BRUNO FATTIZZO
MD
Evans Syndrome

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ROCHE			X				
SAMSUNG BIOEPIS			X		X	X	
SANOFI			X		X	X	
SOBI			X		X	X	
ZENAS	X		X				

Evans syndrome: doubling the risk of relapse and complications!

Association of AIHA, ITP and CIN; 1-9/1,000,000 of whom 60-70% females

Defined by Robert Evans in 1951 as the association of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP).

- **first diagnostic criteria of ES:**

- anemia, reticulocytosis, increased blood bilirubin and fecal urobilinogen, no family history of hemolytic diseases, evidence of antibodies against erythrocytes at 37°C, hemolysis of transfused erythrocytes
- the presence of purpura, prolonged bleeding time
- bone marrow aspiration with normal or increased number of megakaryocytes
- absence of exogenous toxic agents or a baseline disease.

- **modified definition of Evans:**

destruction of **at least two** hematological blood **lineages**, as observed in patients with neutropenia, hemolytic anemia and thrombocytopenia.

Jaime-Pérez JC et al, J Blood Med. 2018
Evans R et al, AMA Arch Intern Med 1951
Michel M et al, Blood 2009
Fattizzo B et al, Blood Adv 2021

blood
Leading the way in experimental and clinical research in hematology

Pediatric Evans syndrome is associated with a high frequency of potentially damaging variants in immune genes

Jérôme Hadjadj, Nathalie Aladjidi, Helder Fernandes, Guy Leverger, Aude Magérus-Chatinet, Fabienne Mazerolles, Marie-Claude Stolzenberg, Sidonie Jacqu

N=203, Median age 16.3 years (1.2-41.0) studied from 2004

- **80 underwent genetic testing**
- **52 (65%) received a genetic diagnosis** : 49 germline mutations/ 3 somatic variants.
- 40% had pathogenic mutations in genes involved in primary immunodeficiencies (TNFRSF6, CTLA4, STAT3, PIK3CD, CBL, ADAR1, LRBA, RAG1, and KRAS)

Mutated cases showed:

- **more severe disease** with a greater frequency of additional immunopathologic manifestations
- and **>number of lines of treatment**.
- Six mutated patients died during the study

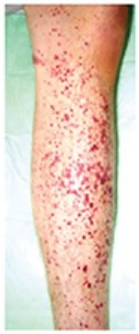
REGULAR ARTICLE

blood advances

Epidemiology in adults is different (> AID and LPD and <PID): which gene panel?

Evans syndrome in adults: an observational multicenter study

Bruno Fattizzo,[1,2] Marc Michel,[3] Juri Alessandro Giannotta,[1] Dennis Lund Hansen,[4] Maria Arguello,[5] Emanuele Sutto,[6] Nicola Bianchetti,[7] Andrea Patriarca,[8] Silvia Cantoni,[9] María Eva Mingot-Castellano,[10] Vickie McDonald,[11] Marco Capecchi,[1] Anna Zaninoni,[1] Dario Consonni,[12] Josephine Mathilde Vos,[13] Nicola Vianelli,[6] Frederick Chen,[11] Andreas Glenthøj,[14] Henrik Frederiksen,[4] Tomás José González-López,[15] and Wilma Barcellini[1]



