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Evans syndrome: Disease awareness and clinical management in a nation-wide ITP-NET survey

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Abstract

Evans syndrome (ES) is rare and mostly treated on a "case-by-case" basis and no guidelines are available. With the aim of assessing disease awareness and current management of adult ES, a structured survey was administered to 64 clinicians from 50 Italian participating centers. Clinicians had to be involved in the management of autoimmune cytopenias and were enrolled into the ITP-NET initiative. The survey included domains on epidemiology, diagnosis, and therapy of ES and was designed to capture current practice and suggested work-up and management. Thirty clinicians who had followed a median of 5 patients (1–45)/15 years responded. The combination of AIHA plus ITP was more common than the ITP/AIHA with neutropenia ($p < .001$) and 25% of patients had an associated condition, including lymphoproliferative syndromes, autoimmune diseases, or primary immunodeficiencies. The agreement of clinicians for each diagnostic test is depicted (i.e., 100% for blood count and DAT; only 40% for anti-platelets and anti-neutrophils; 77% for bone marrow evaluation). Most clinicians reported that ES requires a specific approach compared to isolated autoimmune cytopenias, due to either a more complex pathogenesis and a higher risk of relapse and thrombotic and infectious complications. The heterogeneity of treatment choices among different physicians suggests the need for broader harmonization.

Silvia Cantoni, Francesca Palandri, and Valerio De Stefano should be considered joint last authors.

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KEYWORDS
autoimmune hemolytic anemia (AIHA), chronic idiopathic/autoimmune neutropenia (CIN/AIN), Evans syndrome, immune thrombocytopenia (ITP)

1 | INTRODUCTION

Evans syndrome (ES) is defined by the concomitant or subsequent association of two or more immune cytopenias, namely autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and chronic idiopathic/autoimmune neutropenia (CIN/AIN).[1] ES is rare, with an estimated incidence of 1–9 cases per million people per year, and an associated condition may be observed in about half of cases, including infections, inborn errors of immunity, other autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), lymphoproliferative neoplasms, and transplant.[2,3] While in children disease features and outcomes are well studied in prospective registries,[4–6] less is known about adult patients, with only three retrospective series published so far.[3,7,8] As a result, most clinicians tend to treat the actual autoimmune cytopenia on a case-by-case basis, notwithstanding the different pathogenesis and outcomes of ES. In this multicenter study, we investigated disease awareness and clinical management of adult ES in Italy with the aim to harmonize its diagnosis and treatment.

2 | METHODS

A structured survey was drawn, consisting of three domains: (1) epidemiology, investigating experts' demographics and experience in the management of ES; (2) diagnosis, evaluating the agreement of the experts on a certain diagnostic test/procedure; and (3) therapy of ES, assessing the agreement of the experts on a certain therapeutic settings encountered in the management of ES. The survey was administered to all Italian Centers participating in the ITP-NET initiative. These centers included clinicians expert in the management of autoimmune cytopenias (i.e., dedicating >50% of their practice to follow patients with autoimmune cytopenias). The survey included 11, 8, and 16 multiple-choice questions for each domain respectively (Supplementary Materials). The survey underwent three rounds of validation among eight experts, and it was then shared with 64 clinicians from 50 centers through the ITP-NET forum. The results were analyzed using descriptive statistics and circulated among the centers for approval.

3 | RESULTS

Between December 2022 and February 2023, the survey was completed by 30 clinicians from 29 Italian hospitals. These clinicians worked across Italy in 23 different cities, including 17 university hospitals and 13 public hospitals. They had followed a median of 5 ES patients in the last 15 years, with a range of 1–45 patients. The most commonly reported type of ES was the association of AIHA and ITP, with a mean of 9 patients per center compared to 2.8 patients per center for AIHA + CIN or ITP + CIN, and this difference was statistically significant ($p < .001$). Twenty-five percent of patients had an associated condition, including lymphoproliferative disorders ($n = 16$), other autoimmune diseases ($n = 15$), inborn errors of immunity ($n = 14$), solid tumors ($n = 6$), and stem cell transplant ($n = 5$), and nearly all required treatment. Table 1 shows the level of agreement for each diagnostic test. The diagnostic tests that were most commonly advised included a complete blood count, and a direct antiglobulin test (DAT), which were indicated by all clinicians. Coagulation tests, peripheral blood smear, serum electrophoresis, total IgG, IgA, and IgM dosage, antinuclear antibodies (ANA), extractable nuclear antigen (ENA) antibodies, anti-DNA, anti-phospholipid antibodies, and thyroid function and autoantibodies were also commonly employed, with over 80% of clinicians indicating their use. However, only 40% of clinicians indicated the use of anti-platelets (Anti-PLT) and anti-neutrophil (anti-N) autoantibodies tests. Regarding imaging, over 60% of clinicians suggested an abdomen ultrasound and chest x-ray, while only 43% suggested a contrast-enhanced CT scan. Finally, 77% of clinicians indicated bone marrow evaluation at diagnosis (80% both

TABLE 1 Diagnostic procedures in adult ES patients.

