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A Systematic Review in Primary and Secondary Warm Autoimmune Haemolytic Anemia: an Outcome-Focused Analysis to Inform the Design of Future Studies

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Key Takeaway

It is essential to develop and implement a COS specifically tailored to wAIHA. This will require collaboration among clinicians, researchers, and patient advocacy groups to identify outcomes that are most valuable to both healthcare professionals and patients.

Conclusions

The current SLR identified a wide range of outcomes (partly due to the inclusion of case reports), a significant heterogeneity in outcomes across studies, and a lack of systematically standardized definitions.

These findings highlight the need for improved harmonization of wAIHA outcomes to enhance their relevance and comparability, and to strengthen the robustness of future studies and meta-analyses.

Moreover, the low percentage of patient-reported outcome measures may indicate a need for increased future incorporation of patient perspectives and outcomes in study design.

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Disclosures
All authors contributed to the study conception and design, data interpretation, writing and critical revision of the manuscript. All authors approved the final draft of the manuscript for publication. CS, JPA and AVC contributed to data extraction and data analysis. GR, AL, TV, WN and MF are employees of Johnson & Johnson Innovative Medicine. CS, JPA, AVC are employees of ISBE contracted by Johnson & Johnson Innovative Medicine for planning and performing the literature review, and for medical writing support. This study was funded by Johnson & Johnson Innovative Medicine.

Introduction

- Warm autoimmune hemolytic anemia (wAIHA) is a rare and potentially life-threatening condition characterized by the destruction of red blood cells due to autoantibodies active at body temperature.
- Since wAIHA is uncommon, treatment approaches have mostly been based on expert opinions or retrospective non-interventional studies, with a limited number of randomized / prospective clinical trials (1-6).
- While novel therapies have been proposed, there remains a significant gap in establishing a standardized core outcome set (COS) to guide research.

Aim

- The main goal of this systematic review was to identify and categorize all outcomes and outcome measures reported in studies on primary or secondary wAIHA. Identifying these is crucial for guiding future research and encouraging the inclusion of outcomes that are valuable to both healthcare professionals and patients.

Methods

- This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (7) and registered in May 2024 at the International Prospective Register of Systematic Reviews (8) (PROSPERO CRD42024537669).

Search strategy

- We performed a comprehensive search of PubMed/MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews.
- Study registries and conference proceedings in the field were also reviewed.

Eligibility criteria

- Inclusion criteria
  - Clinical trials, observational studies, case reports, case series, systematic reviews and meta-analysis between January 2000 and April 2024, in English, all ages, diagnosed with primary or secondary wAIHA.
- Exclusion criteria
  - Cold agglutinin disease and Evan's syndrome, animal, *in vitro*, molecular, genetic, pathophysiology, or pharmacokinetic/dynamic studies, and no reported outcomes.

Study selection

- Two independent authors assessed the eligibility of all retrieved articles based on title, abstract, or full-text.

Data extraction

- Extracted data included study design, country, year, setting, number of patients, wAIHA classification, children/adults, treatments, reported outcomes and definitions whenever available.

Data analysis

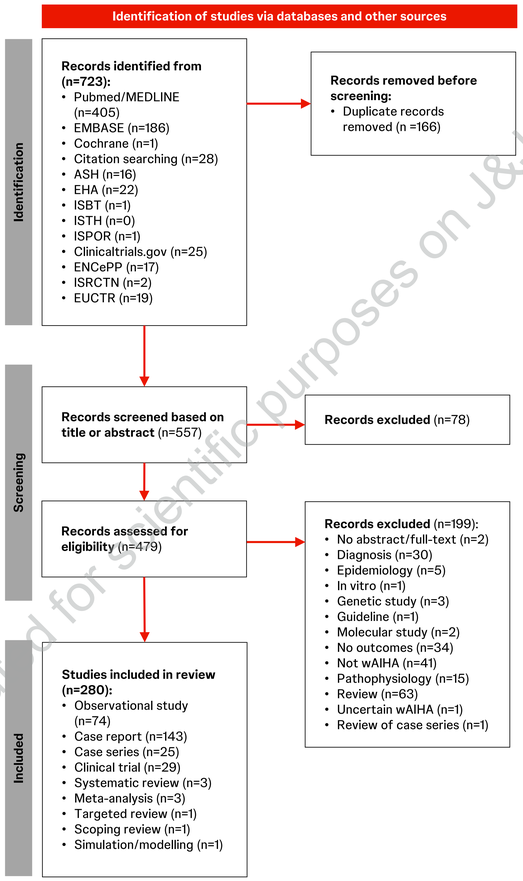
- Extracted data was descriptively summarized.

