Management of autoimmune haemolytic anaemia in low-to-middle income countries: current challenges and the way forward

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Summary

Autoimmune haemolytic anaemia (AIHA) is a common term for several disorders that differ from one another in terms of aetiology, pathogenesis, clinical features, and treatment. Therapy is becoming increasingly differentiated and evidence-based, and several new established and investigational therapeutic approaches have appeared during recent years. While this development has resulted in therapeutic improvements, it also carries increased medical and financial requirements for optimal diagnosis, subgrouping, and individualization of therapy, including the use of more advanced laboratory tests and expensive drugs. In this brief Viewpoint review, we first summarize the diagnostic workup of AIHA subgroups and the respective therapies that are currently considered optimal. We then compare these principles with real-world data from India, the world's largest nation by population and a typical low-to-middle income country. We identify major deficiencies and limitations in general and laboratory resources, real-life diagnostic procedures, and therapeutic practices. Incomplete diagnostic workup, overuse of corticosteroids, lack of access to more specific treatments, and poor follow-up of patients are the rule more than exceptions. Although it may not seem realistic to resolve all challenges, we try to outline some ways towards an improved management of patients with AIHA.

Keywords: Autoimmune haemolytic anaemia; Diagnosis; Low-to-middle income countries; Real-world data; Treatment

Introduction

Autoimmune haemolytic anaemia (AIHA) is anaemia due to haemolysis, mediated by autoimmune mechanisms and usually with involvement of autoantibodies against red blood cell (RBC) surface antigens.[1] AIHA is a collective term for several diseases that differ in terms of aetiology, pathogenesis, and clinical features, and should be treated differently (Table 1).[2–4] During the last decades, several new established or investigational therapies have appeared, resulting in improvements of therapy but also raising medical and financial challenges on how to treat individual patients.

Given the complexity of the disease group and the need for exact diagnosis to select the appropriate treatment, an optimal diagnostic workup will require considerable clinical, laboratory, and economic resources. While the first-line treatment in most cases of warm-antibody AIHA (wAIHA), prednisolone or prednisone,[1,5] is cheap, newer therapies are often not available or affordable in low-to-middle income countries (LMIC), depending on national economy, healthcare services, and social security system. Sutimlimab, an efficient and well-tolerated drug for treatment of cold agglutinin disease (CAD),[6] costs up to $315,000 for the first year of treatment in the USA.[7] The gap in real-world diagnostic workup and treatment of AIHA between rich and LMIC has recently been addressed based on Indian experience.[8]

This review will outline the workup required for an exact diagnosis of AIHA subtype and the optimal therapies for these disorders. For details, we refer to more comprehensive reviews.[1,4,9,10] Subsequently, we will address real-life diagnostic procedure and treatment in India and discuss the gaps, unmet needs, and directions for progress in a global perspective.

Types of AIHA and recommended management

Warm-antibody AIHA

Epidemiology and pathogenesis

The incidence of AIHA was found to be 18 per million per year in Denmark,[11] wAIHA accounting for 65–75%.[2,3] Warm-autoantibodies have highest affinity for the antigen at 37 °C and are polyclonal, mostly of the IgG class, but IgM warm antibodies or IgA can also be involved.[3,12–14] A major haemolytic pathway is antibody-dependent destruction of RBCs by macrophages

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Warm-antibody autoimmune hemolytic anemia (wAIHA)	Cold-antibody autoimmune hemolytic anemia (cAIHA)	Atypical autoimmune hemolytic anemia
Primary wAIHA	Cold agglutinin disease (CAD)	Mixed warm and cold AIHA
Secondary wAIHA	Secondary cold agglutinin syndrome (CAS)	DAT-negative AIHA
Drug-induced AIHA	Paroxysmal cold haemoglobinuria (PCH)	

Table 1: **Types of autoimmune hemolytic anemia.**

(extravascular haemolysis), mainly in the spleen.[15,16] The classical complement pathway is involved in half of the cases,[3,17] resulting in phagocytosis of complement protein fragment 3b (C3b)-opsonized cells (extravascular haemolysis).