Diagnostic test	*N* of indications	% of agreement
Laboratory		
Complete blood count	30	100
Direct antiglobulin test	30	100
ANA/ENA/anti-DNA	29	97
Serum electrophoresis	28	93
IgG/IgA/IgM	27	90
Blood smear	25	83
Coagulation parameters	25	83
Anti-phospholipid antibodies	25	83
Thyroid function/antibodies	25	83
Anti-platelet autoantibodies	13	43
Anti-neutrophils antibodies	11	37
Imaging		
Abdomen ultrasound	22	73
Thorax x-ray	19	63
Whole body CT scan	13	43
Bone marrow evaluation		
Bone marrow aspirate	28	93
Bone marrow trephine	26	87
Both tests	24	80
At diagnosis/at relapse	23/7	77/23

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aspirate and trephine biopsy), while only 23% indicated bone marrow evaluation at relapse.

Concerning therapy for ES, 96% of clinicians surveyed believed that ES requires a specific approach compared to isolated autoimmune cytopenias. This is mainly due to the different risk of relapse/complications for 63% of them. Additionally, 76% of respondents recognized that ES displays a more complex immunopathology.

Various treatment scenarios were proposed, and the clinicians were asked to vote on whether they agreed or not (Table 2). Only the following treatment scenarios reached >50% agreement: for ITP relapse, 60% suggested to repeat steroids if >12 months from previous cytopenia, and to start a second line (with no differences among thrombopoietin receptor agonists, TPO-RA, rituximab, or fostamatinib) if <12 months from previous ES exacerbation. For AIHA relapse, 57% suggested to differentiate treatment according to AIHA type (steroids in warm forms, rituximab in cold ones), and 80% recommended to consider recombinant erythropoietin for inadequate reticulocytosis.

Regarding further therapy lines, more than 80% of clinicians indicated that rituximab and splenectomy may have a higher infectious risk if associated conditions (such as inborn errors of immunity) or neutropenia are present. It was also suggested that TPO-RA and splenectomy may have a higher thrombotic risk (by 66% and 90% of respondents, respectively) in case of additional risk factors (such as bed rest, obesity, etc.), active hemolysis, or platelet oscillations. Thirty percent of the respondents indicated that fostamatinib may be useful in ES at thrombocytopenia relapse, given its efficacy also in AIHA. No clear agreement was reached for anti-microbial or G-CSF prophylaxis in patients with neutropenia.

Finally, more than 60% of clinicians advised anti-thrombotic prophylaxis in ES during severe COVID-19 infection. More than 70% agreed that vaccination is not contraindicated but may be deferred in case of active hemolysis (i.e., anemia and LDH >1.5 × upper limit of normal) and/or platelets <30 × 10^9/L.

TABLE 2 Therapy choices in patients with Evans syndrome according to the relapsing cytopenia.

ITP relapse	Repeat steroids +/− IVIG	6 (20)
	Choose 2nd line	6 (20)
	Steroids if >12 months and 2nd line if <12 months	18 (60)
	Rituximab if previous AIHA	10 (33)
	Rituximab if young woman with positive anti-PLT Ab	12 (40)
	Rituximab if <6 months from diagnosis	11 (37)
	TPO-RA if >6 months from diagnosis	8 (27)
	TPO-RA after evaluation of risk factor for thrombosis	16 (53)
	Splenectomy if young/no comorbid >12 months from diagnosis	7 (23)
	Fostamatinib since also active in AIHA	9 (30)
AIHA relapse	Repeat steroids	2 (7)
	Rituximab	11 (37)
	Steroids for wAIHA and rituximab for CAD	17 (57)
	No EPO	6 (20)
	EPO, if inadequate Retics only at relapse	6 (20)
	EPO, if inadequate Retics at diagnosis and relapse	18 (60)
Prophylaxis in CIN/AIN	Antibiotics/antiviral for ANC <1000/mmc and >2 G3 infections	3 (10)
	Antibiotics/antiviral for ANC <500/mmc and >2 G3 infections	15 (50)
	G-CSF for ANC <1000/mmc and >2 G3 infections	1 (3)
	G-CSF for ANC <500/mmc and >2 G3 infections	11 (37)

Note: Numbers indicate responding clinicians (%). Multiple responses were possible.

Abbreviations: AIHA, autoimmune hemolytic anemia; ANC, absolute neutrophil counts; CAD, cold agglutinin disease; CIN/AIN, chronic idiopathic/autoimmune neutropenia; EPO, recombinant erythropoietin; G-CSF, granulocyte colonies stimulating factor; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonists; wAIHA, warm type AIHA.

