Diagnosis and management of Evans syndrome in adults: first consensus recommendations

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Evans syndrome is a rare disease marked by a severe clinical course, high relapse rate, infectious and thrombotic complications, and sometimes fatal outcome. Management is highly heterogeneous. There are several case reports but few large retrospective studies and no prospective or randomised trials. Here, we report the results of the first consensus-based expert recommendations aimed at harmonising the diagnosis and management of Evans syndrome in adults. After reviewing the literature, we used a fuzzy Delphi consensus method, with two rounds of a 42-item questionnaire that were scored by a panel of 13 international experts from five countries using a 7-point Likert scale. Panellists were selected by the core panel on the basis of their personal experience and previous publications on Evans syndrome and immune cytopenias; they met virtually throughout 2023. The panellists recommended extensive clinical and laboratory diagnostic tests, including bone marrow evaluation and CT scan, and an aggressive front-line therapy with prednisone (with or without intravenous immunoglobulins), with different treatment durations and tapering for immune thrombocytopenia and autoimmune haemolytic anaemias (AIHAs). Rituximab was strongly recommended as first-line treatment in cold-type AIHA and as second-line treatment in warm-type AIHA and patients with immune thrombocytopenia and antiphospholipid antibodies, previous thrombotic events, or associated lymphoproliferative diseases. However, rituximab was discouraged for patients with immunodeficiency or severe infections, with the same applying to splenectomy. Thrombopoietin receptor agonists were recommended for chronic immune thrombocytopenia and in the case of previous grade 4 infection. Fostamatinib was recommended as third-line or further-line treatment and suggested as second-line therapy for patients with previous thrombotic events. Immunosuppressive agents have been moved to third-line or further-line treatment. The panellists recommended the use of recombinant erythropoietin in AIHA in the case of inadequate reticulocyte counts, use of the complement inhibitor sutimlimab for relapsed cold AIHA, and the combination of rituximab plus bendamustine in Evans syndrome secondary to lymphoproliferative disorders. Finally, recommendations were given for supportive therapy, platelet or red blood cell transfusions, and thrombotic and antibiotic prophylaxis. These consensus-based recommendations should facilitate best practice for diagnosis and management of Evans syndrome in clinical practice.

Introduction

Evans syndrome is a rare condition currently defined by the concomitant or subsequent association of multiple autoimmune cytopenias, namely immune thrombocytopenia, autoimmune haemolytic anaemia (AIHA), and autoimmune neutropenia. It was initially described by Evans and colleagues in 1951 as the presence of thrombocytopenia in a patient with AIHA or the presence of anti-erythrocyte autoantibodies in patients with immune thrombocytopenia.[1] Subsequently, the definition was updated to include patients with autoimmune neutropenia.[2–5] The estimated incidence is 1–9 cases per million people per year, and up to half of patients with Evans syndrome have associated conditions, including infections, inborn errors of immunity (particularly in children), systemic autoimmune diseases (eg, systemic lupus erythematosus and rheumatoid arthritis), and lymphoproliferative syndromes, or have had haematopoietic stem-cell transplantation.[2–5] Previous haematopoietic stem-cell transplantation might challenge differential diagnosis and affect Evans syndrome prognosis in terms of response to therapy and complications.[4–6] Prospective paediatric data have been collected,[7] highlighting several differences in terms of outcomes and underlying diagnosis compared with adult-onset Evans syndrome. For the latter, only two retrospective series have been published.[4,5] These reports showed that Evans syndrome management in adults is highly heterogeneous, with the disease being marked by many relapses, severe complications, and high mortality, related to the severity of cytopenia at presentation and thrombotic and infectious complications.[4,5] In the absence of prospective evidence, randomised clinical trials, and guidelines for adult Evans syndrome, we have developed international consensus-based expert recommendations to harmonise the diagnosis and management of Evans syndrome.

Methods

A core panel and an extended panel were convened. The core panel included the project chair (WB), the co-chair (BF), and a methodologist (MoM) recruited by WB and BF. The extended panel, recruited by the core panel included 13 international key opinion leaders from five countries (Denmark, France, Italy, Spain, and the USA). A fuzzy Delphi consensus[8] method was followed (appendix p 1), and, after a systematic review of the literature (detailed in the panel at the end of this

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See Online for appendix

Review), the core panel shaped six domains encapsulating the clinical problems encountered in the diagnosis and management of Evans syndrome. These six domains were diagnostic tests at onset, diagnostic tests at relapse, treatment of thrombocytopenia in Evans syndrome, treatment of haemolytic anaemia in Evans syndrome, management of thrombotic risk during haemolytic anaemia, and treatment of autoimmune neutropenia. The core panel subsequently listed the major clinical problems within the last three domains, namely, indications to start cytopenia-targeted therapy, standard first-line therapy, emergency front-line therapy, therapy of early refractory cytopenias, and further lines of therapy.

The core panel and extended panel extensively discussed the several possible associated conditions configuring specific subtypes of secondary Evans syndrome, finding that the available evidence from the literature was very sparse, mainly relating to isolated immune cytopenias in various contexts and thus not allowing specific recommendations. Moreover, even consensus-based recommendations could not be drawn in some instances where the panel had little real-world experience. The topics that were discussed but not included in the recommendations are reported in the results section.

Finally, one or more questions were developed for each domain and problem. A 42-item questionnaire was developed and circulated to the extended panel by email in December 2022. The experts scored their agreement with the itemised answers to each question in the questionnaire using a 7-point Likert scale, and the scores were converted to fuzzy numbers. Both arithmetic and geometric means of fuzzy scores were calculated using Microsoft Excel 365. Subsequently, the core panel elaborated the recommended clinical actions for each of the questions. Recommendations were graded according to three consensus levels: M, for those considered "mandatory" or "strongly recommended", which were scored 6 or 7 by 80% (or more) of the panellists or for which the average fuzzy score was 90% (or higher); R, for those deemed "recommended" or "should be" (ie, should be implemented), which were scored 6 or 7 by 70–79% of the panellists or for which the average fuzzy score was 75–89%; S, for those "suggested" in a specific subgroup, which were scored 5 (or higher) by more than 50% of the panellists and for which the average fuzzy score was 70% (or higher); and D for those "discouraged" or deemed "not necessary", for which more than 30% of the experts scored the option 1–2 or for which the average fuzzy score was lower than 30%. The statements, numbered progressively within each domain, underwent further approval by the extended panel, with no further need of rephrasing (appendix p 1). Notably, items with average fuzzy score between 30% and 70% and not meeting criteria for M, R, S, or D concern tests that were neither recommended nor discouraged by the extended panel and require case-by-case evaluation (appendix pp 2–8).

