Adult Evans' Syndrome

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KEYWORDS

• Evans syndrome • Autoimmune cytopenia • Autoimmune hemolytic anemia
• Immune thrombocytopenic purpura • Autoimmune neutropenia
• Primary immunodeficiencies

KEY POINTS

- The differential diagnosis of Evans syndrome includes thrombotic thrombocytopenic purpura and the analysis of the blood smear is very important.
- Evans syndrome during childhood is frequently associated with an inborn error or immunity.
- Secondary cases of Evans syndrome in adults represent 20% to 50% of all cases.
- Rituximab is the best second-line treatment option for adult onset Evans syndrome.

DEFINITION AND EPIDEMIOLOGY

Evans syndrome (ES) which was first described by Evans in 1951[1] is a rare auto-immune disease defined as the concomitant or sequential occurrence of immune thrombocytopenia (ITP) and warm autoimmune haemolytic anemia (wAIHA) ± autoimmune neutropenia (AIN) which is present in about 20% of the patients.[2] Autoimmune cytopenias (AIC) may occur either simultaneously in 30% to 50% of the cases[2,3] or sequentially with a mean delay between both cytopenias of 3 years,[4] ITP preceding wAIHA in about a third of the cases %.[2,3] The 3 cytopenias occur concomitantly in only 10% of the cases.[3] The mean delay between the different AIC is of 3 years, but is highly variable.[3,4] ES can be either isolated and defined as primary or secondary if associated with an underlying disease.[3] As for wAIHA,[5] the rate of secondary ES is known varies from 20% to 50% based on the data from the literature.[2,3] Underlying associated conditions are mostly represented by lymphoproliferative disorders (LPD) and systemic lupus erythematosus (SLE) in adults,[2,3] whereas ES in children often reveals and underlying primary immunodeficiency/inborn errors of immunity.[6]

In a recent Danish nationwide epidemiologic study focused on ES, mean age at diagnosis was 58.5 years at diagnosis[7] in keeping with a previous report of 68 adults

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Hematol Oncol Clin N Am 36 (2022) 381–392
https://doi.org/10.1016/j.hoc.2021.12.004 **hemonc.theclinics.com**

with ES,[3] sex ratio was close to 1 (51.2% of women), whereas only 27.3% of the cases were classified as secondary. The annual estimated incidence of ES in Denmark was 1.8 per million person-years with a prevalence of 21.30 per million individuals.[7] When considering isolated AIC, ES represents 0.3% to 7% of AIHA and approximately 2% to 2.7% of all ITP cases.[3,7,8]

DIAGNOSIS OF EVANS SYNDROME

When ITP and wAIHA occur sequentially, each AIC is diagnosed based on usual criteria[5,9] and the diagnosis of ES is considered when the second AIC occurs. As a reminder, the diagnosis of ITP is one of the exclusion in the presence of isolated thrombocytopenia (platelet count $<100 \times 10^9$/L)[9] while the diagnosis of wAIHA implies not only the presence of a newly diagnosed hemolytic anemia but also the positivity of the direct antiglobulin test (DAT) with an IgG or IgG + C3d pattern.[5] When both cytopenias and pancytopenia occur simultaneously in a patient with no previous medical history the diagnosis may be more difficult and some differential diagnosis must be ruled out. Patients with ES may clinically present with both nonspecific symptoms of hemolytic anemia (fatigue, exertional dyspnea, jaundice ± dark urine) and/or bleeding manifestations including petechiae, spontaneous bruises ± gum bleeding and oral bullae and/or epistaxis in case of profound thrombocytopenia. Mild splenomegaly is present at onset in approximately 1/3 of the patients[2] especially in the case of active wAIHA. It must be emphasized that no organ dysfunction/failure, headache, or fever are usually observed in patients with ES except in the very rare event of intracranial hemorrhage. In the presence of concomitant thrombocytopenia and hemolytic anemia, the first step of the diagnostic procedure is to check both the renal function and the peripheral blood smear.[4] In typical ES, renal function is normal and there are no or very few schistocytes on the smear and as for isolated wAIHA, some spherocytes can be observed.[10] The presence of spherocytes reflect the partial phagocytosis of autologous RBCs opsonized by autoantibodies.[5] Another common feature seen on the blood smear in ES being poikilocytosis. In the presence of numerous schistocytes (>10% of RBCs), the diagnosis of thrombotic microangiopathy (TMA) and especially thrombotic thrombocytopenic purpura (TTP) must be suspected. When schistocytes are initially absent or present in a low number and the diagnosis is not obvious, the assessment of schistocytes on blood smear must be repeated over a few days and the diagnoses of ES should be promptly reconsidered especially when first-line treatments are ineffective.[11] When clinical and biological features of TMA are present, based on the French score and/or the PLASMIC score, the presence or absence of organ damage, the level of serum creatinine and the severity of thrombocytopenia are particularly helpful for distinguishing between typical or atypical hemolytic uremic syndrome (HUS) and TTP.[12] When ES occurs during pregnancy[13] and especially at the 3rd trimester other diagnosis such as HELLP (Hemolysis with Elevated Liver enzymes and Low Platelet count) syndrome and preeclampsia must be ruled out. Another diagnosis that may mimic TTP and ES is catastrophic antiphospholipid syndrome (CAPS).[14] The distinguishing features between ES, TTP, and CAPS entities are summarized in **Table 1**. Of note, patients with an underlying SLE are particularly at risk of developing such complications and they have a positive DAT at baseline and develop TTP or CAPS rather than ES.[14,15]

