination of rituximab, cyclophosphamide and dexamethasone effectively treats immune cytopenias of chronic lymphocytic leukemia. Leukemia & lymphoma. 2009;50(6):892-9.
44. Petz LD. Diagnostic complexities in autoimmune hemolytic anemias. Transfusion. 2009;49(2):202-3.
45. Bussone G, Ribeiro E, Dechartres A, Viallard JF, Bonnotte B, Fain O, et al. Efficacy and safety of rituximab in adults' warm antibody autoimmune haemolytic anemia: retrospective analysis of 27 cases. American Journal of Hematology. 2009;84(3):153-7.
46. Kamesaki T, Oyamada T, Omine M, Ozawa K, Kajii E. Cut-off value of red-blood-cell-bound IgG for the diagnosis of Coombs-negative autoimmune hemolytic anemia. Am J Hematol. 2009;84(2):98-101.
47. Seve P, Philippe P, Dufour JF, Broussolle C, Michel M. Autoimmune hemolytic anemia: classification and therapeutic approaches. [Review]. Expert Review of Hematology. 2008;1(2):189-204.
48. Gupta V, Shukla J, Bhatia BD. Autoimmune hemolytic anemia. Indian journal of pediatrics. 2008;75(5):451-4.
49. Seve P, Bourdillon L, Sarrot-Reynauld F, Ruivard M, Jaussaud R, Bouhour D, et al. Autoimmune hemolytic anemia and common variable immunodeficiency: a case-control study of 18 patients. Medicine. 2008;87(3):177-84.
50. Dearden C, Wade R, Else M, Richards S, Milligan D, Hamblin T, et al. The prognostic significance of a positive direct antiglobulin test in chronic lymphocytic leukemia: a beneficial effect of the combination of fludarabine and cyclophosphamide on the incidence of hemolytic anemia. Blood. 2008;111(4):1820-6.
51. Lachenal F, Berger F, Ghesquieres H, Biron P, Hot A, Callet-Bauchu E, et al. Angioimmunoblastic T-cell lymphoma: clinical and laboratory features at diagnosis in 77 patients. Medicine. 2007;86(5):282-92.
52. Elimelakh M, Dayton V, Park KS, Gruessner AC, Sutherland D, Howe RB, et al. Red cell aplasia and autoimmune hemolytic anemia following immunosuppression with alemtuzumab, mycophenolate, and daclizumab in pancreas transplant recipients. Haematologica. 2007;92(8):1029-36.

53. Naithani R, Agrawal N, Mahapatra M, Kumar R, Pati HP, Choudhry VP. Autoimmune hemolytic anemia in children. Pediatric Hematology & Oncology. 2007;24(4):309-15.
54. Sanz J, Arriaga F, Montesinos P, Orti G, Lorenzo I, Cantero S, et al. Autoimmune hemolytic anemia following allogeneic hematopoietic stem cell transplantation in adult patients. Bone Marrow Transplantation. 2007;39(9):555-61.
55. Borthakur G, O'Brien S, Wierda WG, Thomas DA, Cortes JE, Giles FJ, et al. Immune anaemias in patients with chronic lymphocytic leukaemia treated with fludarabine, cyclophosphamide and rituximab--incidence and predictors. British Journal of Haematology. 2007;136(6):800-5.
56. Rottem M, Krause I, Fraser A, Stojanovich L, Rovensky J, Shoenfeld Y. Autoimmune hemolytic anaemia in the antiphospholipid syndrome. Lupus. 2006;15(7):473-7.
57. Poulain S, Dervite I, Leleu X, Fernandes J, Stalnikiewicz L, Moreau AS, et al. Autoimmune hemolytic anemias and IgG antierythrocyte autoantibodies in Waldenstrom's macroglobulinemia: association with FcgammaRIIa polymorphism. Leukemia. 2006;20(6):1179-81.
58. Gomard-Mennesson E, Ruivard M, Koenig M, Woods A, Magy N, Ninet J, et al. Treatment of isolated severe immune hemolytic anaemia associated with systemic lupus erythematosus: 26 cases. Lupus. 2006;15(4):223-31.
59. Oliveira MC, Oliveira BM, Murao M, Vieira ZM, Gresta LT, Viana MB. Clinical course of autoimmune hemolytic anemia: an observational study. Jornal de Pediatria. 2006;82(1):58-62.
60. Naithani R, Agrawal N, Mahapatra M, Pati H, Kumar R, Choudhary VP. Autoimmune hemolytic anemia in India: clinico-hematological spectrum of 79 cases. Hematology. 2006;11(1):73-6.
61. Zent CS, Ding W, Schwager SM, Reinalda MS, Hoyer JD, Jelinek DF, et al. The prognostic significance of cytopenia in chronic lymphocytic leukaemia/small lymphocytic lymphoma. Br J Haematol. 2008;141(5):615-21.
62. Berentsen S, Randen U, Tjonnfjord GE. Cold agglutinin-mediated autoimmune hemolytic anemia. Hematology - Oncology Clinics of North America. 2015;29(3):455-71.
