

Evans syndrome and infections: a dangerous cocktail to manage with caution

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Evans syndrome (ES) is a rare condition characterised by the association of multiple autoimmune cytopenias, usually autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (ITP), and, although rarely, autoimmune neutropenia. Up to 50% of ES cases may be secondary to a variety of conditions including infections, primary immunodeficiencies, particularly in children, systemic autoimmune diseases (such as systemic lupus erythematosus and rheumatoid arthritis), lymphoproliferative syndromes, and transplantation^{1,2}. Infections may either contribute to the development of the autoantibodies, through molecular mimicry, spreading of hidden epitopes, and neoantigen formation, or trigger ES relapses along the natural history of the disease (**Figure 1**)³. The world-wide COVID-19 pandemic represents a further challenge for clinicians dealing with autoimmune cytopenias as SARS-CoV-2 infection can be a trigger for autoimmunity, and it is still not clear whether pneumonia may benefit of or be worsened by concurrent immunosuppressive treatments⁴. In this issue of *Blood Transfusion*, Demir *et al.* describe the case of a 22-year old male patient presenting with ES secondary to COVID-19 pneumonia, in April 2020, at the peak of contagions in Mediterranean countries^{5,6}. Very severe warm type AIHA (haemoglobin [Hb] 3.9 g/dL, direct antiglobulin test [DAT] positive for IgG and strong complement activation) was diagnosed and managed with transfusions and steroids without response. The patient developed concurrent ITP and received plasmapheresis, followed by intravenous immunoglobulins that led to a progressive and eventually complete recovery. Importantly, prophylactic subcutaneous enoxaparin was given during hospitalisation, as long as platelet counts were above $50 \times 10^9/L$. As this case clearly illustrates, ES developing in an infected patient is a challenge at multiple levels (**Figure 1**):

- diagnostic, since the septic state per se (including COVID-19 pneumonia) may cause cytopenia and/or false positive autoimmunity tests⁷;
- therapeutic, given that most therapies for treating ES are immunosuppressive and might worsen host defences;
- prognostic, since infectious complications are an important cause of morbidity and mortality in patients with autoimmune cytopenias⁸.

Regarding diagnosis, ES is marked by the presence of at least two cytopenias of autoimmune origin in the absence of any underlying cause. It is therefore a diagnosis of exclusion and all the above-mentioned associations should be taken into account. Besides the classic workup (complete blood counts, vitamins and iron status, markers of haemolysis), DAT is fundamental for the diagnosis of AIHA, although it might be negative

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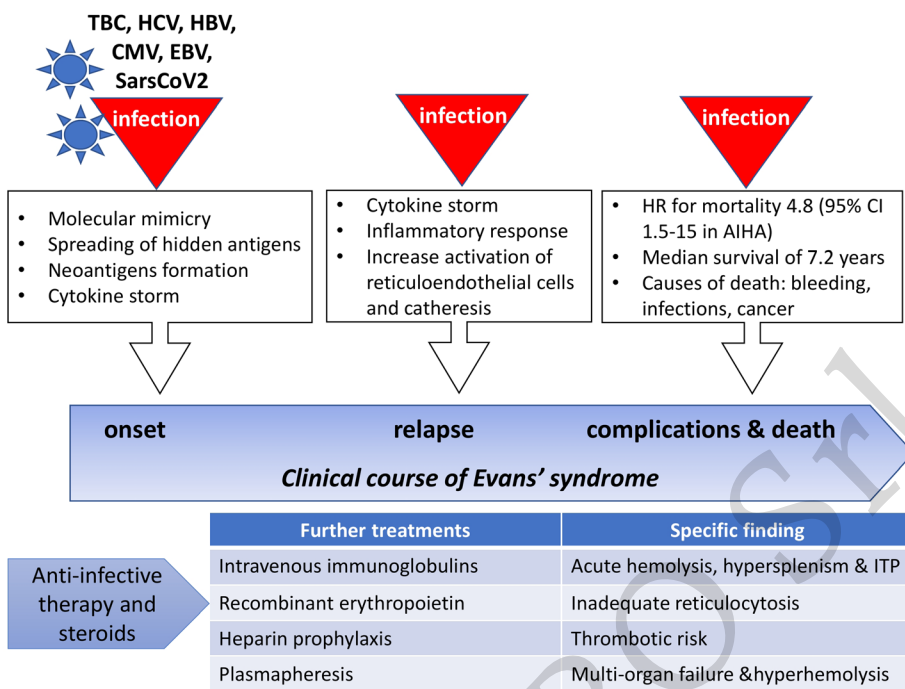


Figure 1 - Infections during the clinical course of Evans syndrome (ES)

Infectious triggers have an important role in ES development and its relapses through various mechanisms. ES patients may have a dismal survival, particularly secondary cases, and infections are one of the major causes of death. An infected patient with ES should promptly receive steroids along with anti-infective treatment. Other therapies are to be tailored on specific findings. Rituximab and splenectomy are well established second-line treatments for relapsing/refractory cases, after underlying secondary causes have been excluded/elucidated.