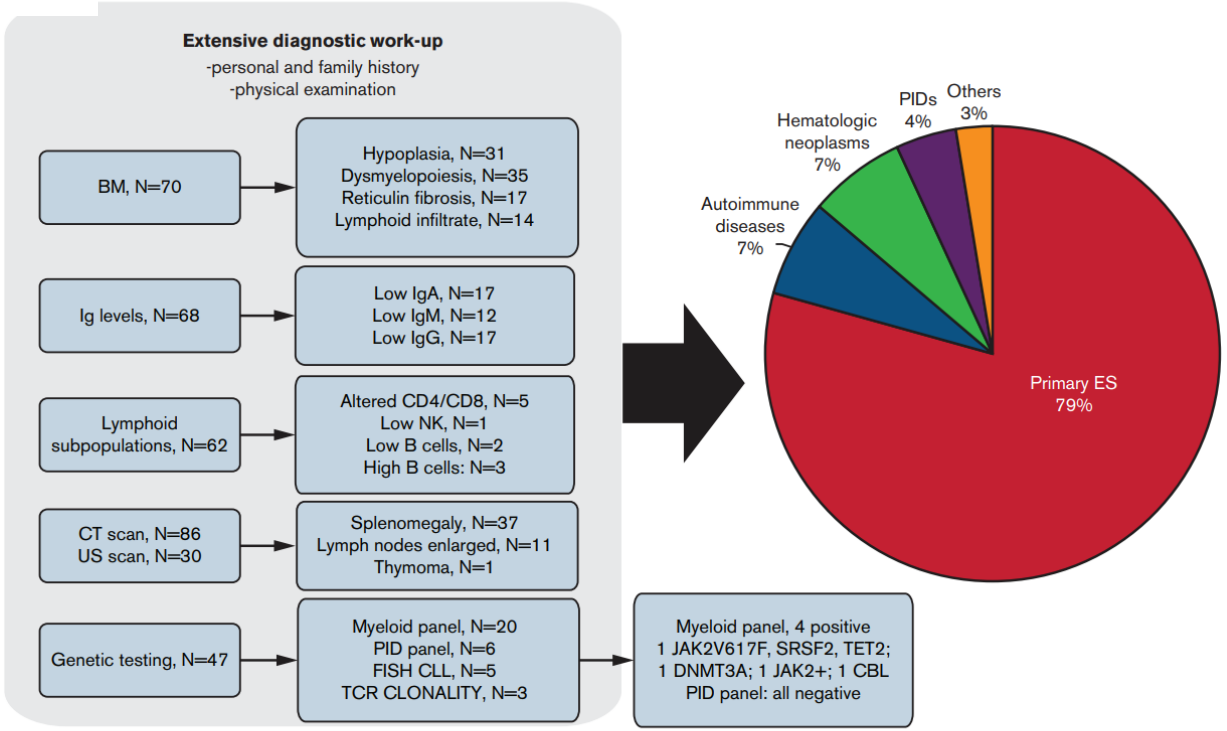
58% severe thrombocytopenia (<30x10$^{9/L}$)

41% severe anemia (Hb < 8 g/dL)

Severe neutropenia12% (<0.5x10$^{9/L}$)

Bleeding 42%

ES was secondary to or associated with underlying conditions in 24 cases (21%), mainly other autoimmune diseases and hematologic neoplasms.



Fattizzo B et al, Blood Advances 2021

The Lancet Haematology
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Review

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

Bruno Fattizzo MD [a b], Monia Marchetti MD PhD [c], Marc Michel MD [d], Silvia Cantoni MD [e], Henrik Frederiksen MD PhD [f], Giulio Giordano MD [g], Andreas Glenthøj MD [h], Tomás José González-López MD PhD [i],

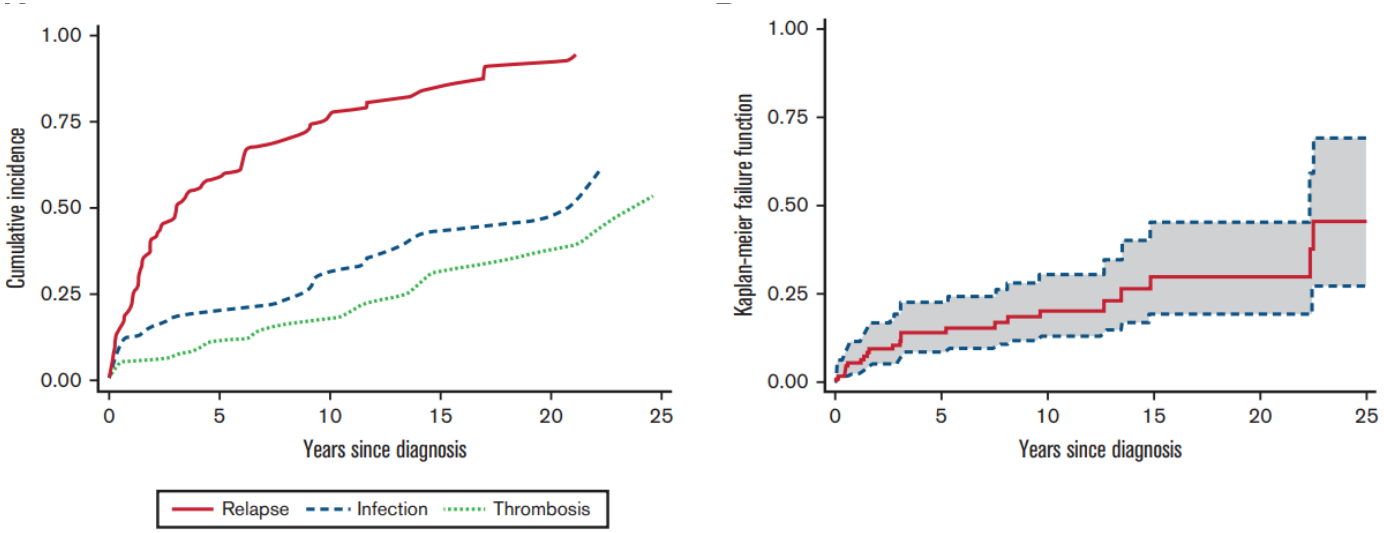
1. **CBC, Blood smear, hemolytic markers + DAT**
2. Serum protein electrophoresis and serum immunoelectrophoresis (immunofixation)
3. **Measurement of serum immunoglobulin concentrations**
4. Antinuclear ± anti-dsDNA antibodies
5. **Anticardiolipin antibodies and lupus anticoagulant assay***
6. **HIV and HCV tests, HBV test**
7. **CT scan of the chest, abdomen, and pelvis**
8. **Bone marrow biopsy**

	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**

Treatments, complications and outcomes

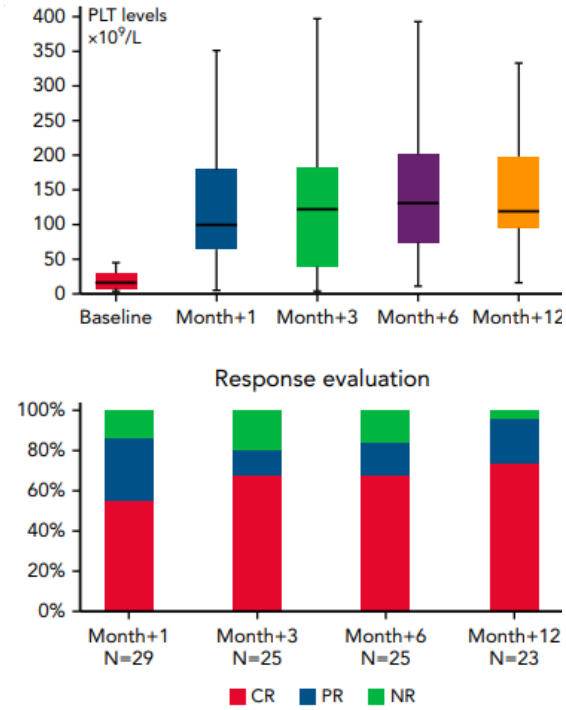


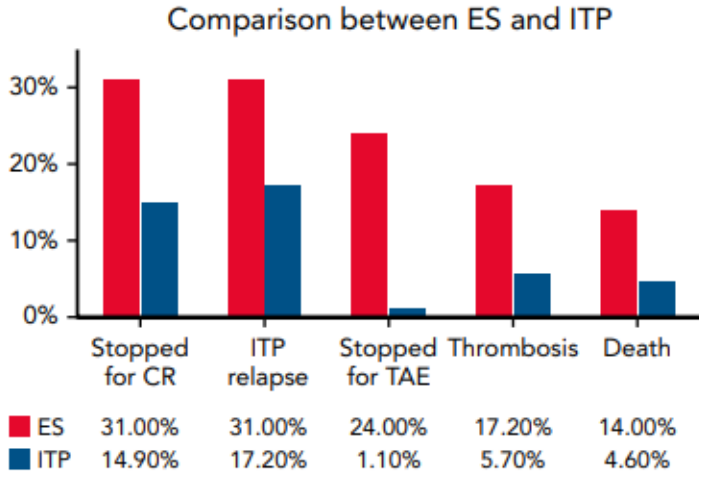
- **All patients received first-line steroids+/- IVIG**
- **23% needed early additional therapy "primary refractoriness"**
- 2nd line rituximab, splenectomy, immunosuppressants, thrombopoietin receptor agonists, and others, with response rates >80%.
- **70% relapsed and 54% required ≥3 therapy lines.**
- Infections in 33% and thrombosis in 21% of patients, mainly grade >3, correlated with n. therapy lines.
- **Mortality of 2.4 per 100 persons year → associated with anemia at onset and occurrence of relapse, infection, and thrombosis.**