Half of wAIHA cases are secondary, i.e., associated with other lymphoproliferative or immunologic diseases (Table 2). Evans' syndrome is defined as the concomitant or sequential occurrence of two autoimmune cytopenias (usually wAIHA with immune thrombocytopenia).[18–20] WAIHA is a chronic relapsing rather than a chronic disease. Patients have an increased risk of thrombosis.[21]

Diagnosis

Fig. 1 shows a diagnostic algorithm.[1,4,9,22] Autoimmune pathogenesis, indicated by the presence of immunoglobulin and/or complement on the RBC surface, is detected by the polyspecific ("simple") DAT (Fig. 2).[23,24] In the monospecific ("extended") DAT, mandatory for subclassification, immunoglobulin class (es) or complement protein(s) on the RBC surface are identified by using specific antibody reagents, usually against IgG, IgM, IgA, C3c, and C3d.[1,3,9,25] In wAIHA, the DAT is typically positive for IgG or IgG + C.[1–3] A positive test for C3d and, sometimes, C3c indicates complement activation, which occurs in all patients with cold-antibody AIHA (cAIHA), about 50% of wAIHA cases, and all cases of mixed AIHA.[3,17]

Treatment

Prednisolone (or prednisone) at high initial doses remains first-line therapy in wAIHA and is effective in

Lymphoproliferative disorders	Chronic lymphocytic leukemia B-cell non-Hodgkin lymphoma T-cell lymphoma (T-LGL leukemia, angioimmunoblastic T-cell lymphoma) Hodgkin lymphoma Castleman disease
Other hematologic disorders	Myelodysplastic syndrome Myelofibrosis Associated immune cytopenia, usually ITP (Evans'syndrome)
Solid tumors	Ovarian dermoid cyst Ovarian carcinoma Thymoma
Non-hematologic autoimmune and inflammatory diseases	Systemic lupus erythematosus Other rheumatic diseases (Rheumatoid arthritis, Sjögren syndrome) Antiphospholipid syndrome Autoimmune hepatitis Ulcerative colitis Sarcoidosis Eosinophilic fasciitis
Primary immunodeficiencies	Common variable immunodeficiency Autoimmune lymphoproliferative syndrome
Infections	Viruses (EBV, hepatitis, CMV, HIV, SARS-CoV-2) Bacteria (Tuberculosis, brucellosis) Protozoa (Babesiosis)
Transplantations	Allogenic bone marrow transplantation Liver transplantation Small bowel transplantation

Some ultra-rare conditions have not been listed. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; ITP, immune thrombocytopenia; LGL, large granular lymphocyte; SARS-CoV, severe adult respiratory syndrome corona virus; SLE, systemic lupus erythematosus.

Table 2: **Secondary warm AIHA: underlying or associated conditions.**

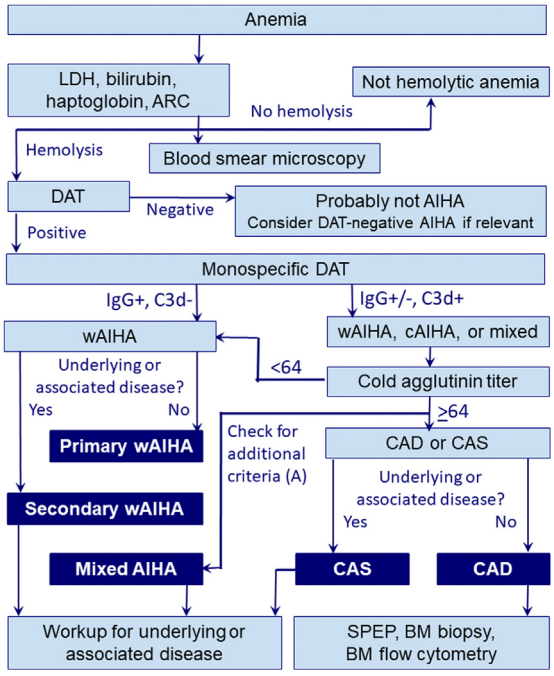

Fig. 1: **Diagnostic algorithm for autoimmune hemolytic anemia.** A, Additional criteria for mixed AIHA (DAT strongly positive for both IgG and C3d, cold agglutinin titer ≥64, warm-reactive IgG demonstrated by indirect antiglobulin test at 37 °C); BM, bone marrow; C3d, complement protein fragment C3d; CAD, cold agglutinin disease; cAIHA, cold-antibody mediated AIHA; CAS, cold agglutinin syndrome; DAT, direct antiglobulin test; IgG, immunoglobulin G; wAIHA, warm-antibody mediated AIHA. Figure first published by Berentsen et al. in Front Immunol,[22] reused under a Creative Commons CC-BY license 4.0 (https://creativecommons.org/licenses/by/4.0/). © S. Berentsen et al., 2023.