Among other differential diagnoses of ES, marked macrocytic anemia with markers of hemolysis (ie, high LDH level due to ineffective erythropoiesis in the marrow) and mild thrombocytopenia with the presence of numerous schistocytes on the blood smear may also rarely reveal vitamin B12 deficiency.[16] The high level of the mean

Table 1
Distinguishing clinical and biological features between Evans syndrome, acquired autoimmune thrombotic thrombocytopenic purpura, and CAPS

	Evans Syndrome	Acquired Thrombotic Thrombocytopenic Purpura (aTTP)	Catastrophic Antiphospholipid Syndrome (CAPS)
Patient's profile: gender, mean age	Women (60%), 55 y	Women (70%), 40–45 y	Women (70%), 35 y, Underlying SLE (40%)
Organ failure	NO	YES + (kidney, central nervous system, heart)	YES ++ by definition (kidney, central nervous system, hear, lung)
Platelet count $<30 \times 10^9$/L Severity of hemolytic anemia	Frequent mild to severe (can be life-threatening)	Frequent mild	Rare mild
Bleeding manifestations	Frequent and sometimes severe when the platelet count is $<20 \times 10^9$/L	Absent or mild	Absent ou minor
Acute renal insufficiency	Absent	Minimal to mild	Mild to severe
Severe hypertension	NO	NO	Frequent
Schizocyte on the blood smear	Absents of few	+ to +++	++
Direct antiglobulin test	Strongly positive in ~ 95% of the cases	Rarely weakly positive (10%–15%)	Usually negative, rarely weekly +
ADAMTS13 activity	Normal	$\leq$ 10%	Normal or mildly decreased

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin type 1 motifs; member, 13; SLE, systemic lupus erythematosus.

corpuscular volume (MCV) associated with a normal reticulocyte count and the absence of organ failure and bleeding manifestations make this hypothesis more likely than TTP of ES.[16]

The next step of the diagnostic procedure is based on the result of the DAT which is classically strongly positive, mostly with an IgG or IgG + C3d pattern in 85% of the cases in keeping with wAIHA.[2] About 5% of patients with ES may have a mixed AIHA subtype or even (~5% of the case) a DAT that is only C3d positive with the presence of cold agglutinins at a significant titer.[2] As for isolated AIHA, the DAT may be negative in about 5% of the cases in ES and in that such other causes of acquired of hemolytic anemia such as paroxysmal nocturnal hemoglobinuria (PNH) must be ruled out, and a PNH clone must be looked for by means of flow cytometry.[17] On the other hand, the DAT may be weekly positive in definite cases of TTP and that can be a source of misdiagnosis which can be avoided by testing rapidly ADAMTS13 activity which is by definition constantly strongly decreased ($\leq$10%) in TTP.[11] Overall, the absence of schistocytes on the blood smear and a strongly positive DAT in a

patient that has not received recently a transfusion of packed red cells makes the diagnosis of ES very likely. **Table 1** summarizes the main distinguishing features between ES, TTP, and CAPS at the time of disease onset.

