REVIEW ARTICLE

AUTOIMMUNE HAEMOLYTIC ANAEMIA: A SYSTEMATIC REVIEW.

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Abstract

Autoimmune haemolytic anaemia (AIHA) is a rare and heterogeneous haematological disorder. The diagnostic criteria of AIHA have been debatable and not clearly defined. We performed a systematic review to evaluate the various definitions of AIHA. The spectrum of clinical features is well established and does not need to be reviewed. However, the treatment as well as the outcome of AIHA has many controversies and will be reviewed in this article. The general terminology, 'autoimmune haemolytic anaemia' supplemented by the Medical search term (MeSH) for selected articles were gathered from PUBMED and COCHCRANE databases. Of the 2812 articles from these databases and 1837 articles from CLINICAL KEY from the years 2010 to 2020, in English full texts only, 57 articles fulfilled the inclusion and exclusion criteria. The definition of haemolytic anaemia was almost homogenous in 48 (84.2%) articles with minor variations in the description. AIHA is characterized by increased destruction of red blood cells (RBC) due to an immune-mediated process. Specific definitions of AIHA was not consistently described. A positive direct anti-globulin test (DAT) with laboratory evidence of haemolysis were the key diagnostic criteria described in 45 of the articles (75%). Clinical features of AIHA were almost similar across all articles viz. anaemic symptoms and complication of haemolysis. Corticosteroid remains the mainstay of treatment followed by anti-CD20 monoclonal antibody (rituximab), immunosuppressant, other biologics and intravenous immunoglobulin (IV Ig) have been used in general and specific AIHA. Treatment response criteria were provided in all the articles but different parameters were monitored and there was no uniformity. Complete remission (CR) was achieved in 25% - 88% of AIHA patients while 4% - 69% had a partial response (PR) to corticosteroid therapy in 11 studies. CR and PR was achieved in 4%-88% and 75%-86% patients respectively in 8 studies using rituximab. In patients who underwent splenectomy, only 4%-6% had CR in 3 studies while 1 study reported 75% PR.

This review revealed both the homogeneity across the studies and areas of inconsistency in definitions and data interpretation.

Keywords: Autoimmune haemolytic anaemia, definition, clinical features, treatment and outcome.

Introduction

Immune haemolytic anaemia (IHA) is the clinical condition in which IgG or IgM antibodies bind to RBC surface antigens and initiate RBC destruction via the complement system and the reticuloendothelial system. This type of anaemia is classified into autoimmune, alloimmune or drug induced based on the antigenic stimulus responsible for the immune response[1].

Autoimmune haemolytic anaemia (AIHA) is a rare haematological disorder with an estimated incidence in adults of 0.8-3 per 10^5 /year, a prevalence of 17:100,000 and a mortality rate of 11%[2]. It is an acquired heterogeneous autoimmune disorder characterized by the destruction of erythrocytes by antibodies against antigen on the red cell[3]. Various definitions and diagnostic criteria were used in previous studies. AIHA is categorized into primary and secondary [4,5,6] and classified into warm (wAIHA) and cold (cAIHA) type of antibody, the latter being either the rare, paroxysmal cold hemoglobinuria (PCH) or cold agglutinin syndrome subtypes[7]. AIHA patients usually present with anemic symptoms which may develop gradually, with physiological compensation, but sometimes it may lead to a life threatening hemolytic crisis[8]. A positive DAT may present with or without clinical evidence of hemolysis [9,10,11]. However, a false-negative DAT has been found in small number of AIHA cases mostly *in vivo*.

We performed a systematic review to assess and evaluate the various definitions for AIHA described in previous studies including diagnostic criteria for AIHA, clinical features and treatment response criteria.

Methodology

Full text published articles with English translation from the year 2010 to 2020 were searched in April 2020 from PUBMED, COCHRANE and ELSEVIER. The heading 'autoimmune haemolytic anaemia' was used and supplemented by advanced medical term search (MeSH) to narrow the search by subheading and other keywords such as 'classification', 'diagnosis', 'epidemiology' and 'therapy'. Other keywords were also used to expand our search result such as 'chronic lymphocytic leukaemia' and 'systemic lupus erythematosus'.

All the searched articles were evaluated, and those which did not meet with the review scope, were eliminated. Only full-text articles were selected for this review. Non-English text and case reports with less than ten subjects were discarded (Figure 1). In this systematic review, clinical trials, clinical and narrative studies together with practical guidelines were included. Title, abstract and full text review was done independently by the three authors and any discrepancies or issues during the selection process were discussed. Cross-checking of articles was also done to avoid duplication. All selected articles went through a checklist before final analysis was made. Each selected article was evaluated, emphasizing any one of the information or scope to be highlighted in this review (Table 1). Data was then collected from these articles and analysed using Excel 2013 version. The definition for each criteria, clinical features, treatment options and response were extracted and summarized as a narrative synthesis into a table in the appendix. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Checklist (PRISMA) guidelines was used for this review[12].

