

Diagnostic and therapeutic challenges of primary autoimmune haemolytic anaemia in children

José Manuel Vagace,¹ Roberto Bajo,¹ Guillermo Gervasini²

¹Service of Paediatric Haematology, Materno Infantil Hospital, Badajoz, Spain
²Division of Pharmacology, Department of Medical & Surgical Therapeutics, Medical School, University of Extremadura, Badajoz, Spain

Correspondence to

Dr Jose M Vagace, Service of Paediatric Haematology, Materno Infantil Hospital, C/La Violeta 4, Badajoz 06010, Spain; jvagacev@aehh.org

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ABSTRACT

Autoimmune haemolytic anaemias (AIHAs) are extracorporeal haemolytic anaemias produced by antierythrocyte autoantibodies which cause a shortened red blood cell life span. There are several reasons why the diagnosis and treatment of AIHAs in children represent a bigger challenge than in adult patients, including the presence of particular AIHA types, the uncertainty of serological tests and the limited clinical experience. All these facts have added up to a poor understanding and management of some topics in childhood AIHA. We discuss some of these questions, for example, the occurrence of AIHA with negative direct antiglobulin (Coombs) test, the correct diagnosis and actual incidence of paroxysmal cold haemoglobinuria, the most appropriate second-line therapy of AIHA in childhood or the management of transfusion procedures in these patients. This review takes a practical point of view, providing with some ground rules on how to identify and deal with these paediatric patients.

INTRODUCTION

Autoimmune haemolytic anaemias (AIHAs) are anaemias produced by anti red blood cell (RBC) antibodies, in which the red cells are lysed either by the mononuclear phagocytic system or by the complement system. This disease is rare in children with an estimated incidence of 0.2 per one million of individuals younger than 20 years. Even so, it still is the most frequent source of extracorporeal haemolytic anaemia in the paediatric patients.¹

AIHAs are classified depending on the thermal range of the antibody and the presence or not of an associated disease² (box 1). *Warm AIHAs* are the most common form of primary AIHA, in children and adults, with reported frequencies around 60%³; it involves the preferential binding of autoantibodies (usually IgG) to the RBCs at 37°C, causing extravascular haemolysis by splenic macrophages. The second type of primary AIHA, *paroxysmal cold haemoglobinuria* (PCH), is seen almost exclusively in children, often subsequent to a viral infection. PCH is characterised by the presence of a 'biphasic haemolysin', an IgG autoantibody that binds preferentially at cold temperatures, fixing the complement efficiently and causing severe intravascular haemolysis. The third form, *cold agglutinin disease*, on the other hand, is much more uncommon in children (approximately 10% of AIHA³), and usually appears after infection by *Mycoplasma Pneumoniae* or *Epstein-Barr virus*. The disease is produced by an IgM that agglutinates RBCs at cold temperatures, fixing the complement with variable efficacy thus leading to intravascular or extravascular haemolysis predominantly in the liver.^{4 5} In this

review we will discuss therapeutic and diagnostic challenges of primary AIHA in paediatric patients.

Secondary AIHAs occur in more than half of the patients. Postinfectious forms in particular account for roughly 10%; however, it is important to emphasise that a primary AIHA can often follow a viral-like syndrome and precede for years the occurrence of another immunological disease, in most cases Evans' syndrome.¹

CLINICAL FINDINGS

There are two different types of AIHAs in the paediatric patient that display different clinical and serological behaviour, namely an acute, transient form that is more common in infants, and a chronic, refractory type, typical of the older child. The first are usually primary cold AIHAs and the latter are either warm or secondary AIHAs.⁶

In young children, the disease is often preceded by an unspecific fever. In all cases, the child shows pallor and conjunctival jaundice on examination. Tachycardia and systolic flow murmur are common and are related to the intensity of anaemia. Splenomegaly is typical of warm AIHA, while haemoglobinuria or acrocyanosis is suggestive of cold AIHA. Abdominal pain, nausea or vomits may suggest hepatitis, although hepatosplenomegaly is

Box 1 Classification of autoimmune haemolytic anaemias (AIHAs)

PRIMARY AIHA*

- ▶ Warm-reactive AIHA
- ▶ Paroxysmal cold haemoglobinuria
- ▶ Cold agglutinin disease, usually IgM

SECONDARY AIHA†

- ▶ Evans' syndrome
- ▶ Autoimmune and inflammatory diseases (eg, systemic lupus erythematosus)
- ▶ Immunodeficiency (eg, autoimmune lymphoproliferative syndrome)
- ▶ Infection (eg, *Mycoplasma pneumoniae* or Epstein-Barr virus)‡
- ▶ Malignancy (eg, haematological-leukaemia or lymphoma or solid tumours)§
- ▶ Drug-induced§

*Often follows a viral-like syndrome, but in the absence of another systemic illness.