Most of the time, when ITP and wAIHA occur concomitantly with typical features of hemolysis are present and reticulocytosis (ie, reticulocytes count >120 $\times$ 10^9/L), there is no need to systematically perform a marrow aspirate ($\pm$karyotype) or biopsy for confirming ES. Conversely, when ES presents only with ITP and AIN or if there are some atypical features (atypical lymphocytes, pseudo-Pelger–Huët anomalies…) on the smear and an LPD with a concomitant bone marrow involvement or an associated myelodysplastic syndrome is suspected, performing a marrow analysis is relevant.[4,5] An s for primary ITP, there is usually no need to look for the presence of antiplatelet antibodies by means of MAIPA (monoclonal antibody-specific immobilization of platelet antigen) in ES when other common causes of thrombocytopenia (liver disease, TMA, coagulopathy…) have been excluded as their specificity is not optimal and the sensitivity of the assay is rather low.[9] When neutropenia is present in combination with thrombocytopenia and/or hemolytic anemia in the setting of ES, there is no consensus about the utility of searching for the presence of antibodies directed toward neutrophils by means of MAIGA (monoclonal antibody-specific immobilization of platelet antigen).[18]

PRIMARY OR SECONDARY EVANS SYNDROME

Once the diagnosis of ES is confirmed and an appropriate treatment has been initiated, the next step of the diagnostic procedure is to search for an underlying disease or condition that may influence both the treatment and the outcome of ES.[4] The occurrence of several AIC in a single patient reflects an important immune dysregulation toward self-antigens and the rate of secondary ES may vary from 20% to more than 50% according to the age population and the intensity of the workup that is performed at the time of disease onset.[2,3,19]

The main causes of secondary ES are summarized in **Box 1**. In children and adolescents, primary immunodeficiencies (PID), now most often renamed human inborn errors of immunity or IEIs,[20] are by far the most frequent causes of ES.[7,21] Common variable immunodeficiency (CVID) is known to be associated with an increased risk of autoimmunity and especially of immune cytopenias including ES[7,22] and, as for primary ITP and wAIHA, checking the level of gammaglobulin in the serum in every child diagnosed with ES before using intravenous immunoglobulin (IVIg) has become a standard and a good practice. The reasons why patients with hypogammaglobulinemia in the setting of CVID or other IEIs are at high risk of autoimmunity and especially of immune cytopenias are far from being fully understood.[23] Autoimmune lymphoproliferative syndrome (ALPS) is also known to cause ES[24] and looking for the presence of excess (>5%) TCR$\alpha\beta^+$ $CD3^+$ $CD4^-$/$CD8^-$ double-negative T cells at disease onset should, therefore, be standard of care in children diagnosed with ES, ideally before the use of high dose of corticosteroids. In the last decade, the extended use of next-generation sequencing (NGS) and whole exome sequencing (WES) has led to the discovery and description of several new genetic defects that may be associated with an increased risk of ES such as CTLA4 (cytotoxic T-lymphocyte-associated protein 4) and LRBA (LPS Responsive Beige-Like Anchor Protein) defects or SOCS1 (suppressor of cytokine signaling 1) haploinsufficiency.[6,25] It is, therefore, very important that physicians who are involved in the management of pediatric ES be aware of the need of looking for possible consanguinity and/or a history of AIC, LPD among relatives throughout a family tree.

Box 1
Main disorders or conditions associated with Evans' syndrome (secondary cases)

1. Lymphoproliferative diseases and other hematologic diseases:
   a. Chronic lymphoid leukemia T-cell LGL leukemia
   b. B-cell lymphoma/Hodgkin lymphoma
   c. Angioimmunoblastic T cell lymphoma
   d. Castleman disease
   e. Chronic myelomonocytic leukemia
2. *Solid tumors*: Thymoma/ovarian dermoid cyst/carcinoma
3. Auto-immune and inflammatory diseases
   a. Systemic lupus erythematosus/Antiphospholipid syndrome
   b. The connective tissue diseases
   c. Ulcerative colitis/Crohn's disease
4. Infections:
   Virus: Ebstein Barr virus/hepatitis C/cytomegalovirus, SARS-CoV-2
5. *Drugs*: checkpoint inhibitors (anti-PD1: nivolumab)
6. Primary immunodeficiencies/inborn errors of immunity
   a. Common variable immunodeficiency
   b. Hyper IgM syndrome[a]/ALPS[a]
   c. CTLA4 deficiency[a], LRBA deficiency[a], SOCS1 haploinsufficiency[a]
   d. IPEX syndrome[a]/APECED syndrome[a]
7. Others:
   a. Postallogenic bone marrow transplantation
   b. Pregnancy
   c. Kabuki syndrome[a]

Abbreviations: ALPS, Autoimmune lymphoproliferative syndrome; APECED, Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy; IPEX, immune dysregulation, Polyendocrinopathy; Enteropathy X-linked; LGL, large granular lymphocytes.