Results

Of a total of 4649 articles that were retrieved, only 185 could be accessed by abstract title screening and full-text articles. After performing the title-abstract, full-text and duplicate screening, 85 articles were included in the eligibility assessment of which only 57 articles were taken for this review and analysis (Figure 1).

General definition of AIHA

AIHA was defined in 48 articles (84.2%) with different terminology. Taxonomy for specific type i.e. subtype of AIHA (warm, cold and Paroxysmal Cold Haemoglobinuria (PCH) was described in 5 articles[13-17]. Nine (15.8%) articles with unclear definitions were excluded. In general, the definitions of AIHA were homogenous across all the articles. The basic fundamental of these definitions was that of 'autoimmune-mediated' which was interpreted by the respective authors by a brief description of the immunopathogenesis of AIHA (Table 2 and 3).

Diagnostic Criteria of AIHA

Forty-three (75.4%) studies used general diagnostic criteria for AIHA and it was repeatedly used in 5 (8.8%) of the studies. Laboratory evidence of haemolysis with positive DAT were the key diagnostic criteria in 26 (45.6%) articles [6, 13, 18-19, 21-40] and with additional of 'exclusion of any other diseases' in another 5 (8.8%) studies[14, 41-44] and 4 (7.0%) studies include sign and symptoms of anaemia in the criteria[16, 45-47]. Seven studies used only positive DAT as its diagnostic criteria for AIHA, and 1 article used the same principles with or without positive DAT[14, 17, 48-52]. Laboratory haemolysis was defined as low Hb $\leq$ 11g/dL, polychromasia, with or without nucleated RBCs, presence of microspherocytes, reticulocytosis, indirect hyperbilirubinemia and elevated serum lactate dehydrogenase (LDH)[41] (Table 4).

Clinical features of AIHA

Clinical features of AIHA were commonly attributed to anaemia and this was included as part of data analysis in all the articles selected. Fatigability was reported in 14 studies followed by dyspnoea on exertion in 12 studies. The less common symptoms were bleeding, coughing, weight loss, myalgia, dizziness, fever, weakness, tachycardia, abdominal pain, anorexia and back pain. Jaundice was the most common sign followed by pallor. Other signs include dark urine, splenomegaly and acrocyanosis. The least common sign is Raynaud phenomenon (Table 5).

Treatment Options (Table 6)

Treatment options were varied with corticosteroid being the most commonly used medication as the first-line treatment. Rituximab was widely used in all types of AIHA except in PCH, as monotherapy or in combination with other immunosuppressants as first or second-line treatment. Splenectomy was commonly performed in wAIHA as second or third-line treatment modality for refractory or relapsed cases.

Definitions of Treatment Outcomes

The recommended criteria for treatment outcomes from the consensus group[51] was applied in all the articles or studies i.e. complete response (CR), partial response (PR) and steroid responsiveness. CR was defined as 'Hb > or $\geq$ 12.0 g/dL' in 19 research papers (n=13)[19,21,25,26,37-39,42,44,48,58,59] and 7 studies with 'Hb > 12.0 g/dL'. Six of the latter studies also had other additional criteria. In another 4 of 6 studies with 'Hb $\geq$ 12.0 g/dL' was also had additional criteria to it. Another definition used was normalization of haemoglobin (n=3) and 2 out of 3 articles also included 'without immunosuppressive therapy and no haemolysis'[16,57,60]. One study had a unique definition which is 'normal haemoglobin with no additional therapy lasting for at least six months after splenectomy or an increase of 2 g/dL with reduction of haemolytic markers and 'no need of transfusion'[40] and two other studies were specific for cAIHA[14, 24].

Different versions of PR was defined in 17 research articles. Ten articles used the definition of 'Hb > or $\geq$ 10.0 g/dL' with 8 studies with 'Hb $\geq$ 10.0 g/dL' [19,37,39] and 2 studies with 'Hb > 10.0 g/dL'[25,48]. Both versions had different additional

criteria as well. Another study used a range of Hb between 10.0 g/dL - 12.0 g/dL as the description with additional criteria [59]. One study used 'Hb < 12.0 g/dL' (n=1) as the definition of treatment response with 4 additional criteria. The term 'increase of Hb by 2.0 g/dL' was used in 3 studies with different set of additional criteria[21,57,44]. This unique description was specifically used for cAIHA. (Table 7)

CR and PR to specific therapy i.e. steroids, rituximab, splenectomy and immunosuppressants were evaluated in all the articles. Eleven studies achieved a high percentage of CR with corticosteroid followed by rituximab (n=7), immunosuppressants (n=4) and splenectomy (n=3) (Table 8).

Relapse Definitions.

Most of the articles used different definition for relapse. Many had 'Hb < 10 g/dL' as their main component in defining relapses that occured in patients with AIHA[13,42,48] or 'decrease in Hb level[42,48,61]. (Table 9).