4 | DISCUSSION AND CONCLUSIONS

This multicentric survey conducted among ITP experts highlights the rarity of ES. In fact, the results showed that the respondents observed a median of only 5 patients with ES in 15 years, making it hard to build experience in managing this disease. Additionally, the heterogeneity of the disease, where two or three cytopenias may present concomitantly or subsequently and in various combinations,[1–3,7,8] further complicates the management. The most common association was found to be between AIHA and ITP, as already reported,[7,8] but during discussions, clinicians reported that CIN is a likely underestimated event in patients with AIHA and ITP, often observed but disregarded given spontaneous fluctuations and absence of specific treatment. The rate of associated conditions in this study was lower than previously reported (25% vs. 50%–60%),[7,8] likely reflecting the heterogeneity in the diagnostic workup among centers. This underlines the usefulness of a deeper diagnostic workup in ES as compared to isolated cytopenias. Respondents suggested several tests, including peripheral blood smears, coagulation assays, and bone marrow evaluation, to aid in the differential diagnosis of bicytopenias from common nutrients-deficiencies to rarer ones needing acute management such as thrombotic microangiopathies. Considering the clinical impact of the latter, and the need of life-saving measures, a peripheral blood smear is recommended in all patients presenting with thrombocytopenia and hemolysis. Interestingly, bone marrow evaluation (including morphologic aspirate and trephine) was suggested by >80% of clinicians at ES diagnosis, differently from what is generally recommended for isolated ITP and AIHA in which the procedure is generally reserved for relapsing/refractory cases.[9,10] This is due to the reported association with lymphoproliferative disorders, as well as for the differential

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diagnosis of bone marrow failure syndromes that may present with bi- or pancytopenia. Autoantibody testing for the identification of the autoimmune nature of cytopenias was considered of little value due to the limited availability and sensitivity/specificity of the tests, apart for the recognized value of DAT. While this is agreed for ITP,[9] recent European guidelines for the diagnosis of neutropenia suggest anti-neutrophil testing and re-testing in patients with less than 1×10^9/L neutrophils.[11] Notably, anti-platelet and anti-neutrophil autoantibodies are not performed at all centers, with possible implications on accessibility. TSH screening belongs to the work-up of unexplained cytopenia and, if altered, should be followed by anti-thyroid autoantibodies screening in a stepwise manner. Finally, it is important to consider the possibility of an underlying inborn error of immunity, even in adults, when hypogammaglobulinemia and signs of lymphoid proliferation are present. This is because autoimmunity in young adults can be an early "red flag."[2,11] Although, age at presentation may influence diagnostic work-up, since inborn errors of immunity are more frequent in younger adult patients while hematologic neoplasms in elderly ones, the clinical suspicion for associated conditions should remain high and broad, since several exceptions exist.

Harnessing treatment for ES patients presenting with one cytopenia and relapsing with another, as well as for those experiencing concomitant events, can be particularly challenging. In fact, a great heterogeneity was noted regarding therapy choice as compared to diagnostic work-up. A high awareness of the great risk of relapse after first line, >70% in recent reports,[8] as well as of thrombotic and infectious complications, >30%,[7,8] emerged from the survey. This highlights the unmet need for a treatment, or combination of treatments, that can induce a durable response in ES patients while minimizing the use of immunosuppression and cytotoxic agents. One possible strategy is the use of recombinant erythropoietin and TPO-RA for hemolytic anemias and thrombocytopenia relapses, respectively. However, TPO-RA may show higher frequency of platelet oscillations and thrombosis in ES versus primary ITP and deserve a proper monitoring.[12] Fostamatinib does not increase thrombotic risk, is indicated for relapsed/refractory primary ITP, and showed some efficacy also in wAIHA. It might be appealing for ES, although the phase 3 trial in wAIHA did not meet the primary endpoint.[13] All in all, the high risk of thrombotic and infectious complications in ES warrants a continuous risk/benefit balance while considering potentially thrombogenic (i.e., TPO-RA, splenectomy, recombinant erythropoietin) or immunosuppressive treatments (rituximab, splenectomy, cytotoxic immunosuppressants). A broader implementation of anti-thrombotic and anti-infective prophylaxis might mitigate the risk and allow the use of such treatments, potentially effective in both AIHA and ITP.

Finally, several ES relapses or de novo cases were reported during COVID19 pandemia; postponing anti-SARS-CoV-2 vaccines in case of active hemolysis and severe thrombocytopenia was suggested in the survey, in line with recent recommendations.[14]

We reckon that this study carries several limitations including the limited number of patients followed by each respondent, the nature of a "multiple-choice" survey and the difficulties of considering each specific scenario of cytopenia combinations and associated conditions, that may require tailored work-up and therapeutic approach. Broader consensus efforts will be necessary to further address ES management.

In conclusion, this survey-based study highlights a high awareness of disease features and complications among Italian experts and aids to build a rationale workup for ES in adults. The heterogeneity of treatment choices among different physicians suggests the need for broader harmonization.

AUTHOR CONTRIBUTIONS

BF, VC, MC, SC, FP, and VDS designed the survey, collected data. BF wrote the paper. All authors participated to the survey, revised the manuscript for important intellectual content and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data have been included in the manuscript and further information may be obtained upon reasonable request to the corresponding author.

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