Acquired hemophilia A: an underdiagnosed, severe bleeding disorder

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KEY WORDS
acquired hemophilia, activated prothrombin bleeding disorder, complex concentrate, recombinant activated factor VII

ABSTRACT
Acquired hemophilia is a rare bleeding disorder caused by autoantibodies that inhibit coagulation factor VIII. In most cases, it manifests with severe, often life-threatening bleeds. Acquired hemophilia may be idiopathic or secondary to another condition, most commonly other autoimmune disease or cancer. Treatment is directed to stop bleeding and eradicate inhibitory autoantibodies. Like in most life-threatening conditions, early diagnosis and treatment are essential for good prognosis. Prompt diagnosis and treatment of acquired hemophilia are constantly improving owing to the increasing availability of laboratory diagnostic tests and growing awareness of physicians of various specialties.

Introduction
Massive hemorrhage in a patient without underlying congenital bleeding disorder may have a number of causes, including intake or overdose of anticoagulant agents, acquired vascular or platelet bleeding disorders (e.g., autoimmune thrombocytopenia), or acquired deficiency of clotting factors. Urgent differential diagnosis and specific treatment are often crucial.

Acquired coagulation factor deficiencies are caused by inhibitory autoantibodies affecting the function and/or increasing clearance of proteins acting at different stages of the coagulation cascade. They are usually directed against clotting factor VIII (FVIII), causing acquired hemophilia A (AHA), and may occur in individuals suffering from other autoimmune disorders or malignancies, or in pregnant women. The clinical picture can range from no or minimal bleeds to life-threatening hemorrhages. Clotting factor inhibitors (except those directed against von Willebrand factor and factor XIII) usually cause abnormalities in screening coagulation tests (activated partial thromboplastin time [aPTT] and/or prothrombin time [PT]).

AHA is a rare but still largely underdiagnosed bleeding disorder, with unique clinical presentation. It was first described in 1940 in a 61-year-old man who died from uncontrollable postoperative hemorrhage. Owing to the rarity of the disease, the knowledge on its clinical picture and treatment modalities is based mostly on case series and single reports. Currently, the most reliable data on its incidence, mortality, and treatment outcome come from prospective national registries: SACHA from France, UKHCDO from United Kingdom, and the pan-European EACH2 registry.

In Poland, AHA is currently registered in the national registry of bleeding disorders at the Institute of Hematology and Transfusion Medicine in Warsaw. A special Polish registry of acquired hemophilia is under development and will be managed by the Working Group on Hemos-tasis of the Polish Society of Hematology and Transfusion Medicine. The first Polish guidelines on the management of AHA were published in 2011 by this Working Group.

Pathophysiology
AHA is caused by polyclonal inhibitory immunoglobulins G (predominantly IgG1 and IgG4) against FVIII. They react with A2, A3, or C2 domains of the FVIII molecule, blocking its interactions with active factor IX, phospholipids, and von Willebrand factor. A disturbed proportion of CD4+ Th1 to Th2 cells plays a role in autoantibody production and reactivity. Predominance of Th2-driven IgG subclasses is associated with higher inhibitor titer and poor outcome, whereas the predominance of Th1-driven IgG correlates with better outcome of immunosuppressive therapy.
The etiology of this immune tolerance breakdown remains unknown. A role of genetic factors (immune response genes and HLA genotype) in the pathophysiology of the disease has been suggested. An association between AHA incidence and the presence of cytotoxic T-lymphocyte antigen 4 polymorphism \((\text{CTLA-4} + 49 \text{G})\) or expression of class II HLA alleles \(\text{DRB1}^1*16\) and \(\text{DQB1}^1*0502\) seem to support this hypothesis.

The kinetics of FVIII autoantibodies in AHA is different from that of the alloantibodies directed against exogenous FVIII in patients with congenital hemophilia. FVIII autoantibodies show a second-order nonlinear inactivation pattern with usually detectable residual FVIII activity. However, this residual activity does not correlate either with inhibitor titer or with bleeding tendency.

**Epidemiology**  
The incidence of AHA is at present estimated at around 1.5 per million per year (equally distributed among men and women), but it is probably much higher as many patients are not correctly diagnosed before fatal complications occur. The newest data show an excess of males in the population over 65-70 years of age. Registry data confirm that AHA incidence increases with age. The median age of the registered patients is around 75 years with more than 80% being older than 65 years. The disease is unusual in children with an estimated yearly incidence of about 0.045 per million below 16 years of age as compared to at least 14.7 per million per year in the population over 85 years.