†It occurs in the context of another clinical diagnosis, with haemolytic anaemia being only one manifestation of a systemic illness

‡Mainly cold agglutinin disease

§More frequent in adult patients

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only observed in 25% of the patients.⁷ The presence of massive hepatosplenomegaly and adenopathies should raise suspicions of an associated infection, malignancy or *autoimmune lymphoproliferative syndrome*.^{5 8}

Mortality is usually due to infection, haemolysis or the underlying disease and has decreased over the years from roughly 30% to less than 5%.^{1 9}

LABORATORY FINDINGS

The anaemia is usually severe and presents with reticulocytosis, although in infants the existence of reticulocytopenia is also common.¹⁰ Corpuscular indexes are normal, with the exception of mean corpuscular haemoglobin concentration, which is generally elevated due to the presence of spherocytes. A mean corpuscular haemoglobin concentration value over 40 may suggest the presence of a cold agglutinin that could be affecting the results of the automated counter.¹¹

Leucocytes and platelets are within or above the normal range, while the presence of neutropenia or thrombopenia is indicative of *Evans' syndrome*. Peripheral blood smears frequently show polychromasia and spherocytosis. Autoagglutination is suggestive of *cold agglutinin disease*, while haemophagocytosis of RBCs by granulocytes is characteristic of PCH¹² (figure 1A).

Biochemistry can confirm the existence of haemolysis if there is indirect hyperbilirubinaemia, high lactate dehydrogenase (LDH) values and low haptoglobin. In addition, haemoglobinuria is manifested by the discrepancy between the presence of haematuria in the test strip and the absence of RBCs in the urinary sediment. Box 2 summarises the main studies to be performed in children with suspected AIHA.

DIAGNOSTIC TECHNIQUES

The direct antiglobulin test

Direct antiglobulin test (DAT) is the technique used to detect the complement and immunoglobulins that are either bound to the RBCs (direct test) or are free in the serum (indirect test). The antiglobulin reagent contains anti-IgG and anti-C3d and is able to detect most cases of AIHA. If the test is positive, a further monospecific test must be performed to identify the type of immunoglobulin and the putative presence of the complement system.¹³ In most positive cases for IgG, the antibody can be detected in the eluate, which is a differential factor from drug-related AIHA.¹⁴ If DAT is positive with anti-C3 but negative with anti-IgG, then cold agglutinin and Donath-Landsteiner tests ought to be carried out. In any case, the latter should

Box 2 Recommended workup in childhood autoimmune haemolytic anaemia (AIHA).

- Complete blood count (including reticulocytes)
 - Blood smear.
 - Biochemistry: urea, creatine, aspartate aminotransferase, alanine aminotransferase, bilirubin, haptoglobin and LDH.
 - Immunoglobulins dosage (IgG, IgA and IgM)
 - ANA and anti-DNA if ANA is positive.
 - Immunophenotyping of peripheral lymphocytes (should include the quantification of 'double-negative T cells: CD3CD4-CD8-TCR α/β +' if an ALS is suspected)
 - Lupus anticoagulant and antiphospholipid antibodies (if antiphospholipid syndrome is suspected or systematically before splenectomy)
 - Bone marrow aspiration (if pancytopenia, lymphadenopathy or visceromegaly)
 - Chest X-ray and abdominal sonography (if a secondary AIHA is suspected).
 - Serological test for Epstein-Barr virus and/or *Mycoplasma pneumoniae* (if cold agglutinin disease has been diagnosed)
- ANA, antinuclear antibody; ALS, autoimmune lymphoproliferative syndrome

always be included in the first battery of diagnostic tests when the anaemia is accompanied with haemoglobinuria (even if the DAT is negative)¹⁰ (see figure 2).

The indirect antiglobulin test is positive in approximately 70% of AIHAs. In most cases a panagglutinin free in serum is detected.¹⁵ Table 1 summarises the serological characteristics of idiopathic AIHA.