Definitions

Diagnosis of Evans syndrome is established when a concomitant or subsequent association of at least two of three autoimmune cytopenias, namely, immune thrombocytopenia, AIHA, and autoimmune neutropenia, is detected. The diagnosis and classification of each cytopenia requires adherence to current recommendations.[9–11] Immune thrombocytopenia is diagnosed in a patient with platelet count less than 10×10^9 platelets per L in the absence of identifiable cause, with or without antiplatelet antibodies, and classified as newly diagnosed (0–3 months), persistent (>3–12 months), or chronic (>12 months).[9] AIHA is defined as the presence of anaemia (haemoglobin <12 g/dL) and positivity of the direct antiglobulin test (DAT), with alteration of haemolytic markers (lactate dehydrogenase higher than the upper limit of normality, unconjugated bilirubin higher than the upper limit of normality, haptoglobin lower than the lower limit of normality, or absolute reticulocytes higher than the upper limit of normality) as an indirect marker of haemolysis. AIHA is classified as warm-type AIHA if the DAT is positive for IgG or IgG plus complement at low titre, as cold-type AIHA if the DAT is positive for complement component C3d with cold agglutinin titre higher than 64, and as mixed if DAT is positive for IgG plus complement with high-titre cold agglutinins.[10] Autoimmune neutropenia and chronic idiopathic neutropenia are defined as the presence of absolute neutrophil count less than $1{\cdot}8\times10^9$ cells per L in White individuals, and less than $1{\cdot}5\times10^9$ cells per L in individuals of African ancestry, in the absence of identifiable causes, with or without positivity for anti-neutrophil antibodies (cutoff values are not available for other ethnicities).[11]

Evans syndrome response is defined as the recovery of immune thrombocytopenia (complete platelet count $>100\times10^9$ platelets per L and partial platelet count $>50\times10^9$ platelets per L), AIHA (complete haemoglobin >12 g/dL, normalisation of haemolytic markers, and partial haemoglobin >10 g/dL or >2 g/dL increase, from baseline), or autoimmune neutropenia (absolute neutrophil count $>1{\cdot}8\times10^9$ cells per L for White individuals or $1{\cdot}5\times10^9$ cells per L for individuals of African ancestry) after treatment. Non-response is defined as at least a partial response not being reached. Evans syndrome relapse is defined as the reappearance of immune thrombocytopenia, AIHA, or autoimmune neutropenia after a previous response to treatment. Refractory Evans syndrome with immune thrombocytopenia with or without AIHA is defined as at least a partial response not being reached after two or more lines of therapy.[9] Refractory primary Evans syndrome with immune thrombocytopenia with or without AIHA is defined as at least a partial response not being reached after 1 week of steroid treatment at 1 mg/kg per day with or without intravenous immunoglobulins.

Results

Literature review

The literature search provided 730 results, of which 277 were articles in English that referred to patients aged 18 years or older. These were mainly case reports (181 [65%]) or adult case series of autoimmune complications in lymphoproliferative disorders (mostly AIHA) including few patients with Evans syndrome. In addition, a proportion of all studies involved Evans syndrome secondary to various autoimmune diseases (eg, systemic lupus erythematosus and thyroiditis). We did not identify any prospective or randomised clinical trials, meta-analyses, or guidelines and found few retrospective studies with substantial numbers of patients.

Table 1 shows the largest case series of adult Evans syndrome.[3,4,5,12–19] The first Evans syndrome case series was reported in 2009 by Michel and colleagues[4] and included 68 patients with a mean age of 52 years (60% women); there were simultaneous cytopenias in 55% of patients and associated conditions in 50% (systemic lupus erythematosus, lymphoproliferative disorders, or common variable immunodeficiency). All patients needed therapy with steroids and 73% required a second-line treatment (splenectomy in two-thirds of these patients and rituximab in one-third). After a mean follow-up of 4·8 years, 24% of patients had died, underscoring that Evans syndrome is a potentially life-threatening condition. The largest Evans syndrome case series was the nationwide retrospective study that linked health registries in

	Patients with Evans syndrome	Comments
Michel et al (2009)[4]	68	Mean age 52 years; 41 (60%) women; simultaneous cytopenias in 37 (55%) of 68; secondary conditions in 34 (50%) (systemic lupus erythematosus, lymphoproliferative disorders, or common variable immunodeficiency); all patients needed therapy with steroids, and 50 (73%) required a second-line treatment (including splenectomy in 19 patients and rituximab in 11 patients); after a mean follow-up of 4·8 years, 22 (32%) were in remission and 16 (24%) had died; in older adults, the risk of AIHA-related cardiovascular manifestations was higher than the risk of bleeding
Barcellini et al (2014)[12]	21	21 (7%) of 308 patients with AIHA, mostly warm-type AIHA, with a severe onset (haemoglobin <6 g/dL); Evans syndrome was associated with increased mortality risk (hazard ratio 6·8, 95% CI 1·99–23·63)
Lecouffe-Desprets et al (2015)[13]	12	12 (30%) of 40 patients with AIHA; 8 (20%) of entire cohort had a pulmonary embolus, and venous thromboembolism was significantly associated with lower haemoglobin
Carli et al (2016)[14]	25	Of 860 patients with chronic lymphocytic leukaemia 25 (3%) patients had Evans syndrome secondary to chronic lymphocytic leukaemia; 13 (52%) patients with Evans syndrome developed AIHA or immune thrombocytopenia concomitantly and others developed the two conditions sequentially; del17p and unmutated *IgVH* were associated with Evans syndrome; 66% had stereotyped B-cell receptor; most patients required at least two therapy lines and had reduced survival
Serris et al (2018)[15]	10	10 (14%) of 71 patients with systemic lupus erythematosus; median age 36 years; patients received rituximab a median of 6·1 years from diagnosis; response to rituximab was 60% (*vs* 80–90% in immune thrombocytopenia and AIHA), complete response in 5 (50%); 30% relapsed, and retreatment was successful in 50%; severe infections were observed in three patients with favourable outcome
Hansen et al (2019)[3]	242	Health registry data from Denmark 1997–2017; median age 58·5 years; 123 (51%) women; 65 (27%) of 242 with secondary Evans syndrome; incidence 1·8 per million person-years; prevalence 21·3 per 1 000 000 people in 2016; median survival 7·2 years (10·9 years in primary cases and 1·7 years in secondary cases; main causes of death bleeding, infections, and haematological cancer)
Sulpizio et al (2020)[16]	7	Seven (8%) of 84 splenectomised patients had immune thrombocytopenia in 23 years; response to splenectomy was 86% (vs 91% in immune thrombocytopenia), and 3 (43%) relapsed within one year; long-term response rate of 43% (*vs* 70% in immune thrombocytopenia)
Fattizzo et al (2021)[5]	116	Median age at diagnosis 51 years (range 1·9–94·8); 59 (51%) women; 24 (21%) of 116 with secondary Evans syndrome; 49 (42%) with bleeding, mainly low grade and at onset; all needed steroids; 27 (23%) with primary refractory Evans syndrome needed further therapy (eg, splenectomy, immunosuppressants, or thrombopoietin receptor agonists), with response rates >80%; 63 (54%) of patients required at least three therapy lines; 38 (33%) had infections, mainly grade ≥3*, correlated with the number of therapy lines; 24 (21%) had thrombotic complications
Fattizzo et al (2022)[17]	29	Median age 61 years (range 24–88); 8 (28%) of 29 with Evans syndrome secondary to lymphoproliferative disorders, haematopoietic stem-cell transplantation, primary immune deficiencies, or antiphospholipid syndrome; all patients had immune thrombocytopenia plus AIHA (n=25), autoimmune neutropenia (n=2), or all three conditions (n=2); the most frequent cytopenia was immune thrombocytopenia (in 18 [62%]), with positive antiplatelet autoantibodies in 10 [45%] of 22 tested patients ; 23 (79%) of 29 received eltrombopag and six (21%) received romiplostim, with 80–90% of responses within the first 12 months; ten patients attained treatment-free remission, but eight relapsed; 11 patients discontinued due to non-response (four), thrombosis (three), thrombocytosis (three), or increased bone marrow fibrosis (one); ten required rescue therapies for immune thrombocytopenia relapses during treatment with thrombopoietin receptor agonists; patients with Evans syndrome showed a higher frequency of grade 3* and grade 4* adverse events (p<0·001), particularly thrombosis, compared with patients with primary immune thrombocytopenia
Jiang et al (2023)[18]	8	Eight (18%) of 44 patients with immune thrombocytopenia; median age 49 years; studied by next-generation sequencing for 375 genes of inborn errors of immunity; eight patients (18%) were carriers of pathogenic inborn errors of immunity variants, which are not disease-causing in the heterozygous state; one case of β1-tubulin-related congenital thrombocytopenia was identified; systematic screening for inborn errors of immunity is proposed for paediatric Evans syndrome but has low diagnostic yield in adults
Zhang et al (2023)[19]	7	Seven (16%) of 44 patients with AIHA had Evans syndrome and were treated with sirolimus; responses ranged from 80% to 90% at 3 months, 6 months, and 12 months, but were mainly partial compared with AIHA; 14% of patients with AIHA relapsed after a follow-up of 25 months