AIHA: autoimmune haemolytic anaemia; CI: confidential interval; CMV: cytomegalovirus, EBV: Epstein-Barr virus; HCV: hepatitis C virus HBV: hepatitis B virus; ITP: immune thrombocytopenia; HR: hazard risk; TBC: tuberculosis.

in 5-10% of cases³; at variance with this, lower sensitivity and specificity have been reported for anti-platelet and anti-neutrophil autoantibody testing, whose negativity does not exclude ES diagnosis. Finally, bone marrow (BM) evaluation and computed tomography scan are important to rule out underlying haematologic conditions, and Ig levels and medical history may suggest the presence of a congenital immunodeficiency¹. Concerning ES secondary to infections (i.e., Parvovirus B19, hepatitis B and C, tuberculosis, etc.), the differential diagnosis may be problematic and could delay appropriate treatment. In fact, microbes may cause cytopenias through several mechanisms, including direct infection of BM precursors, inflammation and iron depletion, and enhancement of immune-mediated catheresis. These confounders also occur in SARS-CoV-2 infection. Other ES cases developing concomitantly to COVID-19 pneumonia have been reported⁹⁻¹¹, and, in the pandemic setting, some symptoms related to a well-known disorder may be

erroneously attributed to the emerging disease making differential diagnosis difficult¹¹. In fact, SARS-COV-2 may also induce thrombocytopenia by favouring platelet aggregation in the lungs with microthrombi formation and consumption^{12,13}. Furthermore, the erythrocyte membrane protein ankyrin-1 was found to share a 100% identity with the SARS-CoV-2 surface glycoprotein Spike¹⁴, suggesting a molecular mimicry mechanism inducing immune-mediated anaemia.

Concerning therapy, ES is treated according to the presenting cytopenia, usually with steroids 1 mg/kg/day. Rituximab and splenectomy are well established second-line treatments for relapsing/refractory cases, after underlying secondary causes have been excluded/elucidated. The case reported by Demir *et al.* points out that “most AIHA therapies are immunosuppressive and therefore potentially harmful during infections”. As a matter of fact, infections in ES may be the putative cause of disease onset/relapse^{15,16} but may also be favoured by ES therapy³. Besides steroids (that

are also part of therapeutic protocols of the severe sepsis), high-dose immunoglobulins may be safely administered to ES patients during acute infections. Although more effective in ITP, their efficacy has been attested to be around 40% in AIHA; in this setting, their use is suggested in the highly haemolytic, potentially infected patient in whom steroids are ineffective and rituximab potentially harmful¹⁷. While the other reported ES cases concomitant to COVID-19 were milder and responded to steroids and intravenous immunoglobulin⁹⁻¹¹, the patient reported by Demir *et al.* required plasma exchange. This procedure is, however, not always feasible and implies cardiovascular stress with risk of fluid imbalance; it can be considered in the acutely ill and younger patient as a “last treatment option”¹⁷. It is worth remembering that recombinant erythropoietin can be safely administered in patients with inadequate reticulocytosis with up to 70% responses even in the acute phase¹⁸. BM failure to compensate haemolysis may be observed in the presence of anti-erythroblast antibodies, in patients with underlying haematologic conditions (i.e., lymphoproliferative disorder, myelodysplasia), and when haemolysis is too acute to allow reticulocyte regeneration or the BM is “shocked” by the septic state⁷. Moreover, it has been shown that about one-third of chronic refractory AIHA cases may display features of BM dyserythropoiesis and fibrosis¹⁹, and most of them have inadequate reticulocytosis and endogenous erythropoietin levels¹⁸. Similar considerations may regard the use of thrombopoietin receptor agonists for ITP, although data in the ES setting are lacking. A final therapeutic challenge may be the higher transfusion requirement due to the blood cell consumption typical of the septic state; this adds to the risk of alloimmunisation of transfused patients^{3,17}. Regarding anti-coagulant prophylaxis, thrombosis may complicate the clinical course of both ES and COVID-19 pneumonia. In the latter, an aberrant increase of D-dimers and prolonged coagulation times (the hallmark of the so-called “thromboinflammation”) are often observed and correlate with worse outcome²⁰. In AIHA, about 15% of patients may experience a thrombotic episode that has been related to highly haemolytic disease (i.e., lactate dehydrogenase levels $>1.5 \times \text{ULN}$) and multi-treatment approaches (particularly splenectomy)^{3,8,17}; similarly,

ITP patients are considered at higher thromboembolic risk due to the increased fraction of “young platelets”. Thromboembolic prophylaxis is even more important when all three conditions (infection, AIHA and ITP) occur simultaneously, and is currently routinely instituted in patients admitted with COVID-19 pneumonia, provided platelet counts are adequate. For instance, the ES case described by Li *et al.* experienced thromboembolism¹¹, while that described by Demir *et al.* received heparin prophylaxis⁵.

Finally, as regards prognosis, the described patient depicts the main clinical predictors of outcome in AIHA: anaemia severity at onset (particularly $\text{Hb} < 6 \text{ g/dL}$) is the major determinant of relapse and mortality risk; in a large retrospective study, each gram of reduction yielded a 7% greater risk of relapse (95% CI: 2-13; $p < 0.013$)⁸. Increased hazard risks for relapse and mortality have also been reported for the presence of complement activation and for ITP association. Finally, infectious complications have been associated with an increase in mortality with an HR of 4.8 (95% CI: 1.5-15; $p = 0.007$)⁸. In this context, a recent epidemiologic study from the Danish registry identified that adult patients with ES had a median survival of only 7.2 years, and this was markedly shorter in secondary cases (1.7 vs 10.9 years in primary cases)². The prevailing causes of death were bleeding, infections, and haematologic cancer. As a matter of fact, the reported survival is not dissimilar to that of neoplastic conditions, like low-risk myelodysplastic syndromes, despite the markedly younger median age (58 vs 71 years) of ES patients.

In conclusion, ES during acute infections should be promptly managed balancing the aggressiveness of immunosuppression and the potential for BM stimulation in patients with inadequate reticulocytosis. Intravenous immunoglobulins and plasmapheresis are powerful “time-gaining” tools to be considered on a patient-by-patient strategy. The thrombotic risk should be taken into account and thromboprophylaxis instituted if platelet count is permissive. Finally, it is important to bear in mind the potential worst prognosis of infected patients with ES, particularly secondary cases.

The Author declares no conflict of interests.

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