The Donath-Landsteiner test

This test, which was first described by Donath and Landsteiner a hundred years ago, is still the only specific diagnostic tool available for the diagnosis of PCH.⁷ The technique consists of incubating the patient's blood at 4°C for 1 h to allow the binding of the antibody, followed by a second incubation at 37°C for 30 min to activate the complement and produce the haemolysis (figure 1B). A correct diagnosis of PCH calls for performing the test as early as possible. In order to avoid autoadsorption it is advisable to draw the blood with a preheated syringe and keep

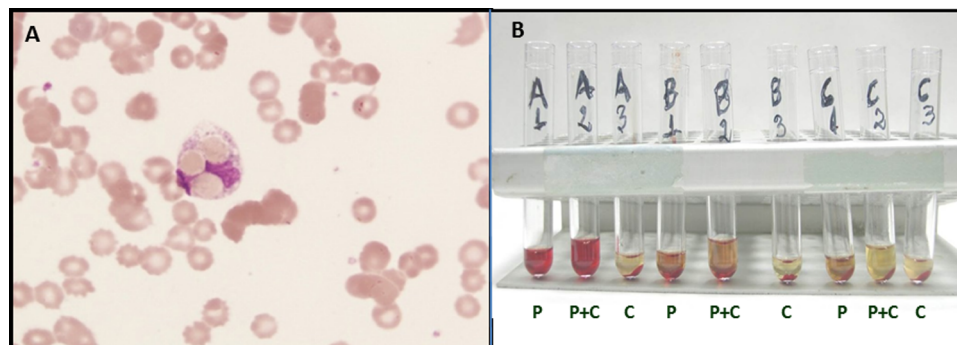
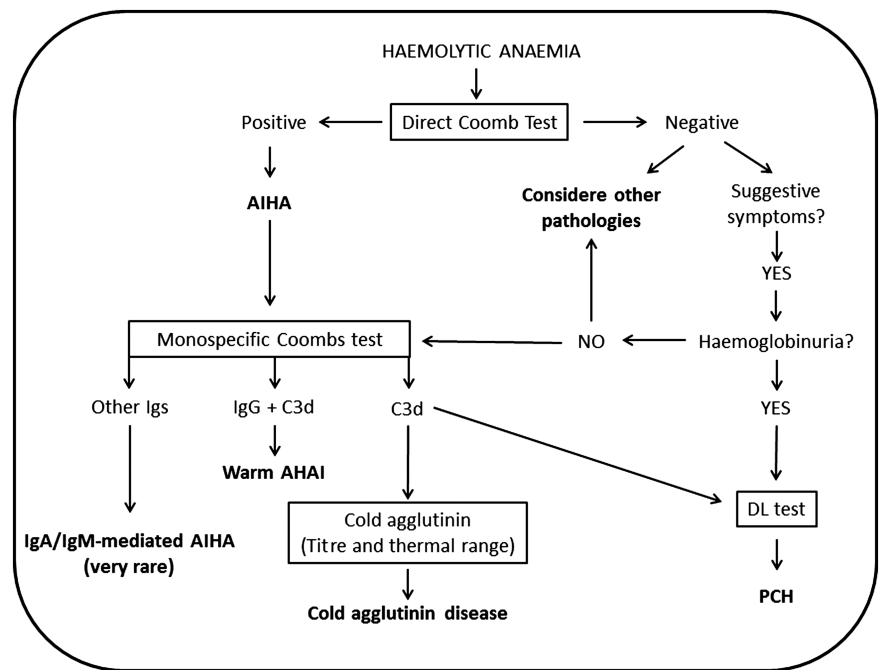


Figure 1 (A) Neutrophil with erythrophagocytosis in an 18-year-old female patient with paroxysmal cold haemoglobinuria (adapted from Chandrashekar V, Soni M [47]). (B) Positive Donath-Landsteiner test in an 18-month-old infant: A, tubes incubated 30 min at 4°C and 30 min at 37°C; B, tubes incubated 1 h at 4°C; C, tubes incubated 1 h at 37°C; P, patient's serum; C, control serum. Note that haemolysis is maximum in the A tubes and mild in the B tubes containing patient's serum.

Figure 2 Diagnostic algorithm for autoimmune haemolytic anaemias (AIHAs). DL, Donath-Landsteiner; PCH, paroxysmal cold haemoglobinuria.



the sample warm throughout the whole process until the serum is separated.