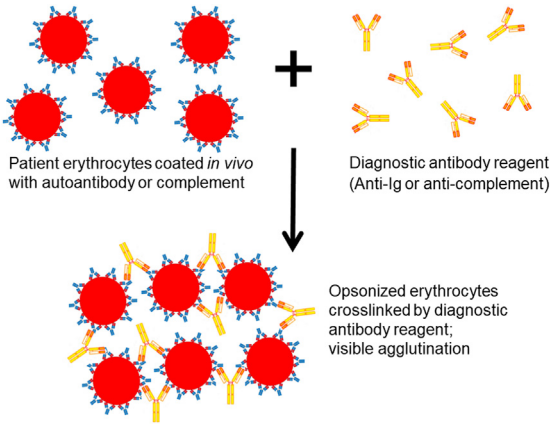

***Fig. 2:* The direct antiglobulin test (DAT)**. In AIHA, erythrocytes are coated *in vivo* with autoreactive immunoglobulin and/or complement. Adding a diagnostic antibody to human serum (polyspecific DAT) or diagnostic antibodies specific for individual immunoglobulin classes or complement proteins (monospecific DAT) will result in visible agglutination.

80% of the patients.[1,5] After 2–3 weeks, a slow taper should start in responders, or prednisolone should be rapidly tapered and discontinued if no response. In responders, gradual tapering is advised until discontinuation within 4–6 months. First-line addition of rituximab has been shown to double the rate of long-term responses[26,27] and should be considered in patients not promptly responding to corticosteroids. It may also be considered in those presenting with haemoglobin <8 g/dL and in IgA-mediated, mixed, or DAT-negative AIHA and Evans' syndrome.[1,4]

Rituximab is the recommended second-line therapy in primary wAIHA.[1,9] Failure on first-line therapy should also prompt a diagnostic re-evaluation. Third-line options include azathioprine and other immunosuppressants. Bortezomib-based combinations are also promising.[28] Fostamatinib, a splenic tyrosine kinase inhibitor, yielded favourable results in a phase 2 trial.[29] Long-term, low-dose prednisolone (≤10 mg/day) is a third-line maintenance option.[1] Erythropoiesis-stimulating agents (ESAs) can be useful in patients with an inadequate endogenous erythropoietin response.[30] Splenectomy, previously often recommended in the second line, is now considered in the third or subsequent lines in low-comorbid patients who are not too old.[1,4]

Cold agglutinin disease

Definition, pathogenesis, and clinical features

CAD is a cAIHA mediated by cold agglutinins (CA), i.e., autoantibodies able to agglutinate RBCs at temperatures below 37 °C. Absence of any underlying clinical disease is also part of the disease definition.[6,10] The CA are produced by a clonal B-cell lymphoproliferative process of the bone marrow, not considered a malignant lymphoma.[31] The lymphoid infiltration can be sparse and easily overlooked or misdiagnosed as non-Hodgkin lymphoma.[31,32]

Patients may have non-complement mediated agglutination symptoms such as acrocyanosis and Raynaud-like phenomena. Classical complement activation results in coating of RBCs with C3b and phagocytosis of opsonized RBCs (extravascular haemolysis), mainly in the liver.[17,33–35] Terminal complement activation and intravascular haemolysis can occur in severe CAD. Patients have an increased risk of thrombosis.[36]

Diagnosis

Fig. 1 outlines the diagnostic procedure. A significant CA titre is required for diagnosis; usually >64, often much higher (Fig. 3).[32] Determination of the thermal amplitude (the highest temperature at which agglutination occurs) is sometimes useful.[10] Serum protein electrophoresis, bone marrow biopsy, and flow cytometry will reveal the clonal nature of CAD in many but not all cases.[31,32] Specific precautions are needed in handling blood specimens (Table 3).[1,37]