Discussion

There was inconsistency in definition of the various taxonomy of AIHA, diagnostic criteria and treatment outcome. The description of the clinical features of AIHA was similar across all articles. Despite advancement in treatment over past decade, the old and conventional options remain the mainstay treatment in AIHA. The variations in the definition of treatment outcome of AIHA may have resulted in different choices of second line therapies. The disparity in defining AIHA had been highlighted by Hill (2019)[62], however, there was no final consensus.

In this review, the general definition of AIHA with its diagnostic criteria was elaborately described across the 43 articles. All authors agreed that AIHA is an autoimmune disease that affects the red blood cell which ultimately causes anaemia. The description for subtypes were slightly different from general AIHA. Addition of 'best reactive at the temperature of 37^0C' is important to distinguish wAIHA from other types. Though paroxysmal cold haemoglobinuria is under the category of cAIHA, this subtype has its own set of criteria to differentiate it from the other cold-type AIHA.

The laboratory definition stated in the analysis was a collection of all laboratory findings related to haemolysis to narrow down the data variability. All the studies except one by Shanbhag (2015) needed to have a positive DAT with additional criteria[15]. Previous literature had emphasized the importance of exclusion of other diseases that cause anaemia as one of the criteria [4,41-43]. Other articles described signs and symptoms as one of the essential criteria in diagnosing AIHA.

Jaundice, splenomegaly and dark urine attributed to haemolysis in AIHA were well described in most of the articles. Raynaud phenomenon had been observed due to cold exposure in patients with cold-type AIHA[24, 40]. As for wAIHA, the features were similar to that of anaemic symptoms in general AIHA.

In general, treatment options were similar, although a few did not specify the treatment according to the type of AIHA. Corticosteroid was the first-line treatment in wAIHA. Folic acid and danazol was introduced as a first-line therapy by Chaudhary[18, 46]. Symptomatic therapy i.e. 'avoiding cold exposure' was recommended in cold-type AIHA in most of the studies. The used of rituximab and cyclophosphamide, however, were still debatable. Newer treatment modalities for AIHA had been advocated using targeted therapy following the discovery of immunopathogenesis factor in AIHA[63].

There was overlap between the second-line and third-line therapies for refractory or relapse cases. Splenectomy and rituximab were commonly given, followed by immunosuppressant, which was also used as the third-line treatment for wAIHA. Hill (2016) suggested that corticosteroid can be used for PCH if the illness persisted for an extended period[43].

The treatment outcome based on the CR/PR was more variable. However, overall, CR values for corticosteroid treatment was mostly above 50% and lower than 50% for other options.

Limitations of the study

There were several limitations in this study. Firstly, our inability to access a wide range of full-text articles due to subscription issues, hence we could not include them in this review. Secondly, we included only articles in English and some of the AIHA associated disease text were excluded to prevent confusion in analysing the results. Thirdly, we limited our search to only the past ten years, therefore, some other significant studies prior that could not be included. Fourthly, most of the results do not include primary and secondary AIHA due to our exclusion criteria.

Conclusion

Despite inconsistency in the definitions of AIHA, the clinical features and treatment options are homogenous across all studies. However, standardization and consensus in defining this rare conditions is crucial and warrant further study.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