It is usually advisable to use the two-step indirect test with enzyme-treated RBCs. Only if the test is negative under these conditions should we consider alternative diagnosis.¹⁶

Under certain circumstances it is obvious that the transfusion cannot be delayed until the test results are obtained, but in any case, a blood sample should be drawn prior to transfusion to do the test when possible.

Controversies in the diagnosis of childhood AIHA

The actual incidence of PCH is a matter of debate in the diagnosis of AIHA. It is noteworthy that while some series of paediatric patients with AIHA report an incidence of 0–5%,^{1 6 15} other authors consider the disease as very common. Thus, Gottsche *et al*³ identified PCH in 32% of AIHA cases. Most strikingly, Sokol *et al*¹⁷ report that PCH is the most common AIHA in the child, with an incidence of 65% in children younger than 4 years. Some reasons that may explain these notable discrepancies are summarised in table 2.

In our centre, out of the six AIHAs diagnosed in the last 8 years, four children had warm AIHA and two infants had PCH (33%). These two patients presented severe, autolimited anaemia with haemoglobinuria. One of these two infants was

immediately diagnosed, while the other one had a DAT negative test and the Donath-Landsteiner test was not performed until 1 month later, when it was negative. This case was initially mistaken for a *glucose-6-phosphate dehydrogenase* deficiency and is an example that illustrates why the incidence of PCH is often underestimated. The diagnostic nomogram proposed in figure 2 may help eradicate these mistakes.

Another controversial issue concerns the incidence of DAT-negative AIHA in children, which is hard to estimate because usually only patients with positive DAT are included in the studies.¹ In adults, the reported incidence ranges from 3% to 11%.¹⁸ In contrast, Vaglio *et al* analysed the serological features of 100 cases of childhood AIHA and showed a high proportion (21%) of negative DAT results, particularly among children with cold AIHA. In these cases, cold antibodies have low affinity for RBCs and may elute in vitro, thus producing the negative result.¹⁵ Exceptionally, DAT-negative AIHA can also be produced by IgA¹⁸ or natural killer cells (NK) cells.¹⁹

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is depicted in figure 3. The type of haemolysis (intravascular or extravascular) and the general condition of the child play a pivotal role.

Table 1 Serological features and antibody specificities of primary autoimmune haemolytic anaemias (AIHAs)

Pathology	IgS isotypes	Specificity of antibodies	Monospecific DAT	Interference with automated counter	Type of haemolysis	Diagnostic test
Warm reactive AIHA	IgG	Anti-Rh	IgG±C3d	NO	Extravascular	Panagglutinin in the elute
Paroxysmal cold haemoglobinuria	IgG	Anti-P	C3d	NO	Intravascular	Donath-Landsteiner test
Cold agglutinin disease	IgM	Anti-I/i*	C3d	YES	Both	Pathological Cold agglutinin

*IgM antibodies are often directed against membrane polysaccharides (mostly anti-I) and are associated with infection by *Mycoplasma pneumoniae*. If the infection is produced by the Epstein-Barr or varicella viruses, the specificity is generally anti-i or anti-PR, respectively.⁴⁴
DAT, direct antiglobulin test.

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Table 2 Difficulties in the diagnosis of paroxysmal cold haemoglobinuria

Fact	Reference
The disease is not clinically suspected	3
The DL test is not systematically included in routine diagnostic tests for AIHA	1
Many patients have a negative DAT	15
The DL test may become negative after a few days	45
Even if it is carried out early, the test may be negative if not done correctly	46

AIHA, autoimmune haemolytic anaemia; DL, Donath-Landsteiner; DAT, direct antiglobulin test.

TREATMENT GUIDELINES

Because of the paucity of randomised and controlled studies with paediatric patients of AIHA, the existing therapeutic recommendations are not based on a large body of evidence. The treatment mainly depends on the severity of the anaemia and the type of antibody involved. In addition, the associated disease, if present, will have to be dealt with adequately.