Another peak in AHA incidence is observed among women of childbearing age. Pregnancy-associated cases account for 2% to 21% of all AHA patients. The inhibitor is usually detected between the third and 150th day postdelivery (median, 89 days \(\text{range, 25–180}\) in the EACH2 registry), but early postpartum hemorhages as well as persistence of the inhibitor over 1 year have also been described. The UKHCDO estimates the incidence of postpartum AHA in the United Kingdom at 1 case per 350,000 births.

Registry data confirm that about half of the AHA cases are idiopathic, whereas the most common underlying conditions include autoimmune disorders (around 20%) and malignancies (around 12%). Dermatologic diseases (approx. 2%) and drug-induced cases constitute the smallest proportion. Possible associations with infection and blood transfusions were also suggested.

**Clinical picture**  
Unlike congenital hemophilias, patients with AHA typically present with diffuse, large subcutaneous hematomas (figure). They are usually painful and cause significant drop in hemoglobin levels. Other manifestations may include: muscle and mucosal bleeds (including gastrointestinal and urogenital), postsurgery and wound bleeding, as well as retroperitoneal hemorrhages. Joint bleeds are uncommon. Intracranial bleedings were also reported. Massive hemorrhages can be induced by anticoagulant or antiplatelet drugs. Venous compression by intramuscular hematomas, mimicking deep vein thrombosis, may lead to erroneous heparin administration. Muscle bleeds may not only lead to a significant blood loss, but also, if too late or inadequately treated, to vascular/nerve ischemia by compression or to future abcess formation. Deep muscle bleeds, for example to the iliopect, may be overlooked or misdiagnosed as acute abdomen, leading to unnecessary surgical intervention. Bleeding after minor surgical procedures (e.g., tooth extraction), organ biopsy, or central venous catheter placement can be extremely difficult to manage and potentially fatal. Now, up to 8% of the patients die early in the course of the disease (median 19 days from diagnosis) owing to uncontrollable hemorrhage.

Deaths within the first week are mainly caused by gastrointestinal and/or lung bleeding, whereas intracranial and retroperitoneal bleeds predominate later. The clinical picture of pregnancy-related AHA may also be heterogeneous. In the EACH2 registry, both severe and mild bleeds were reported, with half of them being spontaneous. Seventy-five percent of women with pregnancy-related AHA were primigravidas. Bleeding episodes were mostly subcutaneous, mucosal, or retroperitoneal (only 2 hemarthroses were reported). Some patients suffered from delayed postpartum hemorrhage (up to 6 weeks postdelivery). In a few women, the disease developed during pregnancy. Pregnancy-related AHA is characterized by a relatively good outcome (spontaneous remissions are observed) and relatively low mortality rates (up to 6%). Several cases of in-utero inhibitor transfer to the newborn have been reported in the literature, with only 2 of them being clinically overt (intracranial bleeding in 1 child and post-surgery bleed in another). Maternal autoantibodies seem to disappear without treatment.

Owing to increased awareness, AHA is often diagnosed before significant bleeds appear, based on aPTT prolongation in routine (e.g., presurgery) tests or after minor bleeding. Up to one-third of the patients do not require any hemostatic therapy. However, severe episodes of bleeding can occur at any stage of the disease, until the inhibitor is successfully eradicated.
Diagnosis An isolated prolonged aPTT in a bleeding, previously healthy, and not anticoagulated patient strongly indicates AHA. A history of prolonged aPTT (if available) as well as a history of bleeds in the individual and within his or her family help differentiate AHA from congenital hemophilias A, B, and C as well as from factor XII deficiency.

A generally accepted algorithm for AHA diagnosis includes: measurement of FVIII activity, mixing studies and the Bethesda assay for the assessment of the inhibitor level. These tests are usually available in hemophilia centers and other laboratories of hemostasis. In Poland, if in doubt, the nearest Hematology Department or Regional Blood Bank should be contacted.