63. Arthold C, Skrabs C, Mitterbauer-Hohendanner G, Thalhammer R, Simonitsch-Klupp I, Panzer S, et al. Cold antibody autoimmune hemolytic anemia and lymphoproliferative disorders: a retrospective study of 20 patients including clinical, hematological, and molecular findings. Wien Klin Wochenschr. 2014;126(11-12):376-82.
64. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood. 2013;122(7):1114-21.
65. Berentsen S, Tjonnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. Blood Rev. 2012;26(3):107-15.
66. Berentsen S. How I manage cold agglutinin disease. [Review]. British Journal of Haematology. 2011;153(3):309-17.
67. Berentsen S, Randen U, Vagan AM, Hjorth-Hansen H, Vik A, Dalgaard J, et al. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. Blood. 2010;116(17):3180-4.
68. Berentsen S. Cold agglutinin-mediated autoimmune hemolytic anemia in Waldenstrom's macroglobulinemia. [Review] [25 refs]. Clinical Lymphoma & Myeloma. 2009;9(1):110-2.
69. Petz LD. Cold antibody autoimmune hemolytic anemias. Blood Reviews. 2008;22(1):1-15.
70. Berentsen S, Ulvestad E, Tjonnfjord GE. B-lymphocytes as targets for therapy in chronic cold agglutinin disease. [Review] [82 refs]. Cardiovascular & Hematological Disorders Drug Targets. 2007;7(3):219-27.
71. Berentsen S, Beiske K, Tjonnfjord GE. Primary chronic cold agglutinin disease: an update on pathogenesis, clinical features and therapy. [Review] [88 refs]. Hematology. 2007;12(5):361-70.
72. Berentsen S, Ulvestad E, Langholm R, Beiske K, Hjorth-Hansen H, Ghanima W, et al. Primary chronic cold agglutinin disease: a population based clinical study of 86 patients. Haematologica. 2006;91(4):460-6.

73. Schollkopf C, Kjeldsen L, Bjerrum OW, Mourits-Andersen HT, Nielsen JL, Christensen BE, et al. Rituximab in chronic cold agglutinin disease: a prospective study of 20 patients. Leukemia & lymphoma. 2006;47(2):253-60.
74. Mayer B, Yurek S, Kiesewetter H, Salama A. Mixed-type autoimmune hemolytic anemia: differential diagnosis and a critical review of reported cases. [Review] [36 refs]. Transfusion. 2008;48(10):2229-34.
75. Li BJ, Yuan X, Jiang YJ, Ning L, Shu XW, Liu KL. Retrospective analysis of 30 severe autoimmune hemolytic anemia patients treated by whole blood exchange transfusion. Transfusion. 2015;55(9):2231-7.
76. Mahevas M, Michel M, Vingert B, Moroch J, Boutboul D, Audia S, et al. Emergence of long-lived autoreactive plasma cells in the spleen of primary warm auto-immune hemolytic anemia patients treated with rituximab. Journal of Autoimmunity. 2015;62:22-30.
77. Reynaud Q, Durieu I, Dutertre M, Ledochowski S, Durupt S, Michallet AS, et al. Efficacy and safety of rituximab in auto-immune hemolytic anemia: A meta-analysis of 21 studies. Autoimmun Rev. 2015;14(4):304-13.
78. Faraci M, Zecca M, Pillon M, Rovelli A, Menconi MC, Ripaldi M, et al. Autoimmune hematological diseases after allogeneic hematopoietic stem cell transplantation in children: an Italian multicenter experience. Biol Blood Marrow Transplant. 2014;20(2):272-8.
79. Dussadee K, Taka O, Thedsawad A, Wanachiwanawin W. Incidence and risk factors of relapses in idiopathic autoimmune hemolytic anemia. J Med Assoc Thai. 2010;93 Suppl 1:S165-S70.
80. Dierickx D, Verhoef G, Van HA, Mineur P, Roest A, Triffet A, et al. Rituximab in auto-immune haemolytic anaemia and immune thrombocytopenic purpura: a Belgian retrospective multicentric study. Journal of Internal Medicine. 2009;266(5):484-91.
81. Bader-Meunier B, Aladjidi N, Bellmann F, Monpoux F, Nelken B, Robert A, et al. Rituximab therapy for childhood Evans syndrome. Haematologica. 2007;92(12):1691-4.
82. Xing LM, Shao ZH, Fu R, Liu H, Shi J, Bai J, et al. Subtypes of B lymphocytes in patients with autoimmune hemocytopenia. Chin Med Sci J. 2007;22(2):128-31.
83. D'Arena G, Califano C, Annunziata M, Tartarone A, Capalbo S, Villani O, et al. Rituximab for warm-type idiopathic autoimmune hemolytic anemia: a retrospective study of 11 adult patients. European Journal of Haematology. 2007;79(1):53-8.
84. D'Arena G, Laurenti L, Capalbo S, D'Arco AM, De FR, Marcacci G, et al. Rituximab therapy for chronic lymphocytic leukemia-associated autoimmune hemolytic anemia. American Journal of Hematology. 2006;81(8):598-602.