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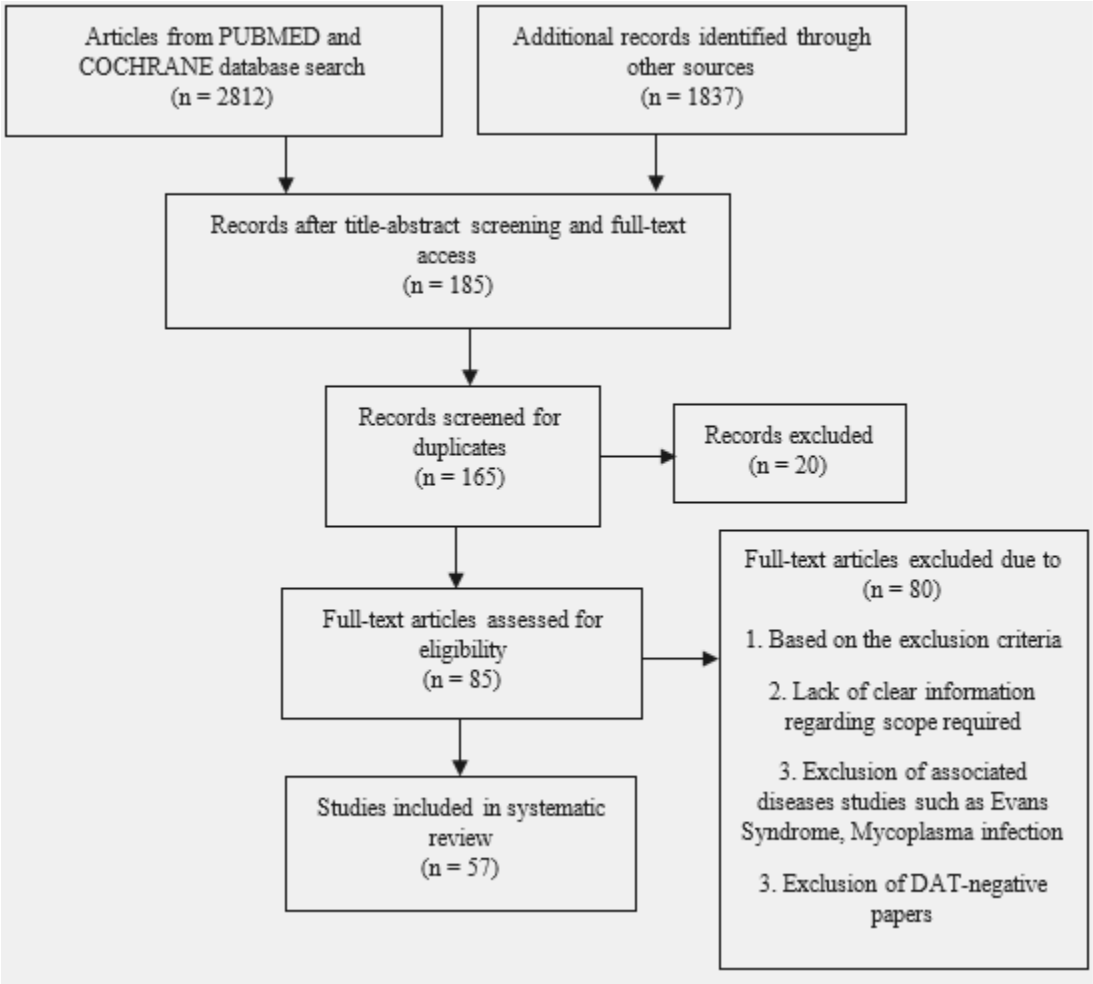

Figure 1. Study selection workflow

Table 1. Scope of interest

Scope/Criteria
Definition of AIHA
Clinical Features of AIHA (includes wAIHA, cAIHA, PCH)
Diagnosis Criteria of AIHA
Treatment Option of AIHA
Definition of treatment outcome of AIHA

Table 2. General definition

General Definition of AIHA	Number of Studies (n)
A rare autoimmune disease characterized by an increased in destruction of RBC, mediated by autoantibodies against autologous red blood cells	21
additional: with or without complement activation	4
additional: decreased of life-span of RBCs	1
Autoantibodies produced against red cell antigens causing haemolytic anaemia	8
additional: results in premature destruction with inadequate compensation	1
additional: heterogeneous condition	1
Relatively uncommon disorder, with an estimated incidence of 1–3 per 100000 per year	5
additional: prevalence of 17 : 100 000	3
additional: caused antibodies directed to RBC	1
Decompensated acquired haemolysis caused by host's immune system acting against its own red cell antigens	5
additional —extra or intra vascular haemolysis	1
Unique Definition	4
Uncommon clinical disorder and required advanced, efficient immune-haematological and transfusion support	
Most common extra corpuscular haemolytic anaemia	
Auto-immune disorder leading to destruction of own red blood cells and platelet respectively	

Table 3. Specific definition for subtype AIHA

Subtypes of AIHA	Number of Studies (n)
wAIHA	
- Characterized by the autoantibodies directing against patient's own antigens on red blood cells with the best reactive temperature at $37^{O}C$ and accounts for about 50% to 70% of all cases of autoimmune haemolytic anaemia	3
cAIHA	1
- Clonal lympho-proliferative disorder and a distinct clinic-pathologic entity.	
Paroxysmal Cold Hemoglobinuria (PCH)	1
- Complement medicated intravascular haemolytic anaemia associated with a biphasic antibody against the P antigen on red cells.	

Table 4. List of diagnostic criteria

Diagnostic Criteria	Number of Studies (n)
Positive DAT *	7
Presence of haemolysis[Ł] + Positive DAT	26
Presence of haemolysis + Positive DAT + Exclusion of any other diseases	5
Sign & Symptoms of Anaemia + Presence of haemolysis + Positive DAT	4
Sign & Symptoms of Anaemia + Presence of haemolysis $\pm$ Positive DAT	1

*DAT, Direct antiglobulin test. ŁLaboratory Haemolysis: low Hb $\leq$ 11g/dL, polychromasia, with or without nucleated RBCs, presence of microspherocytes, reticulolysis, indirect hyperbilirubinemia and elevated LDH

Table 5. Clinical features of AIHA

Clinical features		Number of studies
Symptoms	Fatigue	14
	Weakness	4
	Dizziness	7
	Dyspnoea on exertion	12
	Fever	7
	Bleeding	1
	Coughing	1
	Abdominal pain	3
	Weight loss	1
	Tachycardia	4
	Myalgia	1
	Anorexia	2
	Back pain	2
Signs	Pallor	15
	Jaundice	18
	Splenomegaly	8
	Raynaud phenomenon	2
	Dark urine	11
	Acrocyanosis	4