Typically, aPTT is prolonged by 2 to 3 times. FVIII activity in most cases decreases below 15%. In the registries, from 66% to 76% of the patients had their FVIII activity at diagnosis lower than 5%. Mixing studies show lack of aPTT correction after 1- to 2-hour incubation of patient plasma with an equal volume of normal plasma. However, lack of correction is also typical for the presence of lupus anticoagulant. To confirm AHA diagnosis, it is necessary to perform both FVIII activity assay and the Bethesda assay (preferably in Nijmegen modification), which proves the presence of FVIII neutralizing antibodies and titrates their quantity in Bethesda units [BU].

In the registries, inhibitor titers vary widely (0.1–2800 BU [median, 12.8] and 0.8–717 BU [median, 7]). Neither FVIII activity nor inhibitor titer correlate with each other or with the severity of bleeding and treatment outcome.

While the diagnostic algorithm for AHA is straightforward, one must be aware of potential diagnostic traps. The most common causes of isolated aPTT prolongation—lupus anticoagulant and factor XII deficiency—are nonhemorrhagic states. On the other hand, nonisolated aPTT prolongation does not always rule out AHA because an associated thrombocytopenia, low fibrinogen level, or PT prolongation can be explained by concomitant disorders (e.g., liver function impairment, infection, disseminated intravascular coagulation). Mixing studies should be performed correctly, as an immediate aPTT correction (without 1- to 2-hour incubation) does not rule out AHA due to time-dependent action of FVIII antibodies. In rare cases, the inhibitor may become detectable only after several days; therefore, when in doubt, especially with low FVIII activity, repeated testing can be indicated. FVII inhibitor can interfere with factor IX, XI, and XII assays (false decrease of their activity can be eliminated by sample dilution). This could also be the case with the presence of lupus anticoagulant. In diagnostically difficult cases (e.g., coexistence of FVIII inhibitor and lupus anticoagulant) an enzyme-linked immunosorbent assay may be helpful.

Clinically, FVIII alloantibodies have to be differentiated with FVIII autoantibodies because, in rare cases, a clinically silent mild hemophilia A patient can develop alloantibodies against exogenous FVIII (e.g., after transfusion of blood components) that interfere with native FVIII and cause bleeding.

Treatment of acquired hemophilia Treatment strategy includes 2 major goals: to stop bleeding and prevent its recurrence, and to eradicate the inhibitor. As the disease is characterized by a high early mortality rate, prompt hemostatic treatment is often necessary, depending on the bleeding severity and/or localization. Invasive procedures (including hematoma evacuation or drainage) should not be undertaken unless absolutely necessary, until the inhibitor is eradicated.

Hemostasis in the perioperative period cannot be guaranteed, even with the best available hemostatic treatment. We should also restrict the number of venipunctures to a minimum. Patient education on early symptoms of bleeding, protection from trauma, and avoidance of certain drugs (e.g., over-the-counter nonsteroidal anti-inflammatory drugs) is also important.

Immunosuppressive therapy should be started as soon as possible. No delay is recommended even if spontaneous disease resolution can be anticipated because disease remissions are unpredictable and inhibitor persistence poses high risk of further bleeding. In clinical practice, patients with postpartum or drug-induced AHA are sometimes left untreated for several months postpartum or after drug withdrawal, if the bleeding pattern is mild and close surveillance is possible. An individual risk and benefit ratio should be weighted in such cases.

Another important goal is to identify and treat the underlying condition to promote spontaneous resolution of AHA or facilitate treatment. Screening tests for common neoplasms may be reasonable. In drug-induced AHA, withdrawal of the offending agent usually leads to disease remission.

Hemostatic treatment Patients manifesting with active, severe bleeding at any stage of the disease require hemostatic treatment with one of the two marketed bypassing agents: recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). Bypassing therapy should be started irrespectively of inhibitor titer and residual FVIII activity. If the patient presents with a life-threatening bleeding, treatment can be initiated immediately, based only on typical clinical picture and aPTT prolongation, before definite laboratory results become available.