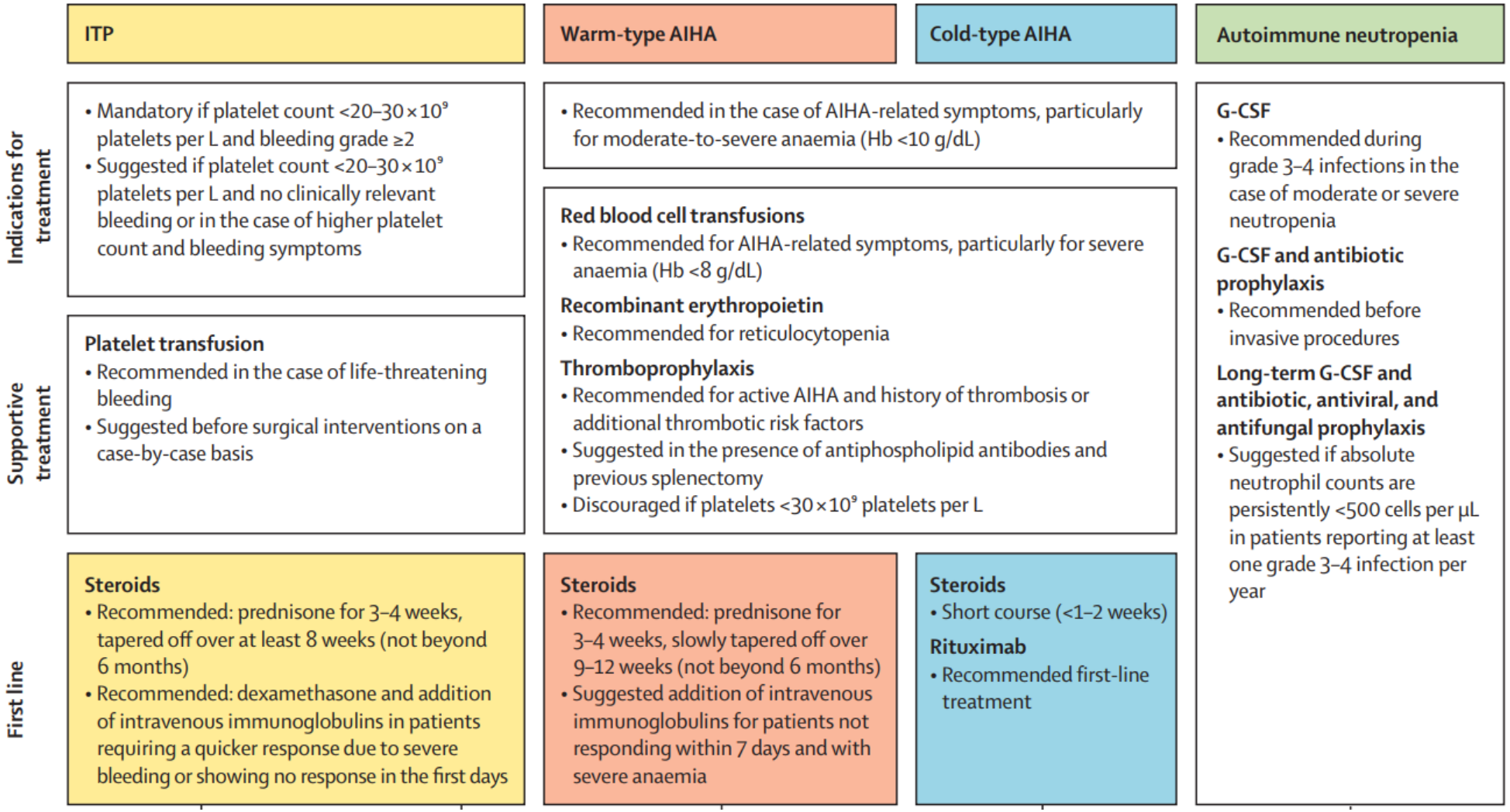
Fattizzo B et al, Blood Advances 2021

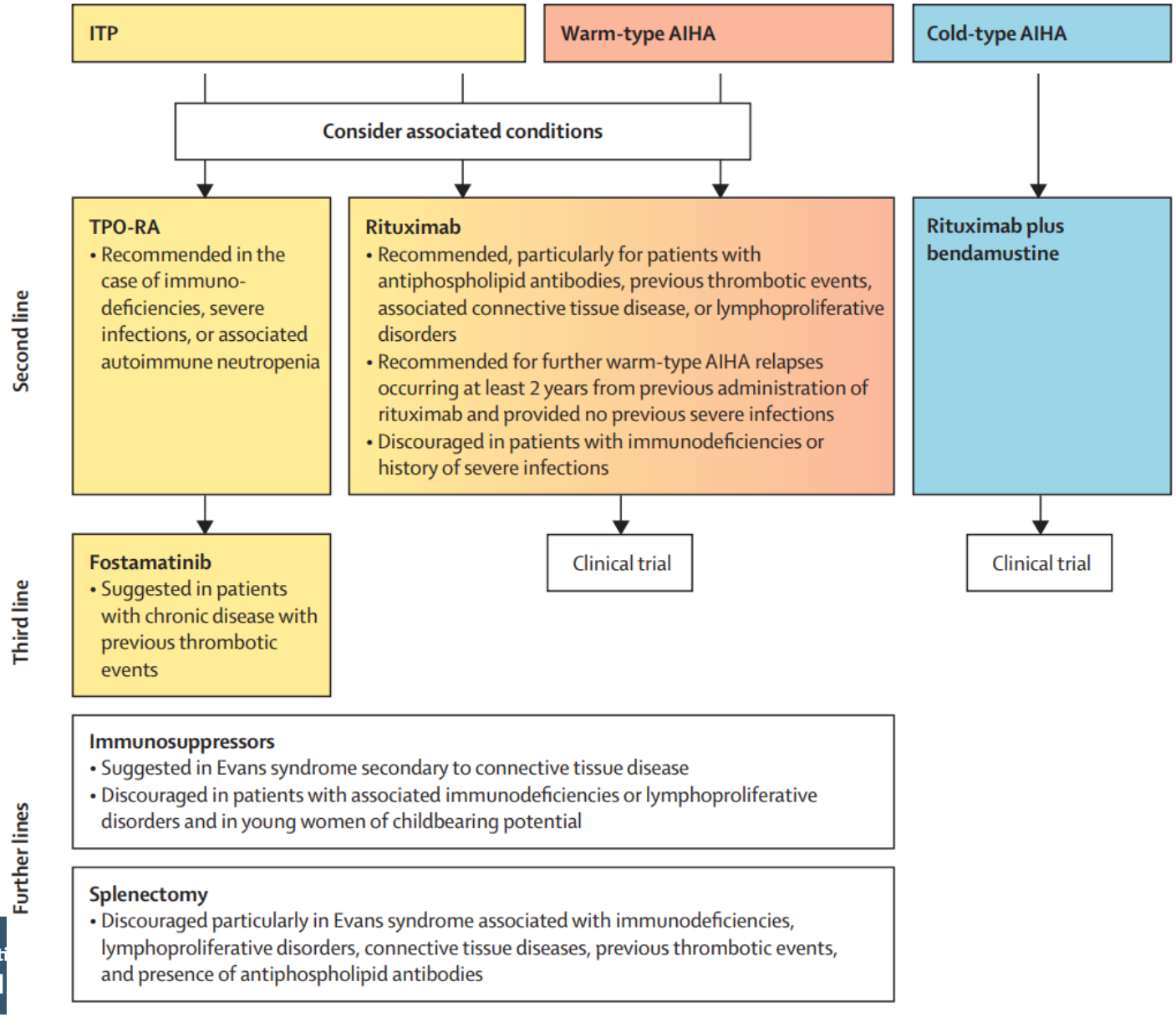
Thrombopoietin receptor agonists in adult Evans syndrome: an international multicenter experience