Table 6. List of treatment options and number of studies (n)

	General AIHA	n	wAIHA	n	cAIHA	n	PCH	n
1st line	Corticosteroid	20	Corticosteroid	16	Avoid cold exposure	6	Corticosteroid	2
	Corticosteroid + IVIG	2	Corticosteroid + Rituximab	1	Rituximab	6		
	Rituximab	3	Folic acid	1	Rituximab + bendamustine	1		
	Corticosteroid + Rituximab	4	Danazol	1	CP	1		
	Low dose Rituximab	1	IVIG	1				
			Splenectomy	17				
2nd line	Rituximab	10	Rituximab	13	Rituximab + fludarabine	2		
	Immunosuppressant*	6	Immunosuppressant	12				
	IVIG	1	IVIG	5	Rituximab + bendamustine	1		
			Corticosteroid + Rituximab	1	Bortezomib	1		
3rd line	immunosuppressant	5	Immunosuppressant	5				
	Corticosteroid + CP	1	Splenectomy	5				
			Danazol	4				

*Immunosuppressant = CP, Cyclophosphamide; Cyclosporine A; Mycophenolate Mofetil; Azathioprine; 6-mercaptopurine. Abbreviations: wAIHA, warm autoimmune haemolytic anemia; cAIHA, cold autoimmune haemolytic anemia; IVIG, Intravenous Immunoglobulin; PCH, Paroxysmal Cold Haemoglobinuria.

Table 7. Treatment outcomes

Definitions	Number of Studies (n)
Complete Response (CR)	19
Hb > or ≥ 12.0 g/dL	13
➢ >12.0 g/dL	7
with no evidence of ongoing haemolysis	3
no blood transfusion recently, no haemolysis features	2
no features of ongoing haemolysis, without any ongoing treatment for wAIHA on two different occasions 4-week apart, no recent transfusion	1
➢ ≥12.0 g/dL	6
with no evidence of ongoing haemolysis	1
no blood transfusion recently, no haemolysis features	3
➢ Normalisation of a normal haemoglobin	4
without immunosuppressive therapy and no haemolysis.	2
no additional therapy lasting for at least 6 months after splenectomy or an increase of 2 g/dL with reduction of haemolytic markers and no need of transfusion	1
Unique Definition:	
➢ cAIHA	
Absence of anaemia, No sign of haemolysis, Disappearance of clinical symptoms, No monoclonal serum protein, No sign of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry	1
Partial Response (PR)	17
Hb > or ≥ 10.0 g/dL	10
➢ >10.0 g/dL	
or at least 2.0 g/dL increase in Hb, no transfusion requirement	2
➢ ≥10.0 g/dL	8
persistent haemolysis, or with ≥2.0 g/dL increment in basal Hb at diagnosis	4
or an increase of at least 2.0 g/dL from the baseline value	3
or at least 2.0 g/dL increase in Hb, no transfusion requirement	1
Hb 10.0-12.0 g/dL	
or at least 2.0 g/dL increase in Hb, no transfusion requirement	1
Hb <12.0 g/dL	
Hb rise was at least 2.0 g/dL, platelet counts within 50-100 109/l, biological parameter improvements, transfusion needs	1
Increase in Hb ＞2.0 g/dL	3
no or reduced transfusion requirement, improvement of clinical and laboratory signs of haemolysis	1
transfusion independency in a previously transfused patient	1
Unique Definition:	
➢ cAIHA	
stable increase in haemoglobin levels by > 2.0 g/dL or to the normal range, reduction of serum IgM levels by > 50% of the initial level or to the normal range, improvement of clinical symptoms, transfusion independence, No sign of clonal lymphoproliferation as assessed by bone marrow histology, immunohistochemistry and flow cytometry	2
Steroid Responsiveness (Hb)	
> 10 g/dL	1
≥ 10 g/dL	1