[a] Almost exclusively diagnosed revealed by ES during childhood or adolescence.

While the diagnosis of ALPS in young adults is possible,[24] CVID is by far the most frequent PID diagnosed in adulthood.[22] Regarding LPDs, B-cell lymphomas, and especially chronic lymphocytic leukemia (CLL) are the most frequent causes of ES[26–28] and therefore, immunophenotyping of B cells should be performed in every adult patient diagnosed with ES and lymphoma must be suspected in a patient with ES and disproportionate splenomegaly and/or lymph nodes. ES has been reported in up to 2.9% in a cohort of patients with CLL. In half of the cases, autoimmune cytopenias occurred simultaneously and revealed CLL in 25% of cases.[27] The median age at ES diagnosis was 66 years and 60% of patients were male. Although there was no difference regarding demographic or Binet stage between patients with or without ES; patient with CLL-associated ES had more frequently immunologic and/or genetic markers of poor prognosis at CLL diagnosis, such as a higher expression of ZAP-70, an increase in unmutated IGHV, del (17) or TP53 mutation leading to the reduction of their overall survival.[27] While other types of B cell lymphoma[28] or T-cell lymphoma[29] may seldom be associated with ES, occurrence of ES in patients with a history of Hodgkin lymphoma is very rare unless they had autologous stem cell transplantation.[4]

Another classical cause of ES in adults is SLE[3,10] and therefore, searching for the presence of positive antinuclear antibodies should be systematic at the time of ES. Regarding infections that may trigger ES, SARS-CoV-2 has been recently recognized

as a potential cause of ES.[30] Drug-induced ES is excessively rare but the increased use of checkpoint inhibitors in oncology and especially the anti-PD1 nivolumab has been associated with an increased risk of ITP/AIHA that may seldom occur concomitantly.[31] There is no consensus about the workup that should be performed in every patient with ES to look for an underlying cause and the need for a systematic bone marrow aspirate or biopsy is a matter of debate as up to 39% of the patients displayed features of underlying myelodysplasia in the recent series from Fatizzo and colleagues.[2] By analogy with the one recommended for wAIHA,[5] a proposal of workup for ES is provided in **Table 2**. Although the onset of ES may sometimes precede by many months or years the occurrence of an LPD[28] or SLE,[32] there are no specific recommendations about the necessity of repeating the initial workup at regular intervals during follow-up.

MANAGEMENT OF ADULT EVANS SYNDROME

ES runs a chronic course (>1 year) in more than 80% of the cases, with multiple relapses.[2,4] Despite continuous progress in the management of AIC and a gradual increase in ES survival, the mortality due to ES which is 20% to 24%[2,3] remains higher than the ones of isolated AIC, the main causes of deaths being infections,

Table 2
Recommendations for the diagnosis of secondary Evans syndrome in adults

Disease or Condition	Tests to be Performed Systematically	Tests to be Considered Only in Some Circumstances
SLE and other autoimmune diseases	• **Antinuclear Abs (ANA)** and if + with titer >1/80: anti-dsDNA Abs and other specificities	• Lupus anticoagulant • Anticardiolipin Abs • Anti-β2gpI Abs (only for patients with overt SLE, strongly positive ANA or past history of thrombosis) • CH50, C3, and C4 in case of SLE
Lymphoproliferative disorders and solid tumors	• **Blood smear** (increase rate of LGL?) • **Serum protein electrophoresis** • **Immunoelectrophoresis** • **Immunophenotyping of B lymphocytes** from peripheral blood • [a]**CT scan** (chest/abdomen/pelvis)	• Bone marrow biopsy ≥especially in the presence of monoclonal gammopathy or hypogammaglobulinemia and/or lymph nodes and/or disproportionate splenomegaly on the CT scan and/or monotypic lymphocytes population • Lymph node biopsy • TEP-scan
Primary immunodeficiency	• **IgG, IgA and IgM levels**	• Extended phenotype of T/NK and memory B cells • Postvaccine (eg, tetanus toxoid, pneumococcal) serologies
Infections	• **HIV, HCV, and (HBV)[b] tests**	• CMV, EBV, Parvovirus B19, SARS-CoV-2, and others based on clinical and/or biological evidence

Abbreviations: Abs, antibodies; ds, double strand; LGL, large granular lymphocytes; SLE, systemic lupus erythematosus.
[a] Unless diagnosis of SLE is obvious.
[b] Mostly pretherapeutic.

thromboembolic events and bleeding and the main predictor of mortality in adults is the severity of AIHA at diagnosis[2,3]

Primary Evans syndrome

The management of patients with ES is mainly extrapolated from the one of the ITP and wAIHA or based on retrospective case series and when both cytopenias occur sequentially, they are treated as single cytopenias according to consensual recommendations of guidelines.[5,9] When both cytopenias occur concomitantly in the setting of primary ES, treatment is most often indicated as spontaneous remissions or durable compensated hemolysis with a stable Hb level above 10 g/dL is very uncommon.[5] Corticosteroids remain the cornerstone of first-line treatment predniso(lo)ne at the initial daily dose of 1 mg/kg is the standard of care. The efficacy of repeated courses of dexamethasone toward predniso(lo)ne has not been specifically tested in ES, but based on the data available in ITP,[33] it can be viewed as a relevant alternative. In case of severe bleeding manifestations, the use of IVIg at a dose of 1 to 2 g/kg in combination with corticosteroids is required to avoid a life-threatening hemorrhage,[9] whereas IVIg has only a little efficacy for the management of severe wAIHA.[34] For patients with severe wAIHA, transfusion, or packed RBCs must not be postponed,[35] and the transient use of recombinant erythropoietin may be useful for those patients with severe wAIHA an inadequate reticulocytosis.[36] Predniso(lo)ne is usually maintained at the initial dose for 3 weeks followed by progressive weaning over at least a 3 months as usually recommended for adult wAIHA.[5] For patients not responding to predniso(lo)ne, the daily dose can be transiently increased up to a maximum of 2 mg/kg, although the efficacy of such a dose has never been fully demonstrated. Most of the patients (~80%) have an initial response, but the time to response and the magnitude of response on the platelet count on one side and hemoglobin levels and parameters of hemolysis in the other side, may be significantly different, and differential patterns of response are not uncommon.[3] In the absence of initial response (~20% of the patients), or in case of corticosteroid-dependency with the need of maintaining a daily dose of predniso(lo)ne of more than 10 mg to maintain at least a partial response (ie, a platelet count $\geq 30 \times 10^9$/L with at least a doubling of the initial count and/or a Hb level $\geq$10 g/dL with a least a 2 g increase from baseline), a second-line therapy is needed. Overall, 60% to 76% of adult with ES require a second line.[2] Although rituximab is not licensed for ITP and/or AIHA, its efficacy and good safety profile have been shown throughout randomized prospective studies.[36–38] To a lesser extent, the efficacy of rituximab has only be reported in both adult and pediatric ES based on retrospective studies[2,3,39] with an overall response rate (ORR) reaching up 96% in some series.[2] For patients not responding to rituximab, the 3rd treatment-line option can be either the use of an immunosuppressant such as azathioprine, cyclosporin or mycophenolate mofetil or yet splenectomy.[2–4] There is not enough data available in ES for recommending a specific immunosuppressant, and the choice mostly relies on the expected risk over benefit ratio on an individual basis as well as on the experience of the treating physician. The ORR with splenectomy varies from 52% to 100% according to the series from the literature[2,3,40] and for ES not responding to rituximab with the sustained activity of both itp and wAIHA, splenectomy definitely remains a good option. When only itp remains active and symptomatic after corticosteroids $\pm$ rituximab, the use of a thrombopoietin receptor agonist (TpoRA) such as eltrombopag or romiplostim is relevant and effective.[2] For patients with multi-refractory ES, targeting long-lived autoreactive plasma cells by means of bortezomib combined with dexamethasone[41,42] or daratumumab[43] may be a

good option. Another option in the future could also be to use fostamatinib, a spleen tyrosine kinase (*syk*) inhibitor that has been approved for adult' primary ITP and that has also shown a promising efficacy for wAIHA in a phase II trial.[44] Other treatment approaches currently developed in both ITP and wAIHA such as FcRn or complement inhibitors could also find a place in the future for the treatment of ES. An algorithm for the management of primary adult ES is provided in **Fig. 1**.

Secondary Evans syndrome

The management of patients with secondary ES must take into account the nature and activity of the underlying/associated disorder. For SLE or CVID-associated ES, the initial strategy is similar to the one of the primary ES, rituximab being a good corticosteroid-sparing 2nd line option[45,46] while splenectomy is not recommended in those settings. If ES occurs in patient with an underlying active SLE with a previous or concomitant history of lupus nephritis, the use of mycophenolate mofetil in combination with prednisone is more relevant.[32] When rituximab is given for treating a patient with ES who has an underlying CVID, replacement therapy with subcutaneous Ig must be systematic to avoid severe infections.[46] Moreover, Tpo-RAs should be used with caution in patients with SLE or APS-associated ES and active itp as there is in increased risk of thrombosis in that setting.[47] For patients with CLL or lymphoma-associated ES, the management of ES must obviously take into account the activity and stage of clonal LPD[27,28] and some regimens combining for example, rituximab + cyclophosphamide and dexamethasone can be helpful for treating CLL-associated ES.[48] For young patients with ALPS, sirolimus may be a good option,[49] whereas splenectomy must be avoided as the risk of overwhelming postsplenectomy infections is very high in this patient population.

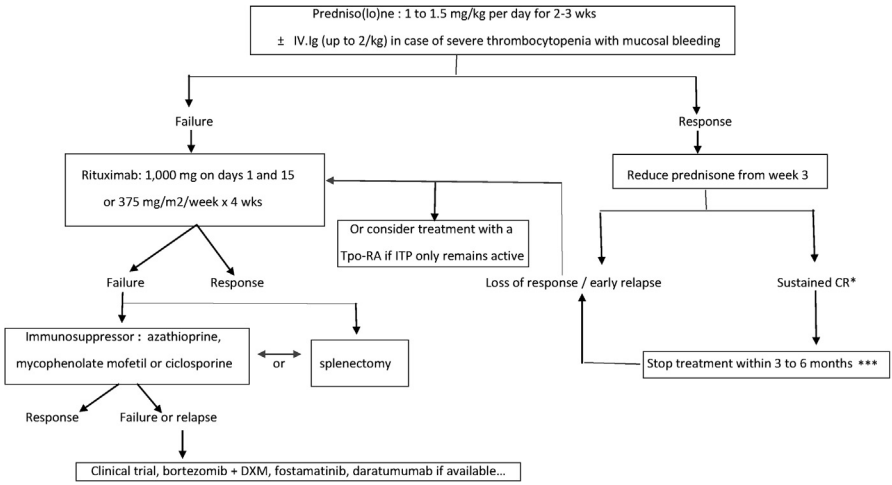

Fig. 1. Proposed algorithm for the treatment of *primary* Evans syndrome* with concomitant AIHA and ITP ± AIN in adults. *Excluding especially patients with an underlying lymphoma or with some immunodeficiencies for which rituximab and/or splenectomy may be contraindicated; ** Complete response = Hemoglobin level greater than 12 g/dL without ongoing hemolysis and platelet count $\geq 100 \times 10^9$/L; *** if a daily dose of predni(solo)ne ≤ 10 mg is sufficient to maintain the hemoglobin level above 10 g/dL and the platelet count greater than 30×10^9/L, it can be maintained on a long-term.

SUMMARY

Evans syndrome is a very rare autoimmune condition reflecting a major breakdown of immune self-tolerance. ES can be life-threatening with an overall mortality rate of approximately 20% and it is associated with a high rate of severe infections and thrombosis. The diagnosis of ES may be difficult and requires a minimal initial workup to rule-out some other diagnoses of bi-cytopenia (ie, thrombocytopenia + hemolytic anemia) and mostly thrombotic microangiopathies. The rate of secondary ES varies from 20 to up to 50% among adults and searching accurately for an underlying disease at the time of diagnosis is important as it may have an impact on both the prognosis and management. The management of ES is mostly extrapolated from the standard of care of both ITP and wAIHA which is currently rapidly evolving. An increasing number of inborn errors of immunity have been described in the last decade especially among children or adolescents with ES, and these new insights are helpful for a better comprehension of the pathophysiology of ES also in adults and preclude the use of more targeted therapies in the future.

