Guidelines for the management of acquired hemophilia A in elderly patients

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Summary

Acquired hemophilia A is an autoimmune disease caused by antibodies against coagulation factor VIII (FVIII). These antibodies, called circulating FVIII anticoagulant or FVIII inhibitor, reduce plasma FVIII activity, which results in excessive bleeding. Acquired hemophilia A is classified as a severe hemorrhagic disorder. Typical for this disease are extensive subcutaneous spontaneous blood extravasations, intramuscular and retroperitoneal hematomas, and post-traumatic bleeds, including post-surgery bleeding. In approximately 30% of cases, acquired hemophilia A is initially manifested merely by minor bleeding, which may be often overlooked by the physician, but as long as FVIII inhibitor is detected, the patient is at risk of severe, sometimes fatal, hemorrhage. Acquired hemophilia A is most common in people aged 60–90 years. Patients in this age group often take anticoagulants, antplatelet and non-steroidal anti-inflammatory drugs, and bruising and purpura are relatively common among them, so acquired hemophilia A can easily be overlooked. On the other hand, the delay in the diagnosis of the disorder may result in delayed initiation of hemostatic treatment and elimination of the FVIII inhibitor, which puts the patient at risk of premature death. The aim of this publication is to present the principles of diagnosis of acquired hemophilia A, the use of hemostatic drugs to inhibit and prevent bleeding, and immunosuppressive drugs to eliminate the FVIII inhibitor in elderly patients.

Key words: acquired hemophilia A, the elderly, factor VIII, circulating anticoagulant, acquired hemorrhagic diathesis

Introduction

Acquired hemophilia A (AHA) is an autoimmune bleeding disorder caused by antibodies against endogenous factor VIII (FVIII). These antibodies, referred to as the circulating FVIII anticoagulant or FVIII inhibitor, reduce plasma FVIII activity and cause excessive bleeding. Unlike congenital hemophilia A, caused by F8 gene mutation on the X chromosome (men suffer from the disorder; women carry the mutant gene) AHA occurs in both men and women [1].

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Translation: dr n. med. Dariusz Stencel

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Acquired hemophilia A is classified as severe hemorrhagic disorder. Typical symptoms of AHA include extensive subcutaneous spontaneous extravasation, intramuscular and retroperitoneal hematomas, and post-traumatic bleeding, including post-surgery bleeds. In about 30% of cases, AHA initially manifests only with minor bleeding, which may often be overlooked by the physician. However, as long as the FVIII inhibitor is detected, the patient is at risk of severe, often fatal, hemorrhage [1]. In the 1980s, AHA mortality was estimated at 42% [2]. Fortunately, effective treatment regimens for AHA are now available and can quickly control bleeding, eliminate the FVIII inhibitor, and reduce overall mortality to ≤ 12% [2].

In the studies conducted almost two decades ago, the AHA prevalence was annually estimated at about 1.5 per million people, but the latest studies indicate that it may be even 2–3 fold higher [3, 4]. In about 50% of cases, AHA coexists with other diseases, mainly autoimmune and neoplastic diseases, clinical conditions such as pregnancy, especially puerperium, and less frequently AHA is associated with drug intake [1]. In the remaining 50% of cases, AHA is not associated with any other diseases or clinical conditions; this form is referred to as idiopathic AHA [1].

The diagnosis of AHA is based on the clinical manifestation and the results of laboratory tests which demonstrate isolated prolongation of activated partial thromboplastin time (APTT), presence of circulating anticoagulant, decreased plasma FVIII activity and presence of anti-FVIII antibodies in the patient plasma in Bethesda assay. Acquired hemophilia A is most common in people aged 60–90 years [1, 4]. Patients in this age group often take anticoagulants, antiplatelet and non-steroidal anti-inflammatory drugs, and bruising and purpura are relatively common among them, so acquired hemophilia A can easily be overlooked. On the other hand, the delay in the diagnosis of this disease may result in delayed initiation of hemostatic treatment and elimination of the FVIII inhibitor, which puts the patient at risk of premature death.

The aim of this publication is to present the principles of diagnosis of acquired hemophilia A, the use of hemostatic drugs to inhibit and prevent bleeding, and immunosuppressive drugs to eliminate the FVIII inhibitor in elderly patients.

**Elderly population**

The population of elderly people in Poland is on the increase. Although there is some discussion about the age to be considered “old”, taking into account the health condition of the Polish population, there is consensus that elderly people are over 60. The number of 60-year-olds in Poland (and older) is now approaching 10 million, with almost 25% being over 75. Notably, the analyzes of the Central Statistical Office (GUS) indicate that in the next 30 years, the number of people in this age group is expected to increase by about 30%. This means that in 2050 the number of people aged 75 or more will exceed 5 million [5].

Since the 7th decade of life, we observe the onset of aging symptoms in the sphere of biology, psychology and changes in the social and economic status. Proper identification of the risks associated with aging is an in-depth assessment in all of the above-mentioned areas [6].

From a biological point of view, the aging process can be defined as a diminished ability to maintain homeostasis as result of impaired cell and organ function associated with accumulation of morphotic and functional changes. As a result, there is an insufficient compensatory reaction to stimuli that are often unnoticeable at an earlier age. For example, even a short-term hospitalization or a change in the environment of healthy elderly person may lead to a loss of fitness or trigger an acute confusional state called delirium. Regardless of the aforementioned consequences of physiological aging, in the elderly, several comorbidities often occur simultaneously (over 60% of people have four chronic diseases), resulting in polypharmacy [7]. Moreover, in old age the consequences of past events, such as physical and mental injuries, surgical operations, chemotherapy, radiation therapy, exposure to stress and environmental pollution may accumulate.