Bypassing agents should be dosed in a bolus injection at clinically effective doses: 90 µg/kg of rFVIIa every 2–3 h or 50–100 IU/kg of aPCCs every 8–12 h to a maximum of 200 IU/kg/d. Therapy should be continued until bleeding is controlled or longer, at reduced intensity, to prevent recurrence of bleeding. This is especially important after intramuscular, intracranial, and other major bleeds.
The overall hemostatic efficacy of rVIIa and aPCC is similar at around 75% to 100% (>90% in the EACH2 registry).4,11,26,27 The choice of the first-line therapy is usually guided by availability and cost of both agents; nevertheless, clinicians sometimes prefer one of them depending on the clinical situation and local experience. One should also consider previous patient’s response and a more convenient dosing schedule.26 There is no high-level data to recommend one agent over the other. A recombinant agent can sometimes be preferred, e.g., in women of reproductive age or patients benefiting from concomitant antifibrinolytic therapy.2,22,28

The major drawback of bypassing therapy is that its efficacy cannot be laboratory-monitored. The use of thrombin generation assays or thromboelastometry is promising but cannot be recommended yet.26 Therapeutic efficacy of bypassing agents can only be assessed based on clinical manifestations, frequent hemoglobin/hematocrit measurement, and transfusion requirements.21,22

It should be stressed that in contrast to congenital hemophilia A, AHA patients are generally exposed to thrombotic risk factors including age, obesity, smoking, diabetes, and other concomitant diseases, e.g., cardiovascular history.21,24,29 It adds to the intrinsic thrombogenic potential of both bypassing agents. Clinical data are scarce here and do not allow for direct comparison of the thrombogenicity of both agents. Owing to methodological flaws, the previously reported incidence of venous or arterial thrombotic episodes should be taken with caution.28 The newest data indicate similar incidence of thrombotic episodes among patients treated (3.6%) and not treated (2.7%) with bypassing agents with no difference between rVIIa (2.9%) and aPCC (4.8%).27 In general, caution is required in elderly people, patients with cardiovascular disease or advanced atherosclerosis, sepsis or signs of disseminated intravascular coagulation, as well as in the postpartum period.2,22,23 Obviously, severe or life-threatening bleeds require hemostatic treatment with recommended doses irrespective of a potential thrombotic risk.22,26,27,30

The risk associated with the concomitant therapy with bypassing agents and tranexamic acid in AHA is unknown. If the patient can benefit from both, experts rather prefer to use rVIIa or suggest that antifibrinolytics administer no sooner than 12 h after the last aPCC dose.27 This approach can change in the future, when more data become available.

The administration of aPCC was reported to induce anamnestic response (inhibitor titer increase; noted in 9.5% of AHA patients in the EACH2 registry), but the clinical significance of this phenomenon remains unknown.22,27

Neither of the bypassing agents offers effective hemostasis in every patient.21 If the first-choice agent fails, an early switch to the other is advisable.29 If both drugs fail, combined (simultaneous) therapy or an alternate scheme (sequential therapy) may be tried, with full or reduced doses (according to a few case reports: 30–100 IU/kg of aPCC every 6–12 h plus 1–3 interim doses of rVIIa at 90–270 µg/kg for sequential therapy; 20–30 IU/kg of aPCC plus 30–70 µg/kg of rVIIa every 6–12 h for combined therapy).30 However, such an approach may increase the risk of thromboembolic events.29

Any, even minor, surgical procedure carries an increased risk of uncontrollable bleeding and, therefore, should be postponed until inhibitor is eradicated. Only life-saving procedures could be considered, if possible in experienced centers, and with the use of bypassing agents (although optimal doses are not determined).22,28

Bypassing therapy is usually not required during minor bleeds (ecchymoses or subcutaneous hematomas without substantial drop in hemoglobin level).21,26 Antifibrinolics and topical hemostatic agents are often sufficient for mucosal or superficial bleeds.17,21,26 Care should be taken to substitute for thrombocytopenia (<100,000/µl), impaired platelet aggregation, and/or decreased fibrinogen levels (<2 g/l), as their proper management spares bypassing agents and improves treatment efficacy.30

When low-titer inhibitor is present, high-dose FVIII concentrate (to overcome the inhibitor) or desmopressin (0.3 µg/kg/d, intravenously or subcutaneously) could be administered for minor bleeds.31 Overall efficacy is lower than that of bypassing therapy but may reach around 70% in selected cases.27 However, care is required because variable, unpredictable treatment outcome, anamnestic response, tachyphylaxis, and metabolic side effects (in the case of desmopressin) are possible.2,21,22 In refractory cases or before surgeries, immunoabsorption or plasmapheresis are sometimes tried to temporarily remove inhibitor and increase FVIII activity.21,22 Porcine FVIII can effectively manage bleeds in patients with AHA because it is far less susceptible to human FVIII inhibitors.22,23 Plasma-derived porcine FVIII is no longer used,24 but a recombinant B-domain deleted preparation is currently being investigated in clinical studies (unpublished data).

In Poland, bypassing agents, FVIII concentrate, and desmopressin for AHA treatment are purchased in central tenders by the Ministry of Health within the National Program for Treatment of Hemophilia and Related Bleeding Disorders and distributed via Regional Blood Banks.

**Immunosuppressive treatment** First-line immunosuppressive treatment in AHA includes corticosteroid monotherapy (prednisone, 1 mg/kg/d for 4–6 weeks) or its combination with cytotoxic agents (e.g., cyclophosphamide, 1.5–2 mg/kg/d for up to 6 weeks).21,23 Inhibitor eradication can be achieved in 58% to 76% of the patients treated with steroids alone and in 77% to 89% of the patients receiving steroids with cytotoxic drugs; with no difference in median time-to-remission.5,17,26 Combination treatment seems
to be more effective in persistent antibody eradication but the overall survival remains similar, probably owing to side effects of cytotoxic therapy (infections and myelosuppression).\textsuperscript{1,5,11} Therefore, the type of treatment should be carefully adjusted to the patient’s age, general condition, and comorbidities. In women in reproductive age, cytotoxic agents should be avoided.\textsuperscript{21,22}

Disease remission, defined as an undetectable increase in FVIII inhibitor and FVIII levels to more than 50%, is usually achieved in a median of 5 weeks.\textsuperscript{21,22} During immunosuppressive therapy, aPTT, FVIII activity, and inhibitor titer should be monitored at least weekly.\textsuperscript{22} With no improvement after 3 to 6 weeks, second-line therapy is recommended,\textsuperscript{1,2,8} e.g., cyclosporine (200–300 mg/d) with steroids or other cytotoxic drugs (azathioprine, 6-mercaptopterine, vincristine, mycophenolate mofetil).\textsuperscript{2,11,21} Rituximab is becoming a preferred second-line option in many hospitals because it is effective in 42% to 87% of the cases and has a good safety profile.\textsuperscript{4,12,22,21} Borg et al.\textsuperscript{4} reported that concomitant steroid and/or cyclophosphamide therapy improves treatment efficacy, which was also confirmed by preliminary studies of Várkonyi et al. and Tiede et al. (unpublished data). A low-dose combined regimen (rituximab 100 mg plus dexamethasone 40 mg once weekly for 4 weeks plus cyclophosphamide 1000 mg on day 1 and 22; 1–3 cycles) has recently been shown to induce a high rate of remission (unpublished data).

High-dose intravenous immunoglobulin alone or in combination is not effective in AHA. The complete remission rate, in very low titer inhibitors only, does not exceed 10% to 25%.\textsuperscript{2,5,11,17,22}

Similarly to inherited hemophilia with an inhibitor, immune tolerance induction protocols have also been applied in AHA. The 3-week-long Budapest protocol (FVIII concentrate at tapered doses, starting from 30 IU/kg/d, with intravenous cyclophosphamide and methylprednisolone) enabled inhibitor eradication in more than 90% of the cases.\textsuperscript{11} Almost the same response rate was reported with a protocol based on oral cyclophosphamide, prednisolone, immunoabsorption, intravenous immunoglobulins, and FVIII concentrate.\textsuperscript{11} However, lack of control groups makes the real benefit from adding FVIII concentrate to combined immunosuppressive regimens difficult to assess.\textsuperscript{17}

If different lines of immunosuppression fail, hemostatic treatment and careful observation are the only option.\textsuperscript{7} In single patients, immunosuppressive treatment cannot be stopped without disease relapse.\textsuperscript{5,17,18}

AHA remission may be associated with excessive increase in FVIII levels. In the case of additional thrombotic risk factors, appropriate thromboprophylaxis should be considered.\textsuperscript{1,17,22}

**Outcome and prognosis** Prognosis in AHA depends on the clinical course, severity of bleeding, and underlying diseases. Spontaneous complete remissions are reported in 25% to 36% of the patients, predominantly in postpartum or drug-related cases.\textsuperscript{12,17,31} Delay in proper diagnosis and treatment significantly worsens the outcome.\textsuperscript{4} Collins et al.\textsuperscript{31} reported the current overall survival at 69% to 78%. Similar rates were reported by Tiede et al. (unpublished data). In the EACH2 registry, the survival of patients who achieved complete remission was not different from that in the general population.\textsuperscript{6} In the English registry (overall mortality of 41%), age was the only factor affecting survival, whereas sex, underlying condition, baseline FVIII level, and inhibitor titer did not affect the outcome.\textsuperscript{3} However, more recent reports by Collins et al.\textsuperscript{31} and Tiede et al. (unpublished data) suggest that higher baseline FVIII activity and lower inhibitor titer (<16 BU) may be associated with better outcome.\textsuperscript{21}

Death may be related to concomitant diseases, side effects of therapy, and serious hemorrhage. In registry data, therapy-related mortality was similar or even higher than mortality related to bleeding.\textsuperscript{4,6,31} Pregnancy-related AHA is exceptional in this respect as the survival approaches 100% (after a median follow-up of about 13 months in the EACH2 registry).\textsuperscript{18}

After remission is achieved, the patient should be closely monitored for disease recurrence. Up to 20% of patients relapse, usually within the first 2 years.\textsuperscript{2,4,5,31} FVIII activity should be monitored every month for the first 6 months, every 2 to 3 months for the next 6 months and every 6 months thereafter.\textsuperscript{2,17,21-23} A relapse rate seems to be lower after rituximab-containing regimens.\textsuperscript{31}

In the case of postpartum AHA, the risk of recurrence in subsequent pregnancies seems to be very low; however, women should be informed about this possibility.\textsuperscript{24} AHA relapse can be successfully treated with the reinstitution of the same immunosuppressive regimen.

**Summary** AHA is a rare but potentially lethal autoimmune bleeding disorder observed mostly in elderly patients and, sometimes, in pregnant women. It is vital to rapidly recognize and properly treat those subjects. AHA may be definitely suspected when a nonanticoagulated patient develops new large skin hematomas together with usually isolated prolongation of aPTT. Prompt consultation with an experienced hematologist and contact with a specialized coagulation laboratory is necessary to confirm the diagnosis and initiate bypassing and immunosuppressive treatment. It is of utmost importance because diagnosis and treatment of AHA is often delayed, leading to major clinical complications, additional costs, and even death. Time from detection of prolonged aPTT or from the first bleeding manifestation to diagnosis and time from diagnosis to treatment can sometimes be counted in weeks to months.\textsuperscript{10,23}

As treatment of this rare disease requires some experience, it has been suggested that AHA patients should be transferred to reference centers.
if possible.\textsuperscript{11,12} In Poland, the best option is to contact hemophilia treatment centers.

Currently, ongoing research in AHA is focused on shorter schemes of immunosuppressive therapy and possibilities of individual adjustment of bypassing therapy with the use of whole blood thromboelastometry and thrombin generation assays. It is also directed towards development of laboratory tools enabling better quantification of autoantibodies in AHA, reflecting their true inhibiting potency, as well as finding alternative hemostatic therapies and immunosuppressive or immunomodulatory agents to improve treatment efficacy and safety.\textsuperscript{24}

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**REVIEW ARTICLE**

Acquired hemophilia A: an underdiagnosed, severe bleeding disorder
ARTYKUŁ POGŁĄDOWY

Nabyta hemofilia A – zbyt rzadko rozpoznawana ciężka skaza krwotoczna

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SŁOWA KLUCZOWE

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STRESZCZENIE

Nabyta hemofilia jest rzadką skaza krwotoczna wywołaną przez autoprzeciwciała skierowane przeciwko czynnikowi VIII krzepnięcia. W większości przypadków objawia się poważnymi, nieraz zagrażającymi życiu krwawieniami. Nabyta hemofilia może być chorobą idiopatyczną lub wtórną do innej choroby, najczęściej choroby z autoagresji lub nowotworowej. Leczenie ma na celu opanowanie krwawienia oraz eradycję autoprzeciwciała. Wczesne ustalenie rozpoznania i leczenie mają kluczowe znaczenie dla rokowania. Wykrywalność nabytej hemofilii oraz rokowanie pacjentów ulegają stałej poprawie dzięki lepszemu dostępowi do badań laboratoryjnych oraz edukacji lekarzy różnych specjalności.

Słowa kluczowe

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