Treatment

Corticosteroids are ineffective and should not be used in CAD.[1,32] Not all patients need drug therapy, but symptomatic anaemia, significant fatigue, or bothersome circulatory symptoms are indications for treatment.[1,10,38] Treatment options are listed in Table 4.[6,38–41]

Other autoimmune haemolytic anaemias

Drug-induced haemolytic anaemia is usually mediated by immune mechanisms.[4,42] The only evidence-based treatment is discontinuation of the suspected drug, but corticosteroids are often also implemented as an initial measure.

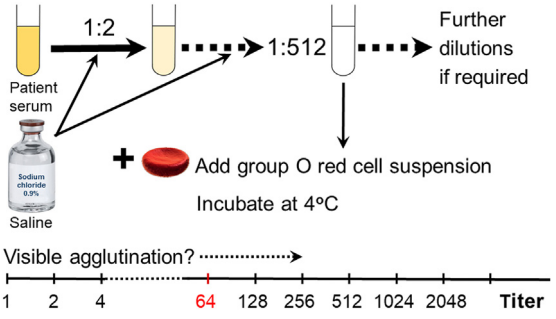

***Fig. 3:* Cold agglutinin titration**. Doubling dilutions of plasma or serum are prepared, ranging up to 1:512. Further dilutions are made if agglutination still occurs at the highest dilution. 1 drop of each dilution is added to 1 drop of a 2% suspension of washed group O donor erythrocytes and incubated at 4 °C. Chilled slides are read macroscopically at room temperature. The titre is the inverse of the highest dilution at which agglutination can be seen.

Analysis	Material	Sampling	Handling of sample
Hemoglobin, blood cell counts	Blood	EDTA vacuum tube	Prewarm at 37–38 °C before analysis if problems with agglutination
Cold agglutinin titer, thermal amplitude, immunoglobulin quantification, electrophoresis, immune fixation	Serum	Blood is drawn into prewarmed vacuum tubes without additive. Place in warming cabinet or water bath at 37–38 °C	Keep at 37–38 °C until serum has been removed from the clot, after which the sample can be handled at room temperature
Flow cytometry	Bone marrow aspirate (Too low sensitivity if performed in peripheral blood)	Add EDTA or heparin	Prewarming before analysis will often be sufficient. If not, wash cells at 37–38 °C.

EDTA, ethylene diamine tetraacetic acid. Table previously published 2019 by Berentsen et al. in Journal of Blood Medicine,[37] reused under a Creative Commons CC-BY license 4.0 (https://creativecommons.org/licenses/by/4.0/). © S. Berentsen 2019.

Table 3: **Cold agglutinin disease: handling of samples.**

Mixed warm and cold-antibody AIHA is rare and often severe. Diagnosis requires a monospecific DAT strongly positive for both IgG and C3d, a cold agglutinin titre ≥64, and the presence of warm-reactive IgG in serum as demonstrated by indirect antiglobulin test at 37 °C.[3,4,43]

Cold agglutinin syndrome (CAS) occurs secondary to overt B-cell lymphoma or specific infections (*Mycoplasma pneumoniae*, Epstein–Barr virus, cytomegalovirus, SARS-CoV-2, and others).

Paroxysmal cold haemoglobinuria (PCH) is an ultra-rare AIHA mediated by biphasic, polyclonal IgG antibodies.[44] Today, virtually all cases occur in children after a viral or other febrile infection. The condition may be underdiagnosed. Diagnosis is established by the Donath–Landsteiner test.[44] There is no documented treatment apart from transfusion, but infusion of the C5 inhibitor eculizumab was followed by immediate resolution in a single case.[44,45]

DAT-negative AIHA, a term for AIHA cases with negative DAT, remains difficult to diagnose and requires a comprehensive exclusion of non-immune causes of hemolysis.[1,46,47] Sensitive methods for detecting immunoglobulin at the RBC surface may confirm autoimmune pathogenesis, but the benefit is limited by lower specificity.[4,24]