AIHA=autoimmune haemolytic anaemia. *Grading according to Common Terminology Criteria for Adverse Events version 5.0.

Table 1: **Largest published case series of adults with Evans syndrome**

Denmark to identify 242 patients over 40 years (1977–2017).[3] Mean age at diagnosis was 58·5 years, 51% of patients were women, and 27% had secondary Evans syndrome. Annual incidence and prevalence were 1·8 per million person-years and 21·3 per million people, respectively, in 2016. Median overall survival was 7·2 years (longer in primary Evans syndrome [10·9 years] and shorter in secondary forms [1·7 years]), with 5-year overall survival of 38% (the prevailing causes of death were bleeding, infections, and haematological cancer). The authors concluded that both primary and secondary Evans syndrome conferred a poor prognosis. More recently, Fattizzo and colleagues[5] analysed a series of 116 patients with Evans syndrome, confirming median age at diagnosis (51 years, range 1·9–94·8), slight female prevalence, and association with other autoimmune diseases and haematological neoplasms in about a fifth of patients. Most patients had combined immune thrombocytopenia and AIHA, followed by the triple combination of immune thrombocytopenia, AIHA, and autoimmune neutropenia in 10% of patients. At onset, a third of patients presented with isolated thrombocytopenia or anaemia or the two conditions simultaneously, whereas only 4% had isolated neutropenia. Regarding therapy, almost all patients received first-line treatment (steroids with or without intravenous immunoglobulin), and 23% needed early additional therapy for primary refractoriness, including rituximab, splenectomy, immunosuppressants, and thrombopoietin receptor agonists. Response rates were above 80%, but relapses were frequent, and 54% of patients required three or more therapy lines. Complications were common, namely infections, mainly grade 3 or worse (according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0), and correlated with the number of therapy lines in a third of patients, and thrombosis in a fifth. The authors concluded that adult Evans syndrome is frequently severe and marked by a relapsing clinical course and potentially fatal outcome, pinpointing the need for high clinical awareness, prompt therapy, and anti-infectious or antithrombotic prophylaxis. Finally, among the several case reports, it is worth highlighting those treated with classic immunosuppressants (cyclosporin, azathioprine, and cyclophosphamide), mycophenolate mofetil, sirolimus, ibrutinib, zanabrutinib, orelabrutinib, bortezomib, and haematopoietic stem-cell transplantation.

	Recommendation status
At onset of Evans syndrome, these tests are mandatory: full blood count, reticulocyte count, direct antiglobulin test, haptoglobin, unconjugated bilirubin, lactic dehydrogenase, peripheral blood smear	M
To complete differential diagnosis of Evans syndrome, the following tests are also recommended: cobalamin and folate serum levels, ferritin, transferrin, and iron, renal and liver function tests, serum protein electrophoresis, anti-nuclear antibodies, serology tests for hepatitis viruses and HIV, immunoglobulins, chest and abdominal CT scans	R
Other tests are suggested at Evans syndrome onset in specific settings: coagulation assays, antiphospholipid antibodies, bone marrow study (morphology, cytometry, cytogenetics, and histology), cytomegalovirus infection status (DNA suggested above serology).	S
According to the extended panel, antiplatelet, anti-neutrophil, and anti-DNA autoantibody tests have low sensitivity and specificity and are not necessary for diagnosis	D
Molecular studies (ie, next-generation sequencing assay for genes mutated in myeloid neoplasms or inborn error of immunity) are not advised unless specific clinical suspicion is present	D
At Evans syndrome relapse, the following tests are stongly recommended: full blood count, reticulocyte count, haptoglobin, unconjugated bilirubin, and lactate dehydrogenase	M
At Evans syndrome relapse, renal and liver function and direct antiglobulin tests are also recommended	R
At Evans syndrome relapse, thorax, and abdominal CT scans and bone marrow study are suggested for those patients who did not receive such test at diagnosis or in the last 12 months	S

All recommendations are based on literature on isolated cytopenias, three large retrospective studies in Evans syndrome, and the personal experience of the expert panel. D=discouraged. M=mandatory (strongly recommended). R=recommended. S=suggested.