In the Polish population, approximately 50% of people aged 80 or more require support in everyday activities, such as movement, eating or dressing. Moreover, the vast majority have difficulties in following medical recommendations, they need assistance in shopping or managing money. Over 90% of people at this age do not use the Internet, which makes telemedicine inaccessible for them. Diseases, often mild in young people are associated with a very high risk in the elderly. For example, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is most often mild in children and young people, in 80-year-olds is severe and associated with a mortality rate of more than 60%.

The epidemiological POLSENIOR-1 and POLSENIOR-2 studies provide, i.a. data on signs and symptoms, which may indicate AHA in elderly
patients. These include anemia and coagulation disorders, as well as diseases conducive to the occurrence of AHA, e.g. malignant tumors and autoimmune diseases. The studies show a potential difficulty in the differential diagnosis of AHA due to the frequent use of antiplatelet and anticoagulant drugs by the elderly. Such drugs increase the risk of bleeding just as corticosteroids, which increase the fragility of blood vessels as manifested by subcutaneous hemorrhages [8].

The incidence rate of AHA increases with age, which is inextricably linked with oncological diseases. In Poland, neoplasms are responsible for about 38% of deaths in the group of people aged 65–75 years and over 12% of deaths in people over 85 years of age [5]. Data from the United States show that the risk of developing cancer after the age of 70 exceeds 32% in men and 25% in women.

Some autoimmune diseases are also more common in the elderly. For example, the average age at diagnosis of giant cell arteritis (GCA) is 75 years, and the incidence of polymyalgia rheumatica (PMR) increases linearly with age up to the 10th decade of life. Arthritis is also most common in people over 60. Age-related immune dysfunctions are responsible for the aging process due to impaired response to pro-inflammatory factors (inflammaging), but may also induce autoaggressive diseases, including AHA [9]. Thymic involution is considered the main cause of the decreased number of naive T-cell, which favors the development of neoplastic diseases and a lower response to vaccines. It cannot be ruled out however, that individual history of immune responses produced by individuals during their lifetime, referred to as “immunobiography” is significant. In the old age, there is a continuous increase in the production of pro-inflammatory cytokines, which reduces the immune system’s potential to respond to the inflammatory factors.

**Pathophysiology of acquired hemophilia A**

The underlying cause of AHA are immune system disorders leading to the production of antibodies that inhibit FVIII activity [10]. The mechanisms responsible for the impairment of the immune system in AHA are not yet fully explained. The result of plasma FVIII deficiency is a reduction in thrombin production with subsequent disturbances in normal fibrin clot formation at the site of vascular injury, which is manifested by a tendency to excessive bleeding, i.e. a hemorrhagic diathesis.

The autoantibodies present in AHA are a mixture of polyclonal IgG1 and IgG4 immunoglobulins G subclasses, with IgG4 mainly contributing to the inhibition of FVIII coagulation activity. The major epitopes for autoantibodies are found in the A2, A3 and C2 domains of FVIII. Anti-C2 antibodies inhibit the interaction of FVIII with phospholipids as well as impair the binding of FVIII to von Willebrand factor (VWF). On the other hand, anti-A2 and anti-A3 antibodies impede the binding of FVIII to factor X (FX) and active factor IX (FIXa), respectively [11]. Antibodies interacting with other FVIII domains may be clinically “mute” or impair FVIII activity by mechanisms other than those mentioned above [12]. For example, antibodies against the B domain may accelerate FVIII clearance.

The kinetics of the interaction between FVIII and autoantibodies in AHA is different from the interaction of FVIII with alloantibodies in congenital hemophilia A complicated by the presence of an FVIII inhibitor. In congenital hemophilia A, alloantibodies completely eliminate plasma FVIII activity (linear type 1 kinetics). In AHA, even with a very high autoantibody titer, residual plasma FVIII activity is detected (the so-called nonlinear kinetics of type 2), which, however, does not protect patients with AHA from heavy bleeding [13]. The complex kinetics of the interaction between autoantibodies and FVIII in AHA make it difficult to precisely determine the concentration (titer) of an inhibitor in the Bethesda assay (see below). The common features of anti-FVIII autoantibodies and alloantibodies are non-immunoprecipitation and non-complement binding, so in both AHA and congenital hemophilia A, the presence of an FVIII inhibitor does not cause tissue and organ damage [14].

**Epidemiology**

In studies conducted nearly two decades ago, the annual incidence rate of AHA in the British Isles was estimated at approximately 1.3–1.5 per million [3]. It has also been shown that the incidence of AHA increases with age, accounting for about 0.045 per million in children under the age of 16 and 14.7 per million in people over 85 years of age [6]. Data from the multicenter, international, web-based European Acquired Hemophilia Registry (EACH2) indicate that the median age at diagnosis of AHA is 73.9 years [1]. In the people aged 20 to 40, AHA is detected more often in women than in men, and the increase in the incidence rate of AHA in young women is closely related to pregnancy, particularly the first 12 months after
In 2021, German authors presented the latest data on the annual incidence rate of AHA from the German-Austrian-Swiss GTH-AH 01/2010 registry [4]. According to this source, the annual incidence rate of AHA is 5–6 cases per million, more than 3 fold higher than would appear from the previously mentioned British study, