Complications of Autoimmune Hemolytic Anemia

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KEYWORDS

• COVID-19 • Autoimmune hemolytic anemia • Venous thromboembolism
• Immunosuppressive therapy

KEY POINTS

- In autoimmune hemolytic anemia (AIHA), the presentation and severity of signs and symptoms depend on the acuity of the development of anemia and patients' underlying comorbid conditions.
- Prophylactic utilization of folic acid 1 mg PO daily in patients with hemolytic anemia has been used to prevent deficiency
- The presence of warm autoantibody can interfere with the screening of alloantibodies for blood product selection in the setting of transfusions.
- Cold antibody hemolytic anemia can cause cutaneous ulceration and necrosis
- There are a plethora of infectious complications that could develop following therapeutic interventions and clinicians should have a low threshold for diagnostic work up.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is the group of acquired autoimmune conditions resulting from the development of autologous antibodies, typically immunoglobulin G (IgG) or complement proteins, directed against autologous red blood cell antigens resulting in red cell lysis. A range of antibodies can arise, varying by immunoglobulin subtype or specific temperature facilitating interaction between the immune system and red blood cell antigen, leading to the terminology of warm AIHA and cold agglutinin AIHA.

The incidence of AIHA is approximately 1 to 3 per 100,00 people per year[1] with potentially 40% to 50% of cases described as secondary AIHA with an underlying condition including distinct autoimmune disorders, immunodeficiency disorders, lymphoproliferative disorders, or infections.[2] Treatment of AIHA depends on the type of antibody present and the severity of anemia.

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The correct diagnosis and treatment of AIHA require careful laboratory assessment and clinical monitoring for response. There are a variety of complications that patients can experience associated with AIHA. Prior studies suggest a variety of mechanisms related to hemolysis that may lead to complications including endothelial activation, inflammation, platelet activation, and red blood cell adhesion.[3,4] The complications include symptoms due to the presence of anemia, existence of the antibody impacting blood bank testing, and side effects from specific therapeutic interventions. Additionally, the presence of active hemolysis and its byproducts can lead to organ dysfunction including renal and vascular complications. The likelihood of these different complications can evolve over time from diagnosis through treatment. Clinicians must remain mindful of the potential complications of AIHA, educating patients and families on the possibilities to facilitate open communication throughout treatment.

COMPLICATIONS RELATED TO ACTIVE HEMOLYSIS

Anemia

The symptoms of AIHA at presentation are driven by the degree of anemia. The National Cancer Institute characterizes anemia as mild with hemoglobin 10.0 g/dL to lower limit of normal, moderate with hemoglobin 8.0 to 10.0 g/dL, severe with hemoglobin 6.5 to 7.9 g/dL, and life-threatening when hemoglobin less than 6.5 g/dL.[5] In AIHA that develops slowly over months, the onset of symptoms will be protracted over time. More commonly, AIHA develops rapidly over days to weeks, and in this case, symptom development will be more severe and thus noticeable by the patient and family.

Common symptoms of anemia, and thus AIHA, include fatigue, dyspnea on exertion, or palpitations. Some patients may also demonstrate jaundice, dark colored urine, or splenomegaly.

A study of 60 patients with warm AIHA revealed that 87% presented with at least one symptom of anemia including fatigue or dyspnea. One in 4 patients in this study reported dizziness and 1 in 3 noted signs of hemolysis including jaundice or dark urine. Fifty-two of the patients had undergone imaging at diagnosis with 10% demonstrating lymphadenopathy.[6]

Symptoms can vary depending on the patient's age. A study of 35 children with AIHA revealed a quarter of patients experienced jaundice, fever, or fatigue at diagnosis. Other symptoms included dark urine or conjunctival pallor noted in 14%, and splenomegaly or abdominal pain in 11%.[7] A larger study of 265 children with AIHA reported dark urine in 80% of patients and organomegaly including splenomegaly in 31% or hepatomegaly in 19%. Importantly, 20% of cases included a concomitant diagnosis of infection.[8] As this second study represents children with all types of AIHA the increase in dark urine reflects an increased rate of Donath–Landsteiner hemolytic anemia, or paroxysmal nocturnal hemoglobinuria, hemolytic anemia in children. This type of AIHA typically follows a viral infection.

On the other hand, elderly individuals who develop AIHA may suffer symptoms at a lesser degree of anemia due to its impact on organ function when considering the symptoms of AIHA in the elderly, a study of 10 patients over the age of 75 years with AIHA revealed 70% experienced chest pain, tachycardia, cardiac failure, confusion, or excessive fatigue.[9] The potential for these cardiac or neurologic symptoms reflects the known increased risk of cardiovascular disease as people age.[10]

In summary, treating clinicians need to have a high index of suspicion for the complications related to the presence of anemia or ongoing hemolysis. The symptoms of

anemia, or lack of symptoms, at diagnosis can be attributed to the duration and degree of anemia present. Patient age or comorbidities can shape the type and severity of symptoms of anemia at presentation.

Cutaneous Symptoms

Cutaneous complications are rare but possible in AIHA. Cutaneous ulceration and necrosis are seen more often in the setting of cold antibody hemolytic anemia.[11,12] In cold environments, cold antibodies can cause agglutination of red cells in distal extremities. This decreased red cell flow can result in the extremity feeling numb, painful, and cold. This can lead to acrocyanosis, a functional peripheral arterial disease resulting in skin discoloration, and in extreme situations cutaneous necrosis.[13] The demonstration of these symptoms depend on the titer of antibodies present and the temperature range in which they are active, meaning there is a spectrum of if, and how, patients will experience this complication. Cold autoantibodies are able to bind to red blood cells at less than 37° Celsius, typically below 31° Celsius.[14] Management of these symptoms is to avoid cold temperatures and keep extremities, particularly the hands and feet, warm.

Folate Deficiency

Folate, or vitamin B9, is necessary for DNA synthesis and cell proliferation. This vitamin is absorbed in the small bowel and folate deficiency occurs due to inadequate oral intake, malabsorption, medications, or increased situations of increased demand. Deficiency of folate impacts rapidly proliferating cells including hematopoietic cells in the bone marrow, leading to megaloblastic anemia or pancytopenia.[15] Increased folate demand can be seen in pregnancy as well as increased red blood cell turn over.

To address the increased folate demand is seen in pregnancy and breastfeeding, some nations fortified flour with folic acid and recommend supplementation during pregnancy.[16] This is not the only situation whereby prophylactic folate supplementation has been recommended due to increased situational demand.

Increased folate demand is seen in cases of peripheral red cell destruction and abnormal hematopoiesis, such as hemolytic anemia.[17–19] In chronic hemolysis, prophylactic doses of folic acid are recommended at 1 mg oral daily.[20] This supplementation either remedies, or prevents, folic acid deficiency and allows ongoing compensatory erythropoiesis. It is imperative to also be aware of other nutritional deficiencies that can limit erythropoeisis including iron deficiency in the setting of blood loss or B12 deficiency in the setting of malabsorption. While supplementation of these nutrients is not implemented in hemolytic anemia, it is important to remain aware of the possible deficiencies.

In summary, the presence of ongoing hemolysis can place strain on the body with regards to increased folic acid demands due to ongoing erythropoiesis. Supplementation has been recommended in patients with chronic hemolytic anemia, including thalassemia and sickle cell anemia, and is typically recommended during the duration of AIHA to facilitate ongoing erythropoiesis regardless of baseline folic acid level.

Venous Thromboembolism

The association of venous thromboembolism (VTE) in AIHA is well-documented.[21–23] As hemolysis could be seen either in the intravascular or extravascular compartment, the postulated mechanisms for the development of thromboembolism are related to free plasma hemoglobin, depletion of nitric oxide, presence of autoantibodies including antiphospholipid antibodies in some patients, reactive oxygen species, increased proinflammatory cytokines and mediators, endothelial activation as well as the need for splenectomy/postsplenectomy status.

The rates of VTE in patients with AIHA range from 10% to 27%.[1,4,6,23–30] Pulmonary embolism is a more common presentation in this patient population. The rates of VTE are high in patients with autoimmune disorders when they are admitted to the hospital and have been reported to be up to 2-fold higher in patients hospitalized with AIHA.[25,31–33]

Due to the complex pathophysiology involved in the autoimmune hemolytic process, patients suffering from AIHA are at heightened risk for VTE complications. Despite the awareness of increased risk, it is not easy to ascertain which group of patients would benefit from thromboprophylaxis. There is a paucity of literature to support the use of serum biomarkers such as hemoglobin, LDH, leukocyte count, bilirubin, antiphospholipid antibody, and D-dimer as the predictor for VTE.[1,4,23]

Multiple pathophysiological mechanisms have been proposed. These include immune mechanisms such as systemic inflammation leading to cytokine-induced tissue factor expression, endothelial dysfunction and inhibition of Protein C and fibrinolysis systems, NET release and increased levels of VWF, fibrinogen and factor 8., and non -immune mechanisms such as endothelial cell damage leading to the activation of the Virchow's triad by microvesicular shedding, release of plasma free hemoglobin and heme leading to the release of nitric oxide scavenger.[34]

This situation is further complicated by the fact that a proportion of patients might have concurrent autoimmune thrombocytopenia which would make prophylactic anticoagulation a high-risk intervention. Thus, routine anticoagulation prophylaxis is not a standard of care for patients with AIHA unless there are other considerations for thromboprophylaxis such as cancer, hormonal exposure, pregnancy, recent postop status particularly splenectomy, and use of high dose steroids.

In the event of the development of a venous thromboembolic event, the duration of anticoagulation depend on the nature of the event. If the thrombus was provoked by other risk factors as described above, finite anticoagulation should be considered as per the Chest Guidelines.[35] Also, the degree of ongoing hemolysis along with platelet count would guide the decisions, carefully balancing the risks versus benefits of ongoing anticoagulation. There is no data comparing different anticoagulants in the setting and the presence of AIHA does not impact the choice of anticoagulant used.

Although arterial events are less frequently described, complications such as myocardial infarction and stroke are seen in the setting of AIHA particularly with severe anemia.[36,37] The underlying pathophysiological mechanisms are not well understood, perhaps these are precipitated by the degree of anemia leading to poor perfusion hence ischemic complications.

In summary, VTE is one of the more frequent complications of autoimmune hemolytic disease but currently there are no standard guidelines in terms of preventative strategy both in the inpatient as well as outpatient clinical setting. Thromboprophylaxis in the inpatient setting should be considered for patients with AIHA, as in other cases of medically complicated hospitalized patients, whenever the risk of bleeding is low. In the setting of the development of a thromboembolic event, the duration of anticoagulation in patients with ongoing hemolysis is not clear at this point and is at the discretion of the treating provider after 3 months of therapy.

Renal Dysfunction

Ongoing uncontrolled brisk hemolysis over time can lead to acute kidney injury. This can be caused by renal tubular obstruction by hemoglobin cast precipitation, cytotoxicity to proximal tubular epithelium, and intrarenal vasoconstriction due to the depletion of nitric oxide.[38,39]

Several cases of patients with Evans syndrome, a syndrome of AIHA and immune-mediated thrombocytopenia, who developed acute kidney injury with renal biopsy have been reported. Evoked mechanisms included direct cytotoxicity to the proximal tubular epithelium as well as the demonstration of hemosiderin deposition within the renal tubules leading to chronic renal dysfunction[40] due to cast nephropathy. In a pediatric patient with Evans Syndrome and no associated underlying autoimmune condition, the biopsy revealed hemoglobin casts in renal biopsy attributed to intravascular hemolysis.[41] Lastly IgG4-related kidney disease has been recently described. This fibroinflammatory condition whereby IgG4 positive plasma cells infiltrate the tissue with storiform fibrosis, may or may not be associated with elevated IgG4 levels.[42]

Ongoing hemolysis, particularly intravascular hemolysis can, rarely, impact renal function through a variety of mechanisms. Other causes of hemolysis besides autoimmune hemolysis, such as thrombotic microangiopathy (TMA) can more commonly impact renal function. In the setting of hemolytic anemia with renal dysfunction, once TMA is ruled out, AIHA must be considered and a renal biopsy may be necessary to distinguish the cause of renal injury.

COMPLICATIONS RELATED TO HEMOLYTIC ANEMIA MANAGEMENT

Treatment-Associated Complications

While the presence of hemolysis or anemia can cause complications at diagnosis and during treatment, there are also considerations for adverse effects of the treatment itself. As this is an autoimmune process, many of the therapeutics are immunosuppressive. This increases the likelihood, and atypical nature, of infections. Patients on long-term immunosuppressive therapy should be covered with prophylactic antimicrobials to prevent the development of opportunistic infections. In addition to the general increased infectious risk of pharmaceutical complications, each agent carries distinct complication risks including psychosis (steroids), cardiotoxicity (cyclophosphamide), nephrotoxicity (cyclosporine), anaphylaxis (plasma exchange), or neutropenia (mycophenolate). The variety of potential adverse events from therapeutic interventions prompts the need to review common, and uncommon, side effect profiles at initiation and during treatment, especially if the agent is not commonly used in a clinician's practice.

Table 1 provides a summary of the most common side effects associated with therapeutic interventions for AIHA, many of which focus on immunosuppressive therapy.[43] Complications of each therapy are specific to that particular pharmacologic or surgical intervention.

Transfusion Considerations

In the setting of AIHA, occasionally red blood cell transfusions may be necessary for significant anemia while awaiting a response from immunosuppressive therapy. Identifying the ideal red blood cell unit for transfusion can prove difficult in the setting of AIHA due to disruption in the alloantibody screening process by the presence of a warm autoantibody.

The initial test to identify the presence of AIHA is the direct antiglobulin test, detecting the presence of either immunoglobulin or complement bound to the patient's red blood cells. When the DAT is positive, the next step is a process of elution followed by exposure to reagent red blood cells with known antigen expression. In some cases, this elution and reagent red blood cell exposure lead to panagglutination, and only rarely in this situation does an autoantibody react strongly with a specific antigen informing donor red blood cell unit selection.[55] Thus, detecting a clinically significant

Table 1
Common Side Effects associated with Therapeutic Interventions for Autoimmune Hemolytic Anemia

Therapy	Common Side Effects
Steroids[44]	immunosuppression, infection, endocrine abnormalities with hyperglycemia, psychosis and neurotoxicity, myopathy, osteoporosis, aseptic necrosis of bone
Intravenous immunoglobulin[45]	hypersensitivity reaction, increase the risk for thrombosis, hemolysis, asthenia, GI upset with pain and diarrhea, injection site ecchymosis, and pruritus
Rituxan[44,46]	anaphylactic reaction, hematological toxicity, and hypogammaglobulinemia, GI upset, antibody development, increased risk for infections. Rare cases progressive multifocal leukoencephalopathy (PML)
Cyclophosphamide[47]	hematological toxicity, nausea and vomiting, hemorrhagic cystitis, pulmonary toxicity, secondary malignancy, cardiotoxicity
Mycophenolate mofetil[48]	hematological toxicity particularly neutropenia, gastrointestinal toxicity, opportunistic infections, progressive multifocal leukoencephalopathy
Azathioprine[49]	hematological toxicity particularly leukopenia, hepatotoxicity with increased liver enzymes and bilirubin, susceptibility to infections, Sweet syndrome, and PML
Danazol[50]	Asthenia, erythrocytosis, hepatic toxicity, fatigue and depression, interstitial pneumonitis, Steven–Johnson syndrome, increased thrombosis
Cyclosporine[51]	gastrointestinal toxicity, nephrotoxicity
Sirolimus[52]	gastrointestinal toxicity, elevation of liver function tests, hypertriglyceridemia, blood pressure changes, headaches, mucous membrane irritation, hematological toxicity, sinusoidal obstruction syndrome
Plasma exchange[53]	coagulation factor depletion, anaphylactic reactions, transfusion-related acute lung injury, infectious risk, hypokalemia, hypocalcemia, hematin globulin depletion, ACE-inhibitor-related complications (flushing, hypotension, abdominal cramping), vascular catheter complication, citrate induced metabolic alkalosis
Eculizumab[46]	hypertension, peripheral edema, headache and fatigue, skin rash, gastrointestinal upset, hypokalemia, leukopenia, infection with meningococcus, respiratory complication
Splenectomy[54]	encapsulated organism infection such as pneumococcus and meningitis, venous thromboembolism, secondary malignancies, cardiovascular immense and pulmonary hypertension, bleeding at the time of surgery

red blood cell alloantibody proves difficult in the setting of a broadly reactive autoantibody which can mask an antigen-specific alloantibody. Additional laboratory testing is necessary as an alloantibody can be capable of causing hemolytic transfusion reactions if not identified and managed by antigen-negative red cell transfusions.[56] It has been reported that up to 20% to 40% of patients with AIHA may have alloantibodies present in their sera.[57] Additional laboratory testing can be performed to detect alloantibodies in the presence of broadly reactive warm autoantibody is referred to as

autoadsorption. In situations when autoadsorption is not effective, alloadsorption technique is performed.[56]

There are reports that concern for masked alloantibodies in the setting of AIHA may be overestimated, leading to detrimental outcomes for patients if necessary red cell transfusions are withheld.[58] In this study of 36 patients with AIHA, 3 were found to have alloantibodies through traditional testing and only one alloantibody required alloadsorption for detection. Therefore, while alloantibody screening may be difficult in the setting of AIHA additional laboratory techniques may be necessary and prove beneficial for comprehensive management of AIHA. Close communication with blood bank colleagues and acknowledgment that additional techniques will require time before resulting is essential.

SPECIAL CONSIDERATIONS

COVID-19

The pandemic has also brought forward a unique presentation and perspective to the patients infected with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), particularly those with underlying B cell lymphoid malignancies. There have been several case reports of patients presenting with AIHA either as a presenting symptom or one that developed during the illness.[59–63] Vice versa, there has been some reporting on the outcomes of the patient with AIHA who developed COVID-19 and it does not seem that patients have worse outcomes.[63–68] One study of 7 patients diagnosed with AIHA associated with COVID-19 infection, revealed that 4 of the 7 individuals were found to have an indolent B lymphoid malignancy, indicating an immune dysfunction which may have predisposed the patient to the infection and/or hemolysis.[69] However, in the era of COVID-19 there is published literature suggesting increased severity of disease for patients who have been treated with Rituxan for their underlying rheumatological or hematological conditions.[70,71] The concern is perhaps there is a reduced ability to mount an immunologic response to active COVID-19 infection, or an appropriate immunologic response to the COVID-19 vaccine, following CD-20 lymphocyte modification. Lastly, there have been case reports of the development of AIHA in the setting of COVID-19 mRNA vaccination which was rather responsive to steroids.[72]

CONCLUSION

AIHA is a collection of conditions requiring accurate laboratory diagnosis and careful consideration for management strategies. In addition to the management of anemia, AIHA can be associated with a spectrum of complications that requires the treating clinician to remain vigilant both at presentation and after treatment initiation. These AIHA complications are not only related to the underlying triggering disease or the process of hemolysis but also complications related to medical therapy. Special considerations related to the COVID-19 pandemic include not only the disease associated with the SARS-CoV-2 virus but also the vaccination process and choice of therapy for AIHA.

SUMMARY

AIHAis a group of acquired autoimmune conditions resulting from the development of autologous antibodies directed against autologous red blood cell antigens resulting in red cell lysis. Beyond the presence, severity and duration of hemolysis which can lead to symptomatic anemia, additional complications at presentation and during treatment require a high degree of clinical vigilance. These include cutaneous, thrombotic,

renal disorders, and infectious disorders. Complications can be due to the presence of the pathologic antibody itself, the process of hemolysis, or attributed to treatment. Comprehensive management of AIHA requires awareness and assessment of complications at diagnosis, during, and following treatment.

CLINICS CARE POINTS

- The presence of warm autoantibody can interfere with the screening of alloantibodies for blood product selection in the setting of transfusions.
- Working closely with Blood Bank colleagues and appreciating that blood product unit selection may take additional time and testing is essential to facilitate safe transfusions when necessary.
- Cold antibody hemolytic anemia can cause cutaneous ulceration and necrosis.
- Ongoing hemolysis can contribute to renal dysfunction through a variety of mechanisms.
- Venous thromboembolism is a widely recognized complication associated with AIHA but there is no consensus about prophylactic management for this complication.

REFERENCES

1. Barcellini W, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood 2014; 124(19):2930–6.
2. Liebman HA, Weitz IC. Autoimmune Hemolytic Anemia. Med Clin North Am 2017; 101(2):351–9.
3. L'Acqua C, Hod E. New perspectives on the thrombotic complications of haemolysis. Br J Haematol 2015;168(2):175–85.
4. Lecouffe-Desprets M, et al. Venous thromboembolism related to warm autoimmune hemolytic anemia: a case-control study. Autoimmun Rev 2015;14(11): 1023–8.
5. Badireddy M, Baradhi KM. Chronic anemia. Treasure Island (FL: StatPearls; 2021.
6. Roumier M, 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(9):E150–5.
7. Sankaran J, et al. Autoimmune Hemolytic Anemia in Children: Mayo Clinic Experience. J Pediatr Hematol Oncol 2016;38(3):e120–4.
8. Aladjidi N, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. Haematologica 2011;96(5): 655–63.
9. Zulfiqar AA, Pennaforte JL, Andres E. Autoimmune Hemolytic Anemia in Individuals Aged 75 and Older: A Study of 10 Individuals. J Am Geriatr Soc 2016;64(6): 1372–4.
10. Sniderman AD, Furberg CD. Age as a modifiable risk factor for cardiovascular disease. Lancet 2008;371(9623):1547–9.
11. Lorenzo-Villalba N, et al. Frostbite and Cold Agglutinin Disease: Coexistence of Two Entities Leading to Poor Clinical Outcomes. Medicina (Kaunas) 2021;57(6).
12. Gregory GP, Farrell A, Brown S. Cold agglutinin disease complicated by acrocyanosis and necrosis. Ann Hematol 2017;96(3):509–10.
13. Sinha A, Richardson G, Patel RT. Cold agglutinin related acrocyanosis and paroxysmal haemolysis. Eur J Vasc Endovasc Surg 2005;30(5):563–5.

14. Kenneth Kaushansky ML. Josef Prchal, Marcel Levi, Olivery Press, Linda Burns, Michael Caligiuri, Williams Hematol, in Williams Hematology. New York: McGraw-Hill Education; 2015.
15. Devalia V, et al. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 2014;166(4):496–513.
16. De Wals P, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med 2007;357(2):135–42.
17. Liu YK. Folic acid deficiency in sickle cell anaemia. Scand J Haematol 1975; 14(1):71–9.
18. Kennedy TS, et al. Red blood cell folate and serum vitamin B12 status in children with sickle cell disease. J Pediatr Hematol Oncol 2001;23(3):165–9.
19. Reed JD, Redding-Lallinger R, Orringer EP. Nutrition and sickle cell disease. Am J Hematol 1987;24(4):441–55.
20. Baghersalimi A, et al. Assessment of Serum Folic Acid and Homocysteine in Thalassemia Major Patients Before and After Folic Acid Supplement Cessation. J Pediatr Hematol Oncol 2018;40(7):504–7.
21. Ungprasert P, Tanratana P, Srivali N. Autoimmune hemolytic anemia and venous thromboembolism: A systematic review and meta-analysis. Thromb Res 2015; 136(5):1013–7.
22. Solari D, et al. Autoimmune hemolytic anemia and pulmonary embolism: an association to consider. TH Open 2021;5(1):e8–13.
23. Audia S, et al. Venous thromboembolic events during warm autoimmune hemolytic anemia. PLoS One 2018;13(11):e0207218.
24. Pullarkat V, et al. Detection of lupus anticoagulant identifies patients with autoimmune haemolytic anaemia at increased risk for venous thromboembolism. Br J Haematol 2002;118(4):1166–9.
25. Ramagopalan SV, et al. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. BMC Med 2011;9:1.
26. Bongarzoni V, et al. Risk of thromboembolism in patients with idiopathic autoimmune hemolytic disease and antiphospholipid antibodies: results from a prospective, case-control study. Haematologica 2005;90(5):711–3.
27. Baek SW, et al. Clinical features and outcomes of autoimmune hemolytic anemia: a retrospective analysis of 32 cases. Korean J Hematol 2011;46(2):111–7.
28. Hendrick AM. Auto-immune haemolytic anaemia–a high-risk disorder for thromboembolism? Hematology 2003;8(1):53–6.
29. Ho G, et al. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with autoimmune hemolytic anemia. Blood Cells Mol Dis 2020;81:102388.
30. Bylsma LC, et al. Occurrence, thromboembolic risk, and mortality in Danish patients with cold agglutinin disease. Blood Adv 2019;3(20):2980–5.
31. Zoller B, et al. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet 2012;379(9812):244–9.
32. Yusuf HR, et al. Risk of venous thromboembolism among hospitalizations of adults with selected autoimmune diseases. J Thromb Thrombolysis 2014;38(3): 306–13.
33. Yusuf HR, et al. Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees. Thromb Res 2015;135(1):50–7.
34. Capecchi M, et al. Thrombotic Complications in Patients with Immune-Mediated Hemolysis. J Clin Med 2021;10(8).

35. Stevens SM, et al. Antithrombotic therapy for VTE disease: second Update of the CHEST guideline and Expert Panel report. Chest 2021;160(6):e545–608.
36. Kizilirmak F, et al. Evans syndrome with non-ST segment elevation myocardial infarction complicated by hemopericardium. Indian Heart J 2016;68(Suppl 2): S280–3.
37. Jin H, et al. Report of cold agglutinins in a patient with acute ischemic stroke. BMC Neurol 2015;15:222.
38. Lin H, et al. Evans Syndrome with Acute Kidney Injury. Arch Iran Med 2019;22(6): 336–9.
39. Villegas A, et al. Presence of acute and chronic renal failure in patients with paroxysmal nocturnal hemoglobinuria: results of a retrospective analysis from the Spanish PNH Registry. Ann Hematol 2017;96(10):1727–33.
40. Couri FS, Kandula M. A Case of Evans Syndrome with Acute Hemolysis and Hemoglobin Cast Nephropathy. Am J Case Rep 2020;21:e920760.
41. Gonzalez I, et al. Evans Syndrome Complicated by Intratubular Hemoglobin Cast Nephropathy. Case Rep Pediatr 2017;2017:5184587.
42. Gou SJ, et al. Immunoglobulin G4-related Kidney Disease Associated With Autoimmune Hemolytic Anemia. Iran J Kidney Dis 2018;12(4):243–6.
43. Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. Haematologica 2014;99(10):1547–54.
44. Birgens H, 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(3):393–9.
45. Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. Transfusion 2006;46(5):741–53.
46. Engel ER, Walter JE. Rituximab and eculizumab when treating nonmalignant hematologic disorders: infection risk, immunization recommendations, and antimicrobial prophylaxis needs. Hematol Am Soc Hematol Educ Program 2020; 2020(1):312–8.
47. Lechner K, Jager U. How I treat autoimmune hemolytic anemias in adults. Blood 2010;116(11):1831–8.
48. Alba P, Karim MY, Hunt BJ. Mycophenolate mofetil as a treatment for autoimmune haemolytic anaemia in patients with systemic lupus erythematosus and antiphospholipid syndrome. Lupus 2003;12(8):633–5.
49. Lawrence Petz GG. Immune hemolytic anemias. 2nd edition. Philadelpha: Churchill Livingstone; 2003.
50. Pignon JM, Poirson E, Rochant H. Danazol in autoimmune haemolytic anaemia. Br J Haematol 1993;83(2):343–5.
51. Emilia G, et al. Long-term salvage treatment by cyclosporin in refractory autoimmune haematological disorders. Br J Haematol 1996;93(2):341–4.
52. Jasinski S, Weinblatt ME, Glasser CL. Sirolimus as an Effective Agent in the Treatment of Immune Thrombocytopenia (ITP) and Evans Syndrome (ES): A Single Institution's Experience. J Pediatr Hematol Oncol 2017;39(6):420–4.
53. Ruivard M, et al. Plasma exchanges do not increase red blood cell transfusion efficiency in severe autoimmune hemolytic anemia: a retrospective case-control study. J Clin Apheresis 2006;21(3):202–6.
54. Kristinsson SY, et al. Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up. Haematologica 2014;99(2):392–8.

55. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol 2002; 69(4):258–71.
56. Buetens OW, Ness PM. Red blood cell transfusion in autoimmune hemolytic anemia. Curr Opin Hematol 2003;10(6):429–33.
57. Sokol RJ, et al. Patients with red cell autoantibodies: selection of blood for transfusion. Clin Lab Haematol 1988;10(3):257–64.
58. Yurek S, et al. Precautions surrounding blood transfusion in autoimmune haemolytic anaemias are overestimated. Blood Transfus 2015;13(4):616–21.
59. Capes A, et al. COVID-19 infection associated with autoimmune hemolytic anemia. Ann Hematol 2020;99(7):1679–80.
60. Maslov DV, et al. COVID-19 and Cold Agglutinin Hemolytic Anemia. TH Open 2020;4(3):e175–7.
61. Jacobs J, Eichbaum Q. COVID-19 associated with severe autoimmune hemolytic anemia. Transfusion 2021;61(2):635–40.
62. Jawed M, Hart E, Saeed M. Haemolytic anaemia: a consequence of COVID-19. BMJ Case Rep 2020;13(12).
63. Barcellini W, Giannotta JA, Fattizzo B. Are Patients With Autoimmune Cytopenias at Higher Risk of COVID-19 Pneumonia? The Experience of a Reference Center in Northern Italy and Review of the Literature. Front Immunol 2020;11:609198.
64. Li M, et al. Evans syndrome in a patient with COVID-19. Br J Haematol 2020; 190(2):e59–61.
65. Perez-Lamas L, et al. Hemolytic crisis due to Covid-19 vaccination in a woman with cold agglutinin disease. Am J Hematol 2021;96(8):E288–91.
66. Demir NA, et al. A case of Evans syndrome secondary to COVID-19. Blood Transfus 2021;19(1):85–8.
67. Huscenot T, et al. SARS-CoV-2-associated cold agglutinin disease: a report of two cases. Ann Hematol 2020;99(8):1943–4.
68. Lopez C, et al. Simultaneous onset of COVID-19 and autoimmune haemolytic anaemia. Br J Haematol 2020;190(1):31–2.
69. Lazarian G, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. Br J Haematol 2020;190(1):29–31.
70. Houot R, et al. Could anti-CD20 therapy jeopardise the efficacy of a SARS-CoV-2 vaccine? Eur J Cancer 2020;136:4–6.
71. Schulze-Koops H, et al. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. Ann Rheum Dis 2021; 80(5):e67.
72. Brito S, et al. A Case of Autoimmune Hemolytic Anemia Following COVID-19 Messenger Ribonucleic Acid Vaccination. Cureus 2021;13(5):e15035.