Table 2: **Recommendations for diagnostic testing for Evans syndrome**

Recommendations for diagnostic tests

The extended panel agreed that Evans syndrome diagnosis must comprise a full blood count with differential leukocyte counts, peripheral blood smear, haemolytic markers (including absolute reticulocyte counts), and DAT (table 2). Additional recommended tests are cobalamin and folate serum concentrations; ferritin; renal and liver function tests; serum protein electrophoresis; antinuclear antibodies; serology for hepatitis viruses and HIV; immunoglobulins; and chest and abdominal CT scans. Further suggested investigations include coagulation assays, antiphospholipid antibodies, bone marrow evaluation, and cytomegalovirus infection status. Specifically, CT imaging was strongly recommended to exclude underlying conditions such as lymphoproliferation (typical of lymphoproliferative diseases and primary immunodeficiencies), solid tumours, and infectious foci. Bone marrow evaluation was suggested with the same intention, as bicytopenia in adults might be associated with lymphoproliferative disorders, bone marrow failures, and myeloid neoplasms. The experts agreed that, unlike DAT, antiplatelet, antineutrophil, and anti-DNA autoantibody tests are not necessary for diagnosis, given their low sensitivity and specificity.[9–11] Likewise, molecular studies are discouraged unless specific clinical suspicion is present. In this regard, the extended panel discussed that although the presence of constitutional variants is a major issue in paediatric patients, both because of ever-expanding descriptions of primary immunodeficiencies and possible targeted therapies,[20] in adults this possibility is unlikely unless family history or suggestive personal history of early onset Evans syndrome is present. Additionally, in bicytopenic adult patients, differential diagnosis includes testing for bone marrow failures and myeloid neoplasms; however, the evidence supporting molecular analysis for clonal haematopoiesis is scarce, and molecular testing is discouraged unless aberrant bone marrow features are present. Detailed scores

and fuzzy averages (geometric and arithmetic means) are shown in the appendix (p 2). Recommendations for diagnostic tests apply to all patients with Evans syndrome and aim to assess differential diagnosis as well as identify associated conditions. Once an associated condition is suspected or diagnosed, further tests are dictated by the clinical setting (eg, CT scan, PET scan, and lymph node biopsies for lymphomas, and IgG subclasses and lymphoid subpopulations for inborn errors of immunity). Notably, besides nutrient concentrations, most tests are both aimed at excluding alternative diagnoses and identifying underlying disease.

Regarding relapse, the extended panel agreed that haematological evaluation is mandatory (ie, full blood count and haemolytic markers), whereas testing of renal and liver function and DAT are recommended, and CT scan and bone marrow study are suggested only for those patients who did not receive such tests at diagnosis or within the last 12 months. The extended panel discussed that quantitation of immunoglobulins and lymphocytes and their subpopulations might be useful before B-cell-depleting therapy, but absence of evidence in Evans syndrome prevented the formulation of a specific recommendation. Detailed scores and fuzzy averages (geometric and arithmetic means) are shown in the appendix (p 3). Recommendations apply to all patients with Evans syndrome (primary and secondary) and could be adjusted according to the eventual underlying condition (eg, PET scan or lymph node biopsy in patients with lymphoma).

Recommendations for therapy of immune thrombocytopenia in Evans syndrome

Recommendations have been formulated for both primary and secondary Evans syndrome, unless otherwise specified (table 3). The extended panel agreed that treatment of Evans syndrome-associated immune thrombocytopenia is mandatory in case of platelet

	Recommendation status	Basis of recommendations*
Treatment of immune thrombocytopenia is mandatory for patients with Evans syndrome reporting platelet counts <20–30 × 10^9 platelets per L and concurrent bleeding ≥ grade 2	M	I, II, and III
Treatment of immune thrombocytopenia is also suggested for patients reporting platelet counts <20–30 × 10^9 platelets per L without clinically relevant bleeding and patients with less severe thrombocytopenia but showing bleeding symptoms ≥ grade 2	S	I, II, and III
Prednisone (1 mg/kg per day) is strongly recommended as upfront treatment for immune thrombocytopenia in patients with Evans syndrome	M	I, II, and III
Full-dose steroids (ie, prednisone or prednisolone at 1 mg/kg per day) are recommended to be continued for 3–4 weeks and tapered off over at least 8 weeks; full steroid course not prolonged beyond 6 months	R	I, II, and III
Intravenous immunoglobulin add-on or dexamethasone (40 mg/day for 4 days) are recommended for patients requiring a more rapid response (eg, because of severe bleeding) or not showing an amelioration trend in the first days of treatment	R	I and III
Platelet transfusions are mandatory for patients with life-threatening bleeding	M	I and III
Platelet transfusions are suggested before surgical interventions, weighed according to the urgency and type of intervention, patients' comorbidities, and global bleeding risk	S	I and III
At first relapse or no response, rituximab is strongly recommended in the following settings: relapse occurring within 12 months from the first episode (ie, persistent thrombocytopenia); presence of antiphospholipid antibodies; previous thrombotic events; associated lymphoproliferative diseases	M	I, II, and III
Rituximab is discouraged in patients with immunodeficiency or a history of grade 4 infections	D	I, II, and III
Thrombopoietin mimetics are recommended at first relapse in patients with history of thrombocytopenia >12 months (chronic) or history of grade 4 infection	R	I, II, and III
Thrombopoietin mimetics or immunosuppressive agents (eg, cyclosporin A and mycophenolate mofetil) are suggested in patients reporting two or more relapses	S	I, II, and III
Splenectomy is discouraged for patients with Evans syndrome in the following settings: first thrombocytopenia relapse; immunodeficiency; lymphoproliferative diseases; connective diseases; and antiphospholipid antibodies	D	I, II, and III
Mycophenolate mofetil and other immunosuppressive agents are discouraged at the first relapse in the following settings: immunodeficiency; associated lymphoproliferative diseases; age <40 years; and women of childbearing potential	D	I, II, and III
Fostamatinib is an option for patients reporting two or more relapses	M	I and III
Fostamatinib is suggested at relapse for patients with Evans syndrome with a history of thrombocytopenia >12 months (chronic phase) and previous thrombotic events	S	I and III

Recommendations have been formulated for both primary and secondary Evans syndrome unless otherwise specified. Definitions of Evans syndrome response and relapse are shown in the Methods. Grading of bleeding and infectious complications was made according to the Common Terminology Criteria for Adverse Events version 5.0. For mucocutaneous bleeding, grade 2 consists of haemorrhagic lesions covering 10–30% of body surface area or traumatic bleeding; grade 3 or worse includes >30% body surface area with or without spontaneous bleeding; grade 3–4 infections include potentially life-threatening infections requiring systemic therapy and hospitalisation. D=discouraged. M=mandatory (strongly recommended). R=recommended. S=suggested. *Recommendations are based on literature on isolated cytopenias (I), three large retrospective studies in Evans syndrome (II), or the personal experience of the expert panel (III).

Table 3: **Recommendations for the management of thrombocytopenia in Evans syndrome**