Current challenges and the way forward in low-to-middle income countries

General challenges

Although little data are available on the epidemiology of AIHA in LMIC,[46,48,49] the real number of patients is quite high. By 2023, India would become the largest country in the world by population (1.43 billion inhabitants; Fig. 4) and a typical LMIC, but it was observed that the median number of AIHA patients managed by an Indian haematologist in the preceding three years was merely 11–20.[8] This figure, indicating only the limited number of AIHA patients who are referred to haematologists for the diagnosis and treatment, is a large underestimation of the actual patient load. If the data can be extrapolated from the Danish registry[11] into the

Target	Treatment	Study (Reference)	Study design	ORR[a] (%)	CR[b] rate (%)	Median response duration (months)	Toxicity
B-cell directed theapies	Rituximab monotherapy	Berentsen et al. 2004[39] Schöllkopf et al., 2006	Prospective, non-randomized	45–55	<5	6–11	Low
	Rituximab plus fludarabine	Berentsen et al., 2010	Prospective, non-randomized	76	21	>66	Significant
	Rituximab plus bendamustine	Berentsen et al. 2017[40] Berentsen et al. 2020[32]	Prospective, non-randomized	78	53	>88	Moderate, manageable
	Bortezomib monotherapy	Rossi et al., 2018	Prospective, non-randomized	32	16	>16	Low
	Ibrutinib monotherapy	Jalink et al. 2021[41]	Retrospective	100	NR[a]	ND[a]	Low
Complement-directed therapies	Sutimlimab	Röth et al. (CARDINAL study) 2021[6]	Prospective, non-randomized	>73[c]	NR[a]	>24	Low
		Röth et al. (CADENZA study) 2021	Prospective, randomized				
	Pegcetacoplan	Grossi et al., 2018	Part of prospective phase 2 study	ND/ high[c]	NR[a]	ND[a]	Low

Candidate drugs that have only been studied in preclinical or phase 1 trials are not listed. Table previously published 2023 by Berentsen et al. in Front Immunol,[22] reused under a Creative Commons CC-BY license 4.0 (https://creativecommons.org/licenses/by/4.0/). © S. Berentsen 2023. [a]ORR, overall response rate; ND, not determined; NR, not relevant. [b]CR, complete response. Criteria for CR included eradication of detectable bone marrow lymphoproliferative disorder. [c]ORR was not an endpoint of this study. Estimated ORR is based on data from the original publication.