REFERENCES

1. Evans RS, Takahashi K, Duane RT, et al. Primary thrombocytopenic purpura and acquired hemolytic anemia; evidence for a common etiology. AMA Arch Intern Med 1951;87:48–65.
2. Fattizzo B, Michel M, Giannotta JA, et al. Evans syndrome in adults: an observational multicentre study. Blood Adv 2021;5(24):5468–78.
3. Michel M, Chanet V, Dechartres A, et al. The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases. Blood 2009;114:3167–72.
4. Audia S, Grienay N, Mounier M, et al. Evans' syndrome: from diagnosis to treatment. J Clin Med 2020;9(12):3851.
5. Jager U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the first international consensus meeting. Blood Rev 2020;41:16648.
6. Hadjadj J, Aladjidi N, Fernandes H, et al. Pediatric Evans syndrome is associated with a high frequency of potentially damaging variants in immune genes. Blood 2019;134:9–21.
7. Hansen DL, Moller S, Andersen K, et al. Evans syndrome in adults - incidence, prevalence, and survival in a nationwide cohort. Am J Hematol 2019;94:1081–90.
8. Barcellini W, Fattizzo B, Zaninoni A, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood 2014;124:2930–6.
9. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 2019;3:3780–817.
10. Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: new insights based on a single-center experience with 60 patients. Am J Hematol 2014;89:E150–5.
11. Grall M, Azoulay E, Galicier L, et al. Thrombotic thrombocytopenic purpura misdiagnosed as autoimmune cytopenia: causes of diagnostic errors and consequence on outcome. Experience of the French thrombotic microangiopathies reference centre. Am J Hematol 2017;92:381–7.
12. Coppo P, Schwarzinger M, Buffet M, et al. French reference center for thrombotic microangiopathies. Predictive features of severe acquired ADAMTS13 deficiency

in idiopathic thrombotic microangiopathies: the French TMA reference center experience. PLoS One 2010;5:e10208.
13. Lefkou E, Nelson-Piercy C, Hunt BJ. Evans' syndrome in pregnancy: a systematic literature review and two new cases. Eur J Obstet Gynecol Reprod Biol 2010; 149:10–7.
14. Cervera R, Rodríguez-Pintó I, Espinosa G. The diagnosis and clinical management of the catastrophic antiphospholipid syndrome: a comprehensive review. J Autoimmun 2018;92:1–11.
15. Lansigan F, Isufi I, Tagoe CE. Microangiopathic haemolytic anaemia resembling thrombotic thrombocytopenic purpura in systemic lupus erythematosus: the role of ADAMTS13. Rheumatology (Oxford) 2011;50(5):824–9.
16. Andres E, Affenberger S, Zimmer J, et al. Current hematological findings in cobalamin deficiency. A study of 201 consecutive patients with documented cobalamin deficiency. Clin Lab Haematol 2006;28:50–6.
17. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood 2014;124:2804–11.
18. Youinou P, Jamin C, Le Pottier L, et al. Diagnostic criteria for autoimmune neutropenia. Autoimmun Rev 2014;13:574–6.
19. Pincez T, Fernandes H, Leblanc T, et al. Long term follow-up of pediatric-onset Evans syndrome: broad immunopathological manifestations and high treatment burden. Haematologica 2021. https://doi.org/10.3324/haematol.2020.27110.
20. Bousfiha A, Jeddane L, Picard C, et al. *Hu*man inborn errors of immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol 2020;40(1):66–81.
21. Besnard C, Levy E, Aladjidi N, et al. Pediatric-onset Evans syndrome: heterogeneous presentation and high frequency of monogenic disorders including LRBA and CTLA4 mutations. Clin Immunol 2018;188:52–7.
22. Feuille EJ, Anooshiravani N, Sullivan KE, et al. Autoimmune cytopenias and associated conditions in CVID: a report from the USIDNET registry. J Clin Immunol 2018;38:28–34.
23. Schmidt RE, Grimbacher B, Witte T. Autoimmunity and primary immunodeficiency: two sides of the same coin? Nat Rev Rheumatol 2017;14(1):7–18.
24. Neven B, Magerus-Chatinet A, Florkin B, et al. A survey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. Blood 2011; 118:4798–807.
25. Hadjadj J, Castro CN, Tusseau M, et al. Early-onset autoimmunity associated with SOCS1 haploinsufficiency. Nat Commun 2020;11(1):5341.
26. Fattizzo B, Barcellini W. Autoimmune cytopenias in chronic lymphocytic leukemia: focus on molecular aspects. Front Oncol 2019;9:1435.
27. Carli G, Visco C, Falisi E, et al. Evans syndrome secondary to chronic lymphocytic leukaemia: presentation, treatment, and outcome. Ann Hematol 2016;95: 863–70.
28. Hauswirth AW, Skrabs C, Schützinger C, et al. Autoimmune hemolytic anemias, Evans' syndromes, and pure red cell aplasia in non-Hodgkin lymphomas. Leuk Lymphoma 2007;48(6):1139–49.
29. Motta G, Vianello F, Menin C, et al. Hepatosplenic gammadelta T-cell lymphoma presenting with immune-mediated thrombocytopenia and hemolytic anemia (Evans' syndrome). Am J Hematol 2002;69(4):272–6.
30. Georgy JT, Jayakaran JAJ, Jacob AS, et al. Evans syndrome and immune thrombocytopenia in two patients with COVID-19. J Med Virol 2021;93(5):2642–4.
31. Delanoy N, Michot JM, Comont T, et al. Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: a descriptive observational study. Lancet Haematol 2019;6(1):e48–57.