counts less than $20–30 \times 10^9$ platelets per L and concurrent bleeding grade 2 or worse (CTCAE version 5.0) and suggested if platelet counts are below the cited threshold without clinically relevant bleeding or, in the case of higher platelet counts, in the presence of bleeding symptoms. Prednisolone or prednisone at 1 mg/kg per day is strongly recommended as upfront treatment and should be continued for 3–4 weeks, then tapered off over at least 8 weeks (not beyond 6 months). This recommendation is mostly based on retrospective data from observational studies of Evans syndrome and the personal experience of the extended panel and partly differs from the recommendations for primary immune thrombocytopenia,[9] which includes both prednisone and dexamethasone. For patients requiring a quicker response due to severe bleeding manifestations or showing no response in the first days of treatment, dexamethasone and addition of intravenous immunoglobulins are recommended. Notably, in secondary Evans syndrome, the need for treatment of the underlying condition should be evaluated, possibly in a multidisciplinary team; immunodeficiencies suspected on the basis of clinical and routine laboratory tests should be referred to dedicated centres. The extended panel strongly recommended platelet transfusions in the case of life-threatening bleeding, suggesting that this intervention should be considered before surgical interventions on a case-by-case basis. In the case of thrombocytopenia relapse or no response, rituximab is strongly recommended in the setting of persistent thrombocytopenia, presence of antiphospholipid antibodies, and previous thrombotic events, and discouraged for those patients with a history of severe infections; furthermore, rituximab is strongly recommended for patients with associated lymphoproliferative diseases but discouraged for patients with immunodeficiency (recommendations valid for Evans syndrome secondary to lymphoproliferative diseases and immunodeficiencies). For patients with chronic thrombocytopenia, a history of severe infections, or immunodeficiency, the extended panel recommended thrombopoietin mimetics either at first or subsequent relapses (recommendations valid for both primary and secondary Evans syndrome and for Evans syndrome secondary to immunodeficiencies). Mycophenolate mofetil and other immunosuppressive agents can be considered in patients reporting two or more relapses but are discouraged in the case of associated immunodeficiency and lymphoproliferative diseases (recommendations valid for secondary Evans syndrome) and in young women of childbearing potential. Splenectomy is discouraged in Evans syndrome associated with immunodeficiency, lymphoproliferative diseases, connective tissue diseases, or antiphospholipid antibodies (recommendations valid for secondary Evans syndrome). Finally, fostamatinib is a recommended option in patients reporting two or more relapses and is suggested for patients with chronic Evans syndrome who have a history of previous thrombotic events (recommendations valid for primary Evans syndrome). The level of agreement of the panel for each treatment according to the clinical context (disease phase, age, sex, concurrent lymphoproliferative disease, connective tissue disease, immunodeficiencies, previous thrombosis or infection, and positivity of antiphospholipid antibodies) is detailed in the appendix (p 4). Post-transplantation Evans syndrome was considered by the extended panel, but the evidence for recommendations and personal experience of the panel were insufficient, mainly relying on isolated thrombocytopenia, and, therefore, no specific recommendation was formulated.

Recommendations for therapy of Evans syndrome-associated autoimmune haemolytic anaemia

Recommendations have been formulated for both primary and secondary Evans syndrome, unless otherwise specified (table 4). The extended panel agreed that treatment of Evans syndrome-associated haemolytic anaemia is recommended in the case of moderate-to-severe anaemia and for patients reporting AIHA-related symptoms. The level of agreement for each treatment for warm-type AIHA and cold-type AIHA according to clinical context is detailed in the appendix (pp 5–6). Regarding supportive treatment, red blood cell transfusions are recommended for those with severe anaemia and related symptoms, and plasma exchange is recommended for patients with very severe anaemia, no response to steroids, and refractoriness to blood transfusions, balancing the risk–benefit ratio of this demanding procedure. Recombinant erythropoietin is strongly recommended in the case of inadequate compensatory reticulocytosis. This recommendation mainly comes from isolated AIHA, where the European group of an international study reported 70% response rates in patients with inadequate bone marrow compensation, who represent about a third of cases.[21] In an observational study of adult Evans syndrome, one patient with inadequate compensatory reticulocytosis was treated successfully.[5] Finally, a recent phase 2 prospective study reported efficacy higher than 70% in patients with AIHA with inadequate reticulocytosis, including six adults with Evans syndrome.[22] Thromboprophylaxis is strongly recommended in patients with active AIHA and a history of previous thrombosis or additional thrombotic risk factors. Additional settings to consider for thromboprophylaxis include patients with antiphospholipid antibodies and previous splenectomy. Finally, thromboprophylaxis is discouraged when platelet counts are less than 30×10^9 platelets per L (details of level of agreement are reported in the appendix, p 7).

Regarding initial therapy for warm-type AIHA, the extended panel strongly recommend prednisone as upfront treatment to be continued at full dose for 3–4 weeks, then slowly tapered over 9–12 weeks and stopped by about 6 months. For patients not responding

	Recommendation status	Basis of recommendations*
AIHA (all types)		
Treatment of haemolytic anaemia in patients with Evans syndrome is recommended for those reporting AIHA-related symptoms, particularly those showing moderate-to-severe anaemia (haemoglobin <10 g/dL)	R	I, II, and III
Red blood cell transfusions are recommended for patients reporting AIHA-related symptoms and any grade anaemia, particularly for those showing severe anaemia (haemoglobin <8 g/dL)	R	I, II, and III
Plasma exchange should be considered in patients with very low haemoglobin (<6 g/dL) and no response to steroids, particularly those also reporting refractoriness to blood transfusions†	R	I and III
Erythropoiesis-stimulating agents are strongly recommended if inadequate reticulocytosis is documented, namely, reticulocyte count $<150\times10^9$ cells per L, or $<250\times10^9$ cells per L if haemoglobin <8 g/dL	M	I and III
Patients with Evans syndrome should receive thromboprophylaxis during episodes of AIHA in the case of history of previous thrombosis or additional thrombotic risk factors (eg, older age or hospitalisation)	M	I, II, and III
Thromboprophylaxis is also suggested for patients with active haemolysis (eg, lactate dehydrogenase >1·5 of the upper normal limit), presence of antiphospholipid antibodies, or previous splenectomy	S	I, II, and III
Thromboprophylaxis is discouraged if platelet count $<30\times10^9$ platelets per L	D	I and III
Warm-type AIHA		
Front-line treatment with prednisone 1 mg/kg per day is strongly recommended for patients with Evans syndrome and a warm-type AIHA episode	M	I, II, and III
Intravenous immunoglobulin add-on is suggested in patients without prompt (within 7 days) response to steroids	S	I, II, and III
Steroids should be continued at full dose for 3–4 weeks and slowly tapered over 9–12 weeks, treatment stopping within 6 months	R	I, II, and III
Rituximab (375 mg/m² per week for 4 weeks) is strongly recommended for patients reporting a first relapse or no response to steroids	M	I, II, and III
A further course of rituximab (375 mg/m² per week for 4 weeks) is strongly recommended for patients reporting a further relapse >2 years from previous rituximab and without a previous severe infection	M	I, II, and III
Case-by-case evaluation of the risk–benefit ratio of splenectomy and immunosuppressive therapy and enrolment in clinical trial is strongly recommended for patients reporting two or more relapses	M	I and III
Splenectomy is discouraged in patients with secondary Evans syndrome or thrombophilia	D	I, II, and III
Cold-type AIHA		
Rituximab (375 mg/m² per week for 4 weeks) is strongly recommended as front-line treatment for patients with Evans syndrome who have cold-type AIHA; steroid treatment limited to 1–2 weeks and rapidly tapered over <10 weeks	M	I and III
If used, steroid therapy in cold-type AIHA is recommended to be limited to <3–4 weeks, possibly <1–2 weeks	R	I and III
Rituximab retreatment is strongly recommended for patients with late cold-type AIHA relapses (>2 years from previous rituximab)	M	I and III
Rituximab plus bendamustine is recommended for fit patients reporting relapsing cold-type AIHA within 2 years of front-line rituximab therapy	R	I and III
Sutimlimab is suggested for patients reporting relapsing cold-type AIHA within 2 years of front-line rituximab therapy	S	I and III
Sutimlimab is recommended at second or further cold-type AIHA relapse	R	I and III

Recommendations have been formulated for both primary and secondary Evans syndrome unless otherwise specified. Definitions of Evans syndrome response and relapse are shown in the Methods. AIHA=autoimmune haemolytic anaemia. D=discouraged. M=mandatory (strongly recommended). R=recommended. S=suggested. *Recommendations are based on literature on isolated cytopenias (I), three large retrospective studies in Evans syndrome (II), or the personal experience of the expert panel (III). †Administration before rituximab and intravenous immunoglobulin is recommended to avoid removal of such therapeutics.