Table 4: **Clinical studies of therapies for cold agglutinin disease.**

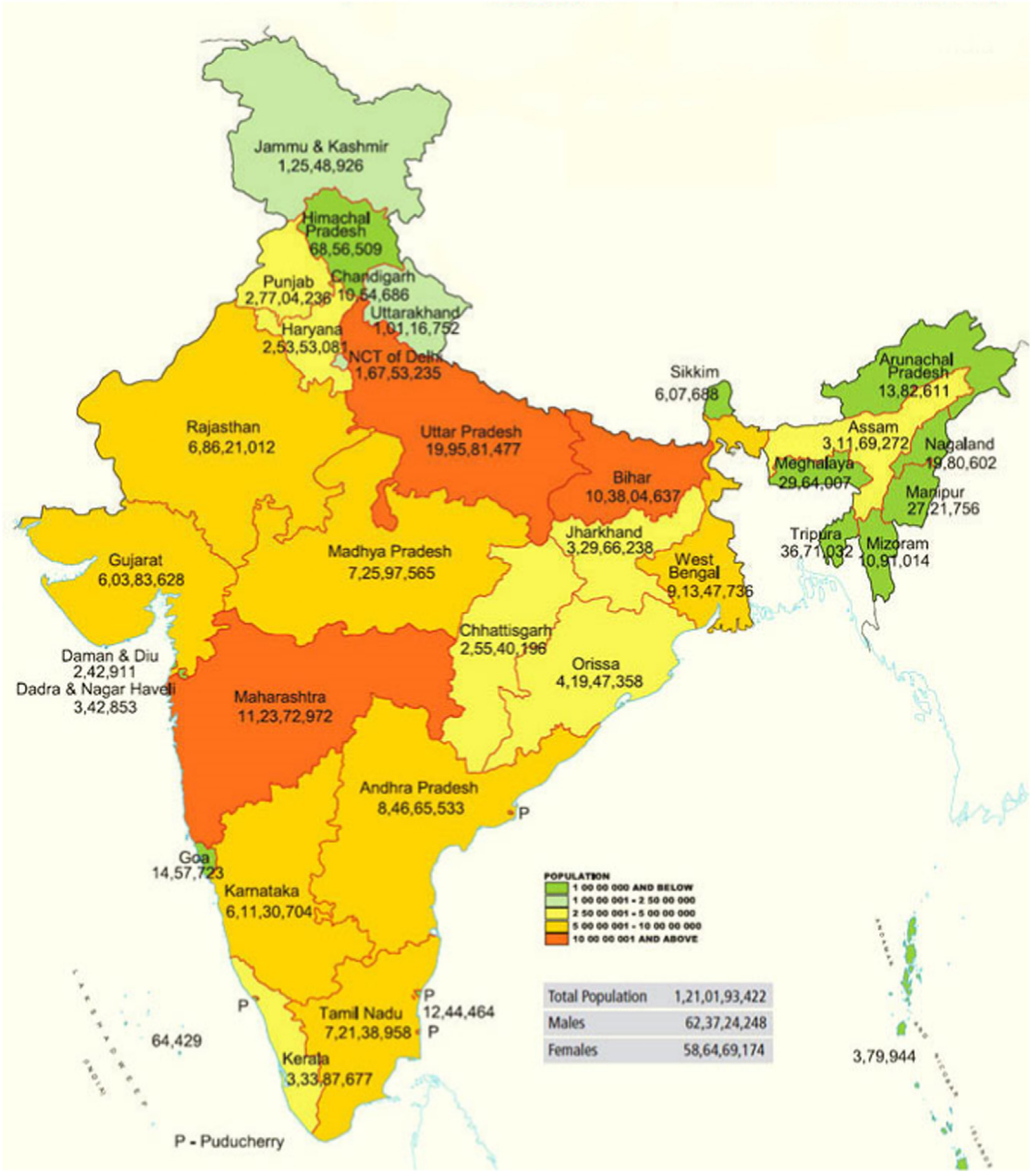

Fig. 4: **Population and provinces of India**. Based on data available at: https://censusindia.gov.in/census.website/(Ministry of Home Affairs, Government of India). Accessed 27.04.23.

Indian population, there will be 25,000 new cases of AIHA in India each year. On the other hand, only 130 doctors are getting specialized training in clinical haematology each year in India which, if compared to most high-income countries, is an extremely low number considering the huge population.[50,51] The situation is similar to the worst in other LMIC.

These patients often encounter medical challenges due to the late diagnosis, treatment failure and life-threatening complications. Considering the limited number of trained doctors, it would be a substantial challenge to manage such a massive capacity of patients in resource constraint settings. Due to the improper referral system in LMIC, most AIHA patients are managed by the general internist or by the paediatrician. Although not well versed with the latest diagnostic algorithm and treatment protocols, these doctors remain the only point of contact, which is a major cause of misdiagnosis and delayed diagnosis of AIHA. Furthermore, it has been observed that very few haematologists could actually recall cases where AIHA was the main cause of death, largely underscoring the clinical

importance of this condition when compared to the data from GIMEMA study.[3,8] Mortality among children with AIHA was reported to be 10–20% in a LMIC.[52] The cause of death can be multifactorial in AIHA patients, including concomitant infection, thromboembolism, or multi-organ failure, but most of these remain underreported in LMIC due to lost to follow-up of the patients.