Cold AIHA

The first, and sometimes only necessary measure, is to keep the patient warm. If a transfusion is required, it may be advisable, but not indispensable, to place the blood bag in a blood warmer. Good hydration and diuresis are also important to avoid the toxic effects of haemoglobinuria on the renal tubules function. In addition, a short therapy with corticosteroids may be useful in some cases, although the efficacy of corticosteroid therapy has not been systematically investigated, and opinions promoted in textbooks and review articles differ widely.²⁰

Warm AIHA

Corticosteroids (1–2 mg/kg/day prednisone) are the first-line treatment, with approximately 80% of patients responsive to therapy.²¹ Once the anaemia has been corrected, the treatment

is slowly tapered during several months to avoid relapse, which even so can be frequent, particularly in the case of AIHA secondary to immunodeficiency or autoimmune diseases. It should be noted that even after complete recovery DAT can be positive for years or even indefinitely. In AIHA only 30% of patients respond well to intravenous immunoglobulins and therefore this should not be a first-choice therapy in this disease.²²

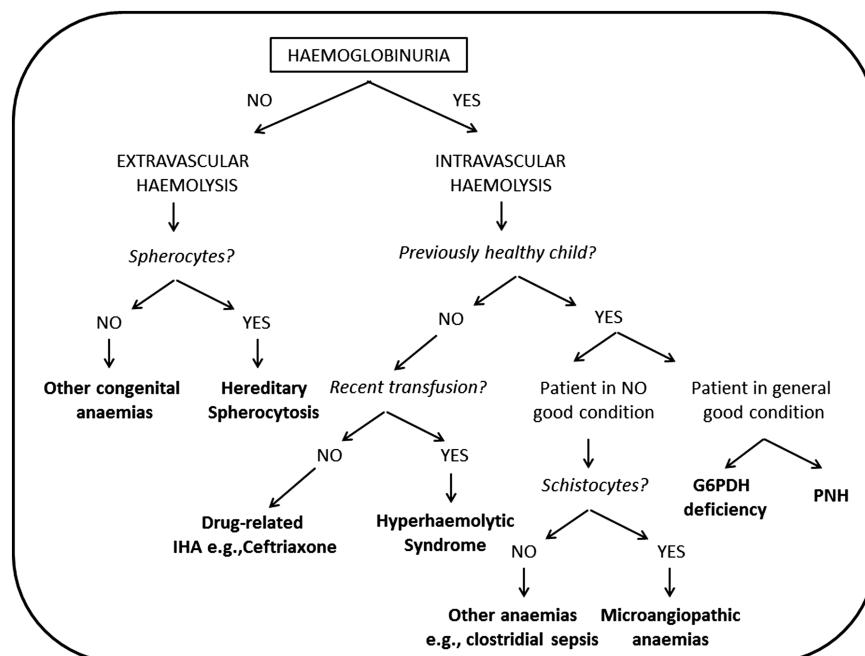
Chronic or refractory AIHA

If corticoids are not effective or if the doses required to maintain a good response are too high, second-line therapies must be implemented. Rituximab and splenectomy are the two choices available in these circumstances. There are no studies explicitly aimed to compare these two options,²³ but in children less than 5–7 years of age, delaying splenectomy as long as possible is strongly recommended. Rituximab should be the first option in these instances.²

The splenectomy was the first really efficient therapy for AIHA and it still is the reference treatment, with a large body of evidence available in the literature.²⁴ It is only indicated for warm AIHA, in which most of the RBCs are phagocytosed in the spleen. Isotopic studies do not accurately predict the patient's response to the procedure and therefore are not required. The percentage of remission varies between 60% and 90% of cases.^{25 26} Over the years, the mortality associated with this technique has decreased. In the largest patient series reported to date, with 255 laparoscopic procedures, mortality was only 0.8%.²³ The main risk of splenectomy in children, especially infants, is the infection by encapsulated micro-organisms. Before the procedure the child must receive vaccines against *Pneumococcus*, *Meningococcus* and *Haemophilus Influenzae*. In addition, one or two doses of prophylactic oral penicillin should be administered daily for a period of at least 5 years. Finally, it is very important that parents are given written information on how to proceed in case of fever or any other circumstances involving risk of infection.²⁴

Rituximab is a monoclonal antibody with specificity anti CD20 which is usually used at doses of 375 mg/m²/week for 1 month and must be administered with premedication to avoid

Figure 3 Differential diagnosis of autoimmune haemolytic anaemias (AIHAs) in children. G6PDH, glucose-6-phosphate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria. The recent occurrence of the anaemia and a positive direct antiglobulin test (DAT) differentiate warm AIHA from these processes indicated below. A DAT, Donath-Landsteiner test and/or the cold agglutinin titre differentiate cold AIHA from the processes described below (see also nomogram in figure 2). In children suffering from thalassemia or sickle cell disease (SCD), a severe intravascular haemolysis should make us consider a post-transfusion hyperhaemolytic syndrome⁴⁸ or a drug-related AIHA, such as that caused by ceftriaxone.⁴⁹ In these cases DAT may be positive.