Table 4: **Recommendations for the management of haemolytic anaemia in Evans syndrome**

within 7 days and with severe anaemia, addition of intravenous immunoglobulins is suggested. In the case of warm-type AIHA relapse or no response, rituximab is strongly recommended. Rituximab is equally recommended for further warm-type AIHA relapses occurring at least 2 years from the previous administration of this drug, provided there have been no previous severe infections. Notably, in secondary Evans syndrome, the need for treatment of the underlying condition should be evaluated, possibly in a multidisciplinary team. In other cases, the risk–benefit ratio of splenectomy and immunosuppressive therapy should be evaluated on a case-by-case basis, and enrolment in a clinical trial is strongly recommended. Finally, the extended panel discourage splenectomy in patients with secondary Evans syndrome-associated warm-type AIHA or thrombophilia (recommendations valid for secondary Evans syndrome and primary Evans syndrome with thrombophilia). Regarding cold-type AIHA, which is rare in the setting of Evans syndrome, steroids are recommended to be limited as much as possible, ideally being administered for less than

1–2 weeks, whereas rituximab should be administered both as front-line treatment and as retreatment in the case of relapses occurring at least 2 years after the previous course. In secondary Evans syndrome, the need for treatment of the underlying condition should be evaluated, possibly in a multidisciplinary team. The combination of rituximab plus bendamustine is recommended for relapses observed within 2 years of front-line rituximab therapy for patients who are fit enough or have no comorbidities (recommendations valid for primary Evans syndrome or Evans syndrome secondary to lymphoproliferative neoplasms, based on a small amount of evidence in isolated cold-type AIHA). Finally, whenever available, the complement inhibitor sutimlimab can be considered for second or further relapses and could be considered after rituximab if the relapse occurs within 2 years of the previous course of rituximab (recommendation valid for primary Evans syndrome, based on a small amount of evidence in isolated cold-type AIHA).

Recommendations for the management of Evans syndrome-associated autoimmune neutropenia

The extended panel recommends granulocyte colony-stimulating factor (G-CSF) during grade 3–4 infections (infections that require systemic therapy and hospitalisation and are life-threatening; CTCAE version 5·0) in patients with moderate (absolute neutrophil count <1000 cells per μL) or severe (absolute neutrophil count <500 cells per μL) neutropenia (table 5). G-CSF and antibiotic prophylaxis are recommended before invasive procedures. Finally, the extended panel suggests long-term G-CSF and antibiotic, antiviral, and antifungal prophylaxis when absolute neutrophil counts are persistently less than 500 cells per μL in patients reporting at least one grade 3–4 infection per year (recommendations valid for both primary and secondary Evans syndrome, based on a small amount of evidence in isolated neutropenia). The level of agreement for each statement regarding the management of chronic idiopathic neutropenia or autoimmune neutropenia is detailed in the appendix (p 8).

	Recommendation status
On-demand G-CSF is recommended during grade 3–4 infections if moderate or severe neutropenia is reported (absolute neutrophil count <500–1000 cells per μL)	R
G-CSF and antibiotic prophylaxis are recommended before invasive procedures	R
Antibiotic prophylaxis, antiviral prophylaxis, and antifungal prophylaxis are suggested if absolute neutrophil counts are persistently <500 cells per μL and the patient reports at least one grade 3–4 infection per year	S

Recommendations are based on literature on isolated neutropenia and on personal experience of the expert panel. G-CSF=granulocyte colony-stimulating factor. R=recommended. S=suggested.

Table 5: **Recommendations for the management of immune neutropenia in Evans syndrome**

Management of Evans syndrome with concomitant cytopenias

The management of Evans syndrome mainly requires the treatment of one cytopenia at a time, but cytopenias might also occur simultaneously. The extended panel concurred that for simultaneous AIHA and immune thrombocytopenia at onset, front-line treatment refers to that given for isolated cytopenias as it is the same for AIHA plus thrombocytopenia (agreement 92%). At relapse of concurrent AIHA and immune thrombocytopenia, rituximab is strongly recommended (agreement 100%). In the case of concomitant autoimmune neutropenia and AIHA or immune thrombocytopenia at onset (or all three), front-line treatment is the same as for AIHA or immune thrombocytopenia (agreement 92%). At relapse of concurrent autoimmune neutropenia and AIHA or immune thrombocytopenia, the treatment is the same as for relapsed AIHA or relapsed immune thrombocytopenia (agreement 100%). According to some experts on the extended panel, special consideration should be given to infectious risk in the case of autoimmune neutropenia and immune thrombocytopenia, with the preferential use of thrombopoietin receptor agonists suggested over rituximab at relapse. Recommendations are valid for both primary and secondary Evans syndrome; in secondary Evans syndrome, the need for treatment of the underlying condition should be evaluated, possibly in a multidisciplinary team. Finally, no clearcut recommendations were formulated regarding anti-infectious prophylaxis during the various treatments for Evans syndrome. However, the panel discussed that the same precautions recommended for isolated cytopenias should be applied (ie, anti-capsulated bacteria vaccines for splenectomy and hepatitis B prophylaxis for patients who are hepatitis B positive and receiving rituximab).

Discussion

Here, we present the first consensus recommendations on the diagnosis and treatment of adult Evans syndrome, a rare condition marked by a severe clinical course, high relapse rate, underestimated occurrence of infectious and thrombotic complications, and frequent fatal outcome.[3–5] The attempt to address this unmet need in adults was difficult, given the heterogeneity of the disease and the scarcity of evidence available in the literature, mainly encompassing retrospective series and several case reports, of which the latter are generally biased because they report favourable results only.[3–5,12–19] Additionally, evidence regarding the management of Evans syndrome secondary to several possible conditions is sparse, and the literature mainly refers to the diagnostic