Diagnostic challenges

As outlined (Fig. 1), a monospecific DAT for at least IgG, IgM, IgA, and C3d should be performed in all patients with DAT-positive haemolytic anaemia. In LMIC, however, most of the clinical haematologists do not have access to subtyping of AIHA.[8] Diagnostic workup for secondary AIHA also seems insufficient.[53]

In most LMIC, the DAT is performed in the local transfusion laboratories by using the same reagent/platform that is being used for the compatibility testing. As the polyspecific reagent containing anti-C3d and anti-IgG is the only serological reagent available, it is impossible to further distinguish between IgG and C3d. In DAT-negative AIHA, no further laboratory workup can be done due to the unavailability of higher-sensitive tests such as flow cytometry in the majority of centres.[54,55]

Diagnostic criteria for CAD include a monospecific DAT positive for C3d and a CA titer >64 at 4 °C. However, methods for CA detection varied widely between laboratories, as did the interpretation of results.[8] Only a handful of laboratories routinely performed a CA titre, specificity antigen determination (i.e., anti-I vs. anti-i), and thermal amplitude testing. Despite published guidelines, there remains variability in the ordering of CA assessment by the clinicians, too. Some considered these tests as unnecessary whereas others highlighted the lack of access.

The situation is similar in drug-induced AIHA cases because of unavailability of confirmatory testing facilities. Therefore, even after introduction of new drugs such as immune checkpoint inhibitors in cancer patients, known to be able to induce AIHA, most of the haematological adverse effects due to these drugs remain underreported.[42] Overall, the lack of immunohaematology reference laboratories for serologic workup remains the main diagnostic challenge.

Transfusion related challenges

Although blood transfusion remains as a supportive treatment in AIHA cases, the situation is quite different in LMIC.[56] Due to the late diagnosis and improper referral system most of the time, paediatric patients present with very low haemoglobin between 3 and 6 g/dL.[52] Therefore, transfusion management becomes critical.[46] Pre-transfusion testing for these patients should include ABO, CcDEe and Kell typing as well as assessment for alloantibodies.[4,43,57] This can only be achieved by special techniques, such as auto- or alloadsorption (warm autoantibodies) or prewarming screening cells and patient's plasma separately to 37 °C before use in the indirect antiglobulin test (cold autoantibodies), which are either unavailable or not practiced in most of the transfusion laboratories. Red cell genotyping is only available in very few centres.[58]

The term 'least incompatible' donor blood is considered obsolete among experts.[57] Still, transfusions with 'least incompatible' RBCs remain the routine practice in LMIC with very few exceptions.[59] Thus, the majority of transfused AIHA patients face a potential risk of delayed haemolytic transfusion reaction. Moreover, the early and frequent communication between the clinician and transfusion services that is essential for safe transfusion in AIHA is mostly missing in LMIC.[59]

Treatment related challenges

Although corticosteroids are recommended as a first line therapy mainly for wAIHA, in LMIC they are being used in all types of AIHA, partly due to the unavailability of the diagnostic facility for sub-typing.[1,8,60] Even in a retrospective study in which appropriate subtyping was performed, corticosteroids were the preferred therapeutic agents in CAD, resulting in only 14% response rate at 3 months of treatment and a "drug dependency" rate of 71% at 1 year,[61] probably explained by patients being maintained at high doses because of no real effect.[1,10] Similarly, current guidelines recommend rapid tapering and discontinuation of steroids from 3 weeks in non-responding primary wAIHA patients since continued treatment results in greater cumulative steroid toxicity while the probability of a late response is low.[1,62] In real life, however, it has been observed that most clinicians in India would prefer to continue administering high dose steroids for 6 weeks or more in non-responding patients before considering any dose reduction.[8,61] In clinical practice, therefore, AIHA patients face a high risk of being maintained on inappropriately high doses of corticosteroids, with an unnecessary risk of skeletal events, diabetes, and infection.[60,62,63]

Rituximab is recommended as a second line therapy in wAIHA and may be considered in combination with steroids in the first line in selected patients, whereas in CAD it is considered as the first line therapy, alone or in combination with bendamustine.[1,10,26,27,39] The cost of rituximab, however, remains one of the major challenges in LMIC.[43] Furthermore, the recommended pre-administration screening with serology for hepatitis B virus surface antigen and core antibody is not being followed universally in LMIC.[64,65] In a South-Asian population, where hepatitis B is an endemic disease, it would be devastating if the drug induced reactivation due to the inadequate screening. There is no provision for novel agents such as sutimlimab, as these extremely costly drugs are unaffordable for most people. ESAs are available in LMICs but rarely used in AIHA.[30] Haematologists are well aware of ESAs but the cost is quite

high and limits their use. The lack of accessibility of newer drugs ultimately leads to long-term treatment related toxicity, poor disease control and higher risk of complications such as infections and thrombosis.