Table 8. Treatment response

	Author [Ref]	CR (%)	PR (%)	Total patients numbers in the study
Corticosteroid				
	Kamesaki T *et al.* [41]	62	-	154
	Chen C *et al.*[19]	87.6	-	129
	Wang M *et al.* [20]	-	32	533
	Baek SW *et al.*[21]	25	68.8	32
	Prabhu R *et al.* [48]	62	28	29
	Birgens H *et al.* [16]	28	67	65
	Barcellini *et al.*[42]	32	50	308
	Jaime-Pérez *et al.* [39]	70	30	64
	Mauro FR *et al.*[36]	72.1	4.4	68
	Sudulagunta *et al.*[37]	48.3	27.6	37
	Alonso HC *et al.* [38]	50.6	33.7	89
Rituximab				
	Chen C *et al.*[19]	3.9	-	129
	Michel M *et al.*[25]	-	75	27
	Birgens H *et al.*[16]	14	77	65
	Barcellini *et al.*[36]	16	86	
	Dierickx D *et al.*[60]	32	79	53
	Barcellini *et al.*[42].	19	80	308
	Barcellini *et al.*[58]	31	-	23
	Barcellini *et al.*[52].	88	-	378
Splenectomy				
	Chen C *et al.*[19]	3.9	-	129
	Rattarittamrong E *et al.*[13]	6.1	-	101
	Barcellini *et al.*[42]	0	75	308
Immunosuppressant				
	Rattarittamrong E *et al.*[13]	21.2	-	101
	Chen C *et al.*[19]	10.8	-	129
	Barcellini *et al.*[42]	30	70	308
	Barcellini *et al.*[52].	53	46	378

Abbreviation: CR- complete response; PR- partial response

Table 9. Relapse definition

Definition Relapse	n
Re-emergence of disease	1
Hb <10.0 g/dL during maintenance treatment of prednisolone less than 15mg/day and due to AIHA not from other causes.	1
CR or PR at the end of the hospitalization	1
Decrease in Hb to ＜10 g/dL	1
Hb <10 g/dL or at least 2.0 g/dL decrease in Hb with or without increase serum LDH	1
Decrease in Hb while tapering steroid treatment or following discontinuation of corticosteroids.	1
Decrease in the Hb level or the appearance of haemolytic markers after the patient achieved a CR or PR	1

References

1. Gehrs BC, Friedberg RC. Autoimmune Hemolytic Anemia. Am. J. Hematol. 2002;69:258–271.
2. Petz L, Garratty G: Immune Hemolytic Anemias, 2nd ed. Philadelphia, Churchill Livingstone, 2004
3. Böttiger LE, Westerholm B. Acquired haemolytic anaemia. I. Incidence and aetiology. Acta Med Scand. 1973;193(3):223-226.
4. Crosby WH, Rappaport H. Autoimmune hemolytic anemia. I. Analysis of hematologic observations with particular reference to their prognostic value; a survey of 57 cases. Blood. 1957;12(1):42-55.
5. Rathore, B. (2012). Ferri's Clinical Advisor. Philadelphia: Saunders
6. Bass GF, Tuscano ET, Tuscano JM. Diagnosis and classification of autoimmune hemolytic anemia. Autoimmun Rev. 2014;13(4-5):560-564. doi:10.1016/j.autrev.2013.11.010

7. King KE, Ness PM. Treatment of autoimmune hemolytic anemia. Semin Hematol. 2005;42(3):131-136. doi:10.1053/j.seminhematol.2005.04.003
8. Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. Haematologica. 2014;99(10):1547-1554. doi:10.3324/haematol.2014.114561
9. Zeerleder S. Autoimmune haemolytic anaemia - a practical guide to cope with a diagnostic and therapeutic challenge. Neth J Med. 2011;69(4):177-184.
10. Meulenbroek EM, Wouters D, Zeerleder SS. Lyse or not to lyse: Clinical significance of red blood cell autoantibodies. Blood Rev. 2015;29(6):369-376. doi:10.1016/j.blre.2015.05.001
11. Wouters D, Zeerleder S. Complement inhibitors to treat IgM-mediated autoimmune hemolysis. Haematologica. 2015;100(11):1388-1395. doi:10.3324/haematol.2015.128538
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
13. Rattarittamrong E, Eiamprapai P, Tantiworawit A, Rattanathammethee T, Hantrakool S, Chai-Adisaksopha C, et al. Clinical characteristics and long-term outcomes of warm-type autoimmune hemolytic anemia. Hematology. 2016;21(6):368–74. doi:10.1080/10245332.2016.1138621
14. Berentsen S, Randen U, Tjønnfjord GE. Cold agglutinin-mediated autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2015;29(3):455-471. doi:10.1016/j.hoc.2015.01.002
15. Shanbhag S, Spivak J. Paroxysmal cold hemoglobinuria. Hematol Oncol Clin North Am. 2015;29(3):473-478. doi:10.1016/j.hoc.2015.01.004
16. 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):393-399. doi:10.1111/bjh.12541
17. Liu B, Gu W. Immunotherapy treatments of warm autoimmune hemolytic anemia. Clin Dev Immunol. 2013;2013:561852. doi:10.1155/2013/561852
18. Chaudhary RK, Das SS. Autoimmune hemolytic anemia: From lab to bedside. Asian J Transfus Sci. 2014;8(1):5-12. doi:10.4103/0973-6247.126681.