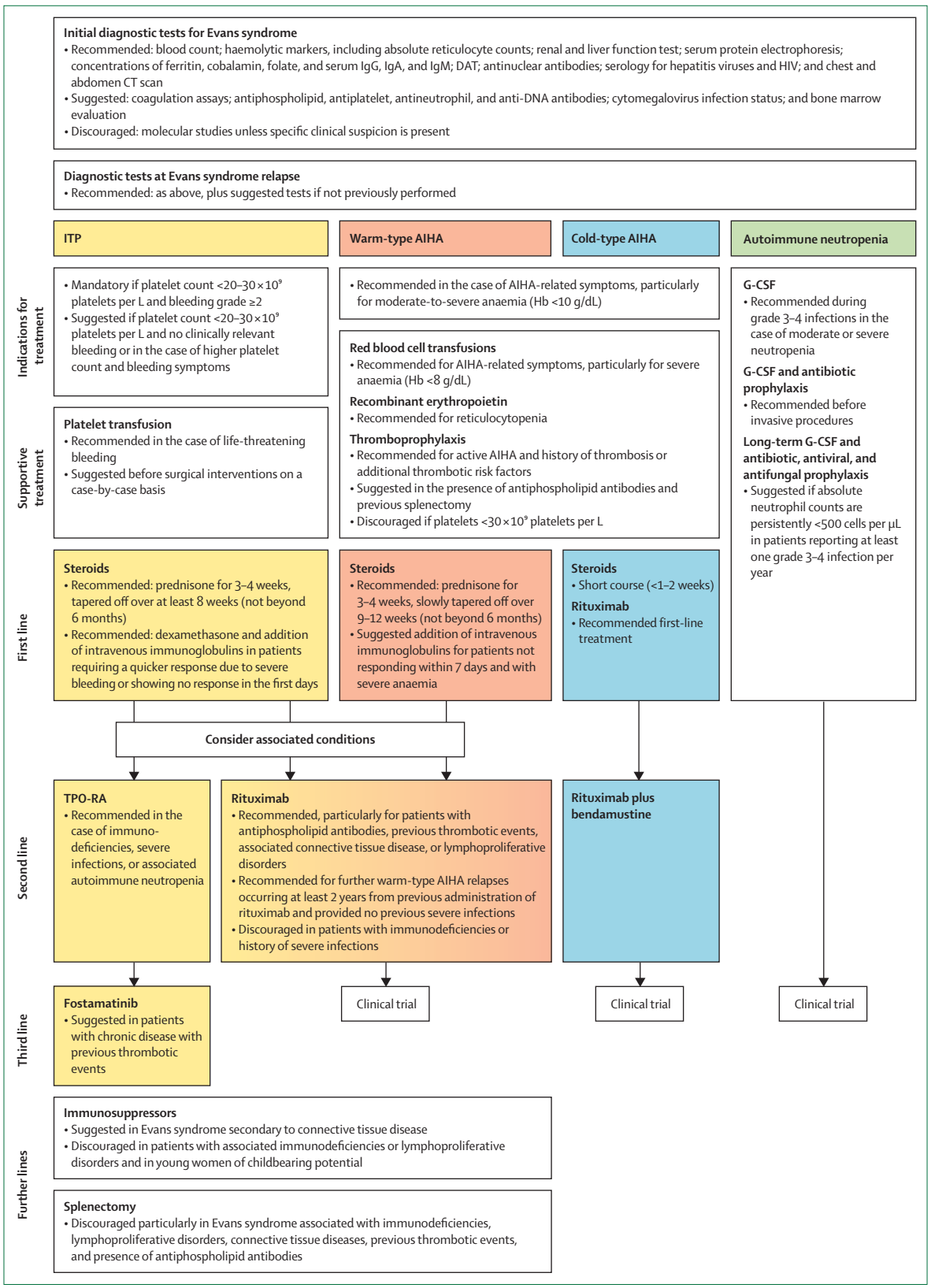

Figure: **Diagnostic and therapeutic algorithm for Evans syndrome**
The diagnostic pathway for Evans syndrome is divided into diagnosis and relapse. Indications for treatment and supportive therapies are provided for each cytopenia. First-line therapy for immune thrombocytopenia, warm-type AIHA, and cold-type AIHA includes steroids with different doses and schedules. Associated conditions should be considered both at diagnosis and before moving to second-line treatment, as thrombopoietin receptor agonists and rituximab have preferential indications. For further immune thrombocytopenia relapses, fostamatinib is an option, whereas for warm-type AIHA and cold-type AIHA, a clinical trial should be considered. Immunosuppressors and splenectomy have been moved to further lines and are generally discouraged, except for immunosuppressors in connective tissue diseases. In patients with autoimmune neutropenia, G-CSF treatment and anti-infectious prophylaxis are recommended according to the infectious history of the patients and severity of neutropenia. AIHA=autoimmune haemolytic anaemia. DAT=direct anti-globulin test. G-CSF=granulocyte colony-stimulating factor. Hb=haemoglobin. ITP=immune thrombocytopenia. TPO-RA thrombopoietin receptor agonists.

testing and treatment of isolated immune cytopenias in various contexts. Consensus-based recommendations could not be formulated in some instances where the real-world experience of the panel was insufficient (eg, treatment of secondary Evans syndrome with cold-type AIHA with sutimlimab).

The figure summarises the recommended diagnostic tests and therapeutic strategies in adult Evans syndrome. Regarding the diagnosis of Evans syndrome, the extended panel recommended an extensive set of clinical and laboratory tests, including bone marrow evaluation, which is not always advised for diagnosis of isolated cytopenia. In particular, neutropenia is often disregarded, whereas it should be considered together with anaemia and thrombocytopenia in the most recent definition of Evans syndrome.[2] It should be noted that the DAT, which is the cornerstone test for AIHA diagnosis, is neither 100% sensitive nor 100% specific,[23] and that antiplatelet and antineutrophil antibodies carry even lower sensitivity and specificity.[9,10] Thus, in several cases, Evans syndrome is a diagnosis of exclusion and, therefore, dependent on physician awareness and resource availability, including laboratory expertise. Consistently, the extended panel recommended evaluation by chest and abdomen CT scans and further analyses (eg, antiphospholipid antibodies, autoantibodies, total immunoglobulins, and viral serologies), also encompassing bone marrow evaluation to exclude the most frequent secondary forms reported in adults.[2,4,5] Future studies for the evaluation of mutations possibly associated with inborn errors of immunity or clonal haematopoiesis might provide insights into the pathogenesis of Evans syndrome in adults, but the extended panel does not recommend such tests (which are not indicated even in patients with isolated autoimmune cytopenias) at present.