The risks of thrombotic events in AIHA are mostly overlooked, and many clinicians are reluctant to consider venous thromboembolism (VTE) prophylaxis in patients.[8,66] The long-term outcome of thrombosis is unknown because of a high number lost to follow-up. Lastly, evaluating quality of life by simply asking questions is difficult because of highly heterogeneous communication skills of patients and clinicians.[8]

The way forward

A few ways might be used to mitigate these limitations partially but not completely. Diagnostic challenges such as unavailability of subtyping might be resolved by performing a polyspecific DAT in the local transfusion laboratory and monospecific DAT in a reference laboratory. However, the most critical tests like the monospecific DAT are not very sophisticated (Fig. 2), and an effort for standardization would facilitate a widespread use. A clinically significant CA can be excluded if saline suspended normal RBCs are not agglutinated by patient serum after incubation at room temperature for 30–60 min.[67] Patients with positive screening can then have CA titre assessed (Fig. 3). DAT-negative AIHA can be diagnosed by careful exclusion of alternative causes of haemolysis,[1,4] confirmed by a response to steroid challenge therapy, as DAT-negative AIHA often responds to prednisolone after a week of administration of 1 mg/kg/day.[68]

Blood smear microscopy provides a good clue to the differentiation between wAIHA and CAD/CAS and should be mastered and performed by all haematologists.[1,10] If no agglutination is seen, the likelihood of CAD/CAS is very low. In fact, simply improving clinicians' awareness of the clearcut differences in treatment of wAIHA and CAD is of paramount importance and would be a first step towards a more precise diagnosis and therapy.

Countrywise immunohaematology reference laboratories are required for specialized tests like CA titration, testing for drug-induced immune haemolytic anaemia, Donath–Landsteiner test, etc.[1] It is difficult to have all types of red cells for adsorption studies in local transfusion laboratories; hence, efforts must be made to establish reference laboratories through collaboration between academia and governments. To avoid adverse outcome of transfusions, these laboratories should provide allo- and autoadsorption testing available for all clinicians who treat AIHA, and extended phenotyping should become the routine whenever time permits. It is important to create countrywise AIHA registries, especially for patients requiring transfusion support, elderly patients and those with significant co-morbidities. This can also reduce the incidents of loss to follow-up.

There is also a need for standardization of diagnosis and treatment of AIHA in general in LMIC. The limited access of the latest treatment protocols should be addressed by disseminating educational materials and online support. Participation in clinical trials should be encouraged. Frequent clinical case reviews could be effective in small groups by involving both clinical haematologists and transfusion medicine specialists to overcome the diagnostic difficulties and the underestimation of the number of AIHA cases in LMIC. Clinical haematologists should have easy access to consult with a transfusion medicine specialist before administering transfusion or other treatment to AIHA patients.

The limited availability and/or lack of reimbursement of expensive drugs will not be easy to resolve and will depend on political decisions, resources, and agreements with the pharmaceutical companies. To mitigate this unmet need to some extent, one might consider moving splenectomy upwards in the therapeutic algorithm for wAIHA as it is a cheap and efficacious treatment.[60] However, the disadvantages and precautions should still be observed.[1,4]

An international AIHA network should be established to stimulate basic research, clinical studies, and update guidelines by forming a joint platform of experts. A European-American AIHA network of clinical haematologists already exists, responsible for the published international recommendations for diagnosis and treatment of AIHA in adults.[1] Strengthening such a network with transfusion specialists and paediatric haematologists, including experts from LMIC, might make it possible to better standardise AIHA management across the world.

Contributors

The authors contributed to the manuscript on an equal basis. Both authors collected data. SB drafted the first part of the manuscript and SSD drafted the second part. Both authors read and approved the submitted version.

Declaration of interests

The authors did not receive any funding or writing assistance for this paper. Outside this work, SB has received consultancy and advisory board honoraria from Annexon, BeiGene, Momenta, Sanofi, and Sobi; lecture honoraria from BeiGene, Janssen-Cilag, Sanofi, and Sobi; and royalties from Wolters Kluwer. SSD declares no conflicts of interest.

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