19. Chen C, Wang L, Han B, Qin L, Ying B. Autoimmune hemolytic anemia in hospitalized patients: 450 patients and their red blood cell transfusions. Medicine (Baltimore). 2020;99(2):e18739. doi:10.1097/MD.0000000000018739
20. 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):60-66. doi:10.1016/j.bbmt.2014.09.009
21. Baek SW, Lee MW, Ryu HW, Lee KS, Song IC, Lee HJ et al. Clinical features and outcomes of autoimmune hemolytic anemia: a retrospective analysis of 32 cases. Korean J Hematol. 2011;46(2):111-117. doi:10.5045/kjh.2011.46.2.111
22. Park SH. Diagnosis and treatment of autoimmune hemolytic anemia: classic approach and recent advances. Blood Res. 2016;51(2):69-71. doi:10.5045/br.2016.51.2.69
23. Zulfiqar AA, Mahdi R, Mourot-Cottet R, Pennaforte JL, Novella JL, Andrès E. Autoimmune hemolytic anemia-a short review of the literature, with a focus on elderly patients. J Hematol Thrombo Dis. 2015;3:228.
24. Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. Blood Rev. 2012;26(3):107-115. doi:10.1016/j.blre.2012.01.002
25. Michel M, Terriou L, Roudot-Thoraval F, Hamidou M, Ebbo M, Le Guenno G, et al. A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm auto-immune hemolytic anemia in adults (the RAIHA study). Am J Hematol. 2017;92(1):23-27. doi:10.1002/ajh.24570
26. 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-E155. doi:10.1002/ajh.23767
27. Yaralı N, Bilir ÖA, Erdem AY, Çulha V, Kara A, Özbek N. Clinical features and treatment of primary autoimmune hemolytic anemia in childhood. Transfus Apher Sci. 2018;57(5):665-668. doi:10.1016/j.transci.2018.07.014
28. Packman CH. Hemolytic anemia due to warm autoantibodies. Blood Rev. 2008;22(1):17-31. doi:10.1016/j.blre.2007.08.001

29. 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):655-663. doi:10.3324/haematol.2010.036053
30. Kim TO, Despotovic JM. Primary and Secondary Immune Cytopenias: Evaluation and Treatment Approach in Children. Hematol Oncol Clin North Am. 2019;33(3):489-506. doi:10.1016/j.hoc.2019.01.005
31. Rogers KA, Woyach JA. Secondary autoimmune cytopenias in chronic lymphocytic leukemia. Semin Oncol. 2016;43(2):300-310. doi:10.1053/j.seminoncol.2016.02.011
32. Robertson JJ, Brem E, Koyfman A. The Acute Hemolytic Anemias: The Importance of Emergency Diagnosis and Management. J Emerg Med. 2017;53(2):202-211. doi:10.1016/j.jemermed.2017.02.018
33. Naik R. Warm autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2015;29(3):445-453. doi:10.1016/j.hoc.2015.01.001
34. Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. Pediatr Clin North Am. 2013;60(6):1489-1511. doi:10.1016/j.pcl.2013.08.009
35. Hill A, Hill QA. Autoimmune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2018;2018(1):382-389. doi:10.1182/asheducation-2018.1.382
36. Mauro FR, Coluzzi S, Paoloni F, Trastulli F, Armiento D, Ferretti A, et al. Clinical characteristics and outcome of patients with autoimmune hemolytic anemia uniformly defined as primary by a diagnostic work-up. Am J Hematol. 2016;91(7):E319-20.
37. Sudulagunta SR, Kumbhat M, Sodalagunta MB, Nataraju AS, Bangalore SK, Thejaswi KC et al. Warm Autoimmune Hemolytic Anemia: Clinical Profile and Management. J Hematol. 2017;6(1):12-20. doi:10.14740/jh303w
38. Alonso HC, Manuel AV, Amir CG, Sergio RR, Allan P, Xavier LK, et al. Warm autoimmune hemolytic anemia: experience from a single referral center in Mexico City. Blood Res. 2017;52(1):44-49. doi:10.5045/br.2017.52.1.44
39. Jaime-Pérez JC, Aguilar-Calderón P, Salazar-Cavazos L, Gómez-De León A, Gómez-Almaguer D. Treatment of autoimmune hemolytic anemia: real world data from a reference center in Mexico. Blood Res. 2019;54(2):131-136. doi:10.5045/br.2019.54.2.131