Results

Eligible studies

- During the literature search, 723 articles/studies were identified (Figure 1). After removing duplicates, 557 articles were further screened. Based on the initial screening of titles and abstracts, 78 studies were excluded; 479 articles underwent full-text review, and 199 were excluded.
- Of the 280 studies included in the systematic review, the majority were case reports/series (60%). There were 26% were observational studies and 10% were clinical trials.

Figure 1: PRISMA flowchart



Characteristics of the studies

- Regarding included studies' characteristics: about half were published or performed over last 5 years (2019-2024); the majority involved a single country; and one-third were performed in the USA; 23% included more than 20 patients; 42% of the studies included patients with secondary wAIHA only (38.5% due to infectious diseases), 29% primary, 25% both and 4% unknown; most of the studies included adults only (72%); most reported use of corticosteroids and 43.6% reported monoclonal antibodies (Table 1).

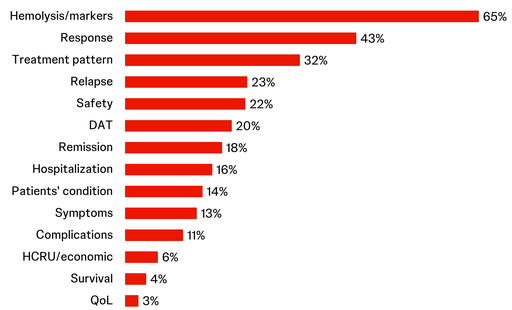
Table 1: Description of the studies included in our systematic review

Included studies, n (%)	N=280
Year of study	
2000-2018	135 (48.3%)
2019-2024 (until 16 April)	145 (51.7%)
Countries involved	
Single country	271 (96.8%)
Multi-country	9 (3.2%)
Geography	
United States of America	99 (35.4%)
Europe	80 (28.6%)
Other	101 (36%)
Type of study	
Case report	143 (51.1%)
Case series	25 (8.9%)
Observational	74 (26.4%)
Retrospective	57 (77.0%)
Clinical trial	29 (10.4%)
Phase 2	18 (62.1%)
Systematic review	3 (1.1%)
Meta-analysis	3 (1.1%)
Scoping review	1 (0.4%)
Targeted review	1 (0.4%)
Simulation/modelling	1 (0.4%)
Age	
Adults	202 (72.1%)
Children	44 (15.7%)
Children and adults	24 (8.6%)
Unknown	10 (3.6%)
Type of wAIHA	
Secondary	117 (41.8%)
Primary	81 (28.9%)
Primary and secondary	70 (25%)
Unknown	12 (4.3%)
Reported treatments (alone or in combination) (>10%)	
Corticosteroids	185 (66.1%)
Monoclonal antibodies	122 (43.6%)
Blood transfusion	112 (40%)
Immunoglobulins	66 (23.6%)
Immunosuppressant	62 (22.1%)
Splenectomy	33 (11.8%)

Outcomes

- A total of 401 outcomes were identified and categorized into 14 domains (Figure 2). Most outcomes reported were within the domains of hemolysis, hemolytic markers, response and treatment pattern.
- There was no consistent or universal definition for 'response' and 40% of the publications did not provide a definition. Quality of life was only reported in 3% of the studies. Validated patient reported outcome measures were identified in only 12 (4%) studies.

Figure 2: Description of outcome domains in wAIHA studies



Domain	Examples of outcomes
Hemolysis	• Resolution of hemolysis • Time to resolution of hemolysis
Hemolytic markers	• Changes in Hb, bilirubin, reticulocytes, LDH, haptoglobin • Normalization of hemolytic marker
Response	• Complete, partial and non-response • Overall response • Time in/to response
Treatment pattern	• Corticosteroid tapering • Time to corticosteroid free • Need for transfusions • Use of rescue therapy
Relapse	• Relapse rate • Time to relapse
Safety	• Incidence of AEs, TEAEs, SAEs • Frequency of dose interruptions, dose reductions or treatment discontinuations due to AEs
DAT	• Negativity of DAT retest
Remission	• Complete, partial, continuous remission • Time in remission
Hospitalization	• Frequency of hospital/ICU admissions and length of stay
Patients' condition	• Quality of life • Functionality for daily life activities • Clinical stabilization/improvement/resolution of clinical condition
Symptoms	• Improvement/resolution/free of symptoms • Fatigue level
Complications	• Incidence of infections, thrombotic events, renal failure, malignancy, osteoporosis and drug-induced diabetes
HCRU/economic	• Frequency of hospitalizations, ER visits, consultations, transfusions, tests
Survival	• Overall survival • Frequency of death
QoL	• Change in QoL scores

Abbreviations: HDL, lactate dehydrogenase; Hb, hemoglobin; HCRU, healthcare resource use; ICU, intensive care unit; DAT, direct antiglobulin test; ER, emergency room; SAE, serious adverse event; AE, adverse event; TEAE, treatment-emergent adverse event; QoL, quality of life

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Warm Autoimmune Hemolytic Anemia (wAIHA)

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