Bruno Fattizzo,[1,2] Nicola Cecchi,[1,2] Marta Bortolotti,[1,2] Giulio Giordano,[3] Andrea Patriarca,[4] Andreas Glenthøj,[5] Silvia Cantoni,[6] Marco Capecchi,[1,2] Frederick Chen,[7] Maria Eva Mingot-Castellano,[8] Mariasanta Napolitano,[9] Henrik Frederiksen,[10] Tomàs José Gonzaléz-Lopez,[11] and Wilma Barcellini[1]








ITP
Warm-type AIHA
Cold-type AIHA
Consider associated conditions
Second line
TPO-RA
• Recommended in the case of immuno-deficiencies, severe infections, or associated autoimmune neutropenia
Rituximab
• Recommended, particularly for patients with antiphospholipid antibodies, previous thrombotic events, associated connective tissue disease, or lymphoproliferative disorders
• Recommended for further warm-type AIHA relapses occurring at least 2 years from previous administration of rituximab and provided no previous severe infections
• Discouraged in patients with immunodeficiencies or history of severe infections
Rituximab plus bendamustine
Third line
Fostamatinib
• Suggested in patients with chronic disease with previous thrombotic events
Clinical trial
Clinical trial
Further lines
Immunosuppressors
• Suggested in Evans syndrome secondary to connective tissue disease
• Discouraged in patients with associated immunodeficiencies or lymphoproliferative disorders and in young women of childbearing potential
Splenectomy
• Discouraged particularly in Evans syndrome associated with immunodeficiencies, lymphoproliferative disorders, connective tissue diseases, previous thrombotic events, and presence of antiphospholipid antibodies

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Review

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

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
If used, steroid therapy in cold-type AIHA is recommended to be limited to <3–4 weeks, possibly <1–2 weeks	R
Rituximab retreatment is strongly recommended for patients with late cold-type AIHA relapses (>2 years from previous rituximab)	M
Rituximab plus bendamustine is recommended for fit patients reporting relapsing cold-type AIHA within 2 years of front-line rituximab therapy	R
Sutimlimab is suggested for patients reporting relapsing cold-type AIHA within 2 years of front-line rituximab therapy	S
Sutimlimab is recommended at second or further cold-type AIHA relapse	R

Take home messages

- ES is the **combination of multiple immune mediated cytopenias**.
- Disease **course is unpredictable and marked by multiple relapses, and high risk of infections and thrombosis** associated with mortality
- **Each cytopenia should be treated as it presents but considering the disease and ist potential complications as a whole.**
- **Steroids are the preferred first line** therapy to be used with different schedules in ITP, wAIHA and CAD
- **Rituximab is the preferred second line** in most cases but in those with increased infectious risk
- **TPO-RA pose the challenges of frequent oscillations and higher thrombotic risk** than in primary ITP
- **Splenectomy is overall discouraged** given the increased infectious and thrombotic risk in ES
- **Thromboprophylaxis** should be always considered **during hemolytic crises**
- **Recombinant erythropoietin** is suggested in anemic patients with **reticulocytopenia**

Thank You!

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