40. Giudice V, Rosamilio R, Ferrara I, Seneca E, Serio B, Selleri C. Efficacy and safety of splenectomy in adult autoimmune hemolytic anemia. Open Med (Wars). 2016;11(1):374-380. Published 2016 Nov 19. doi:10.1515/med-2016-0068
41. 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):93-96. doi:10.1002/ajh.23356
42. Barcellini W, Fattizzo B, Zaninoni A, Radice T, Nichele I, Di Bona E, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood. 2014;124(19):2930-2936. doi:10.1182/blood-2014-06-583021
43. Hill QA, Stamps R, Massey E, Grainger JD, Provan D, Hill A. The diagnosis and management of primary autoimmune haemolytic anaemia. Br J Haematol. 2017;176(3):395-411. doi:10.1111/bjh.14478
44. 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):473-478. doi:10.1038/leu.2010.278
45. Ghosh K, Ghosh K, Agarwal R, Shah K, Mishra K. Anti tissue transglutaminase antibody in idiopathic autoimmune haemolytic anemia. Transfus Apher Sci. 2019;58(5):693-696. doi:10.1016/j.transci.2019.06.034
46. Barros MM, Blajchman MA, Bordin JO. Warm autoimmune hemolytic anemia: recent progress in understanding the immunobiology and the treatment. Transfus Med Rev. 2010;24(3):195-210. doi:10.1016/j.tmrv.2010.03.002
47. Petz LD. Cold antibody autoimmune hemolytic anemias. Blood Rev. 2008;22(1):1-15. doi:10.1016/j.blre.2007.08.002
48. Prabhu R, Bhaskaran R, Shenoy V, G R, Sidharthan N. Clinical characteristics and treatment outcomes of primary autoimmune hemolytic anemia: a single center study from South India. Blood Res. 2016;51(2):88-94. doi:10.5045/br.2016.51.2.88
49. Barcellini W. Immune Hemolysis: Diagnosis and Treatment Recommendations. Seminars in Hematology. 2015 Oct 1;52(4):304-312. https://doi.org/10.1053/j.seminhematol.2015.05.001

50. Packman CH. The Clinical Pictures of Autoimmune Hemolytic Anemia. Transfus Med Hemother. 2015;42(5):317-324. doi:10.1159/000440656
51. Jäger U, Barcellini W, Broome CM, Gertz MA, Hill A, Hill QA, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020;41:100648. doi:10.1016/j.blre.2019.100648
52. Barcellini W, Fattizzo B, Cortelezzi A. Autoimmune hemolytic anemia, autoimmune neutropenia and aplastic anemia in the elderly. Eur J Intern Med. 2018;58:77-83. doi:10.1016/j.ejim.2018.05.034
53. Kalfa TA. Warm antibody autoimmune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):690-697. doi:10.1182/asheducation-2016.1.690
54. Nazel Khosroshahi B, Jafari M, Vazini H, Ahmadi A, Shams K, Kholoujini M. Cold Autoimmune Hemolytic Anemia due to High-grade non Hodgkin's B cell Lymphoma with Weak Response to Rituximab and Chemotherapy Regimens. Int J Hematol Oncol Stem Cell Res. 2015;9(3):157-160.
55. Salama A, Hartnack D, Lindemann HW, Lange HJ, Rummel M, Loew A. The effect of erythropoiesis-stimulating agents in patients with therapy-refractory autoimmune hemolytic anemia. Transfus Med Hemother. 2014;41(6):462-468. doi:10.1159/000366244
56. Salama A: Treatment Options for Primary Autoimmune Hemolytic Anemia: A Short Comprehensive Review. Transfus Med Hemother 2015;42:294-301. doi: 10.1159/000438731
57. Barcellini W, Zanella A. Rituximab therapy for autoimmune haematological diseases. Eur J Intern Med. 2011;22(3):220–9. doi.org/10.1016/j.ejim.2010.12.016
58. Barcellini W, Zaja F, Zaninoni A, Imperiali FG, Battista ML, Di Bona E, et al. Low-dose rituximab in adult patients with idiopathic autoimmune hemolytic anemia: clinical efficacy and biologic studies. Blood. 2012;119(16):3691-3697. doi:10.1182/blood-2011-06-363556
59. Thabet AF, Faisal M. Pulse cyclophosphamide therapy in refractory warm autoimmune hemolytic anemia: a new perspective. Indian J Hematol Blood Transfus. 2014;30(4):313-318. doi:10.1007/s12288-013-0290-z

60. Dierickx D, Verhoef G, Van Hoof A, Mineur P, Roest A, Triffet A, et al. Rituximab in auto-immune haemolytic anaemia and immune thrombocytopenic purpura: a Belgian retrospective multicentric study. J Intern Med. 2009;266(5):484-491. doi:10.1111/j.1365-2796.2009.02126.x
61. Sarper N, Çakı Kılıç S, Zengin E, Gelen SA. Management of autoimmune hemolytic anemia in children and adolescents: A single center experience. Çocuk ve ergenlerde otoimmün hemolitik anemi tedavisi: Tek merkez deneyimi. Turk J Haematol. 2011;28(3):198-205. doi:10.5152/tjh.2011.54
62. Hill QA, Hill A, Berentsen S. Defining autoimmune hemolytic anemia: a systematic review of the terminology used for diagnosis and treatment. Blood Adv. 2019;3(12):1897-1906. doi:10.1182/bloodadvances.2019000036
63. Barcellini W, Fattizzo B. The Changing Landscape of Autoimmune Hemolytic Anemia. Front. Immunol, 03 June 2020 | https://doi.org/10.3389/fimmu.2020.00946.