32. Zhang L, Wu X, Wang L, et al. Clinical features of systemic lupus erythematosus patients complicated with Evans syndrome: a case-control, single center study. Medicine 2016;95:e3279.
33. Mithoowani S, Gregory-Miller K, Goy J, et al. High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis. Lancet Haematol 2016;3(10):e489–96.
34. Flores G, Cunningham-Rundles C, Newland AC, et al. Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: results in 73 patients. Am J Hematol 1993;44:237–42.
35. Buetens OW, Ness PM. Red blood cell transfusion in autoimmune hemolytic anemia. Curr Opin Hematol 2003;10:429–33.
36. Gudbrandsdottir S, Birgens HS, Frederiksen H, et al. Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. Blood 2013;121:1976–81.
37. Michel M, Terriou L, Roudot-Thoraval F, et al. A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm autoimmune hemolytic anemia in adults (the RAIHA study). Am J Hematol 2016. https://doi.org/10.1002/ajh.24570.
38. Birgens H, Frederiksen H, Hasselbalch HC, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. Br J Haematol 2013;163:393–9.
39. Bader-Meunier B, Aladjidi N, Bellmann F, et al. Rituximab therapy for childhood Evans syndrome. Haematologica 2007;92(12):1691–4.
40. Sulpizio ED, Raghunathan V, Shatzel JJ, et al. Long-term remission rates after splenectomy in adults with Evans syndrome compared to immune thrombocytopenia: a single-center retrospective study. Eur J Haematol 2020;104(1):55–8.
41. Fadlallah J, Michel M, Crickx E, et al. Bortezomib and dexamethasone, an original approach for treating multi-refractory warm autoimmune haemolytic anaemia. Br J Haematol 2019;187(1):124–8.
42. Pasquale R, Giannotta JA, Barcellini W, et al. Bortezomib in autoimmune hemolytic anemia and beyond. Ther Adv Hematol 2021;12. 20406207211046428.
43. Crickx E, Audia S, Robbins A, et al. Daratumumab, an original approach for treating multi-refractory autoimmune cytopenia. Haematologica 2021. https://doi.org/10.3324/haematol.2021.279232.
44. Boccia R, Cooper N, Ghanima W, et al, FIT Clinical Trial Investigators. Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia. Br J Haematol 2020;190(6):933–93.
45. Serris A, Amoura Z, Canoui-Poitrine F, et al. Efficacy and safety of rituximab for systemic lupus erythematosus-associated immune cytopenias: a multicenter retrospective cohort study of 71 adults. Am J Hematol 2018;93:424–9.
46. Gobert D, Bussel JB, Cunningham-Rundles C, et al. Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. Br J Haematol 2011;155(4):498–508.
47. Guitton Z, Terriou L, Lega JC, et al. Risk of thrombosis with anti-phospholipid syndrome in systemic lupus erythematosus treated with thrombopoietin-receptor agonists. Rheumatology (Oxford) 2018;57(8):1432–8.

48. Rossignol J, Michallet AS, Oberic L, et al. Rituximab-cyclophosphamide-dexamethasone combination in the management of autoimmune cytopenias associated with chronic lymphocytic leukemia. Leukemia 2011;25(3):473–8.
49. Bride KL, Vincent T, Smith-Whitley K, et al. Sirolimus is effective in relapsed/refractory autoimmune cytopenias: results of a prospective multi-institutional trial. Blood 2016;127:17–28.