allergic reactions.²⁷ Stasi *et al*²⁸ have reported a clinical response in 85% of adults and children treated with this agent. The DAT is negative in most of good responders and the success rate does not seem to be dependent on the number of previous treatments (including splenectomy), the type of antibody or the AIHA form.²⁹ In a reported series of paediatric patients, Rituximab was well tolerated and provided durable responses in 75–100% cases.³⁰ Furthermore, children with a poor response can improve after dose escalation.³¹

Rituximab-associated infections and viral reactivation are reasonable concerns due to the depletion of the B cell lymphocytes. However, serious infections are generally rare, occurring in roughly 1–4% of patients, particularly in those with lymphoma.³² In any case, all available reports in paediatric patients conclude that more studies are needed to define the role of this drug in childhood AIHA.

Other treatments that have been used in refractory AIHA are immunosuppressants (azathioprine, ciclosporin and analogue drugs), cytotoxic agents (vincristine or cyclophosphamide) or androgens (danazol).³³ Overall, the rate of good responders with these drugs ranges between 40% and 60%. Azathioprine, being less toxic, may be used in primary cases to discontinue the corticosteroids and delay the splenectomy.² However, in children, most of the experience with these therapies has been retrieved from secondary AIHA.³⁴

Catastrophic haemolysis

Catastrophic haemolysis has been described in cold/mixed AIHA and courses with an extremely severe intravascular haemolysis that may be fatal within hours. Some experimental treatments such as plasmapheresis, which only eliminate IgM antibodies or complement inhibitors such as eculizumab, have been proved useful.³⁵ Interestingly, the experience with haematopoietic stem cell transplantation in refractory immune cytopenias has been recently summarised by Pession *et al*,³⁶ who concluded that the transplant may be effective in approximately half of the patients, albeit with a high mortality rate (26%).

When and how to transfuse in AIHA?

If the anaemia is severe and presents with reticulocytopenia, or if it is causing cardiovascular compromise (usually haemoglobin <5 g/dL), the transfusion must not be delayed and the blood bank staff must be promptly warned so an adequate planning of pretransfusion studies can be performed. In all cases, a complete RBC phenotype should be performed in order to anticipate putative alloimmunisations. The autoantibody may cause phenotyping problems and incompatible crossmatch with all the units available at the blood bank; in these circumstances, searching for the 'least incompatible' is generally not useful.³⁷ Instead, there are two different ways to proceed. First, if the patient has never received blood before (as is usually the case), time is of essence and the patient should be transfused even with positive cross-tests. In this situation, alloantibodies are very rare and acute transfusion reactions are uncommon, because the transfused RBCs and the patient's own RBCs have the same survival in the presence of the autoantibody.³⁸ On the contrary, if the child has previously undergone transfusion, the coexistence of alloantibodies and autoantibodies is common.³⁹ In these patients, the alloantibody is very often shadowed by the panagglutinin, and therefore may produce a delayed haemolytic reaction that would worsen the anaemia.^{40–42} There are certain guidelines that should be followed in this case, namely (1) call any other hospitals involved to collect previous serological studies, (2) perform a quick autoabsorption technique that does

not require enzymatic treatment of RBCs⁴³ and (3) in the case of cold AIHA, all pretransfusion tests should be carried out at 37°C using anti-IgG Coombs reagents. If blood typing is still unclear, O-type RBCs should be used.³⁷

CONCLUSION

This review is focused on the practical aspects of primary AIHA in childhood. There are several reasons that explain why the diagnosis and treatment of AIHA in children represent such a great challenge. For instance, the presence of specific AIHA types, the uncertainty of serological tests or the limited clinical experience. This disease is the immune cytopenia in which immunohaematological tests play a more relevant role for diagnosis and treatment. Indeed, paediatric AIHA is the paradigm of how haematological tests in the laboratory and clinical practice must go hand in hand for the patient's benefit.

While the pathways leading to haemolysis are well known, the mechanisms underlying the breakdown of immunological self-tolerance are still an enigma. A greater knowledge of autoimmune phenomena and the development of new immunosuppressive drugs, such as monoclonal antibodies, will most likely replace traditional treatments such as splenectomy, and hopefully improve the survival of children with AIHA in the future.

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José Manuel Vagace, Roberto Bajo and Guillermo Gervasini

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