Regarding treatment, similar front-line therapies with prednisone or prednisolone and with or without intravenous immunoglobulins were recommended for immune thrombocytopenia and AIHA, the most frequent Evans syndrome-associated conditions, with differing treatment duration and tapering—ie, a very short course for cold-type AIHA, intermediate course for immune thrombocytopenia, and longer course for warm-type AIHA. In cold-type AIHA, steroids might be useful in the acute phase but are discouraged in the chronic setting, and in immune thrombocytopenia, steroids are clearly effective, and tapering over about 8 weeks is advised. In warm-type AIHA, steroid tapering should be slower, with interruption within 6 months. Notably, at variance with primary immune thrombocytopenia, where dexamethasone and prednisone can be used interchangeably,[9] prednisone was recommended by the extended panel on the basis of retrospective data in Evans syndrome and personal experience. Rituximab was recommended as first-line treatment in cold-type AIHA and second-line treatment for warm-type AIHA, and can be repeated in the case of further relapses, given the broad evidence for its efficacy in this disease.[12,24] The main difference that emerged between treatment of primary immune thrombocytopenia[9] versus Evans syndrome-associated thrombocytopenia was the recommendation of rituximab as second-line treatment in the latter, particularly in the setting of persistent disease, antiphospholipid antibodies, previous thrombotic events, or associated lymphoproliferative diseases. Conversely, rituximab was discouraged in patients with immunodeficiency or history of severe infections. Although some evidence suggested the use of first-line rituximab in isolated AIHA and immune thrombocytopenia, no data are available in Evans syndrome, preventing any specific recommendations. Splenectomy, the historical second-line treatment for Evans syndrome, was discouraged by the extended panel due to the infectious and thrombotic risks, particularly in secondary cases (eg, patients with inborn errors of immunity, lymphoproliferative disorders, or antiphospholipid antibodies). Splenectomy appears to be the only treatment also dictated by age, as per common recommendations in primary cytopenias. In fact, the thrombotic risk described in primary immune thrombocytopenia and AIHA is even more pronounced in Evans syndrome[4,5] and might further increase with the use of thrombopoietin receptor agonists.[17] The latter were otherwise recommended in the case of chronic thrombocytopenia associated with immunodeficiency or a history of severe infections. Bone marrow stimulation instead of heavy immunosuppression was also advised in AIHA in the case of inadequate bone marrow compensation or reticulocytopenia.[21] Although this recommendation mainly comes from evidence in isolated AIHA, at least seven patients with Evans syndrome have been reported as benefiting from erythropoietin.[5,22] Consistently, immunosuppressive agents have been moved to further lines and should be considered on a case-by-case basis if the patient is not a candidate for a clinical trial and as steroid-sparing agents. The extended panel agreed that fostamatinib is a novel therapeutic option with a different mechanism of action to that of immunosuppressive and bone-marrow stimulating agents, targeting both antibody-mediated cellular cytotoxicity and B cells.[25,26] Fostamatinib can be considered in patients with Evans syndrome reporting two or more thrombocytopenia relapses, particularly in the case of previous thrombotic events. A novel treatment for cold-type AIHA, the complement inhibitor sutimlimab,[27,28] was recommended for relapses occurring within 2 years of a previous rituximab course or for further relapses. Another option is the combination of rituximab plus bendamustine, particularly in Evans syndrome secondary to lymphoproliferative disorders.[29]

Regarding supportive therapy, platelet transfusions were recommended in the case of life-threatening bleeding, whereas red blood cell units were advised in case of severe anaemia and related symptoms and according to patient comorbidities, regardless of haemoglobin threshold. The risk of alloimmunisation, associated with reduced

haemoglobin increase after transfusions and with possible febrile reactions, should be considered; thorough transfusion matching is pivotal to prevent such risk.[30]

Thromboprophylaxis is an important issue in Evans syndrome, whereby the risk of thrombosis should be balanced against the instance of severe thrombocytopenia in the absence of a specific assay to predict or evaluate this risk.[5] Although therapy and prophylaxis are largely addressed in immune thrombocytopenia,[9] no consensus exists for AIHA and Evans syndrome. The extended panel recommended primary thromboprophylaxis in patients with active AIHA and a history of previous thrombosis or additional thrombotic risk factors (particularly antiphospholipid antibodies and previous splenectomy), provided safe platelet counts exceed 30×10^9 platelets per L.

Concerning chronic idiopathic or immune neutropenia, management is mainly based on avoidance of sources of infections and prompt treatment with broad-spectrum antibiotics in case of fever or infections.[11] Long-term G-CSF and antibiotic, antiviral, and antifungal prophylaxis should be considered in neutropenic patients with severe infections; low doses of G-CSF (ie, about 50 µg twice weekly) can be considered. Additionally, the extended panel recommended that special consideration should be given to the use of rituximab and immunosuppressants in patients with neutropenic Evans syndrome, possibly suggesting the preferential use of thrombopoietin receptor agonists over rituximab in patients with autoimmune thrombocytopenia associated with autoimmune neutropenia.

In conclusion, adult Evans syndrome generally presents a more severe clinical picture than isolated primary immune cytopenias, likely mirroring a more profound immunological derangement that results in a broader immune attack against multiple antigens. Evans syndrome is harder to diagnose than isolated cytopenias, with a more complex differential diagnosis requiring extensive diagnostic tests, such as bone marrow evaluation and CT scan at onset. Although steroids and rituximab are highly effective, management of Evans syndrome is complicated by multiple relapses and a high risk of infectious and thrombotic complications, requiring clinician awareness to establish proper prophylaxis. Finally, several drugs licensed for immune cytopenias are used off label in patients with Evans syndrome, who are also often excluded from clinical trials of isolated immune cytopenias. A huge unmet need for further treatment options remains for patients with relapsed or refractory disease after rituximab administration.

Contributors

BF, WB, and MoM conceived the study. MoM was responsible for the methods. All authors participated in the conceptualisation of the statements and scoring and revised the manuscript for important intellectual content.

Declaration of interests

WB has received consultancy or advisory board honoraria and speaker's bureau from Alexion, Novartis, Agios, Pfizer, Sanofi, and Sobi. BF has received consultancy or advisory board honoraria and speaker's bureau from Agios, Alexion, Apellis, Janssen, Novartis, Roche, Samsung, Sanofi, and Sobi. HF has received research support from Sanofi and Novartis. AG has received consultancy and research funds from Agios, Bristol Myers Squibb, Novo Nordisk, Saniona, Sanofi, Pharmacosmos, Novartis, AbbVie, and Vertex Pharmaceuticals. TJG-L has received research support from Sobi, Novartis, Amgen, Grifols; speakers bureau from Sobi, Novartis, Amgen, Grifols, argenx, Sanofi, Momenta, and Alpine; and fees for participation in data safety monitoring for Novartis and Alpine. IM has received consultancy honoraria from Alexion, Janssen, Novartis, Apellis, and Sanofi. MaM has received consultancy or speaker's bureau from Alexion, argenx, Sanofi, Novartis, and Sobi. MoM has received consultancy from Gilead, Novartis, AbbVie, and Pfizer. M-EM has received research support, consultancy and speaker's bureau from Amgen, Novartis, Novo Nordisk, Sanofi, Grifols, Sobi, Takeda, and CSL Bering. MN has received speaker fees from Sobi, Novo Nordisk, Amegn, Novartis, Kedrion, Bayer, Takeda, CSL Behring, and Sanofi, and consultancy honoraria from Bayer and CSL Behring. AP has received consultancy or speaker's bureau from Sanofi, Alexion, Novartis, Sobi, Pfizer, Gilead, and Morphosys. SR has received consultancy honoraria from Sanofi, Novartis, and Alexion. NV has received speaker's bureau from Sanofi, Amgen, and Grifols. All other authors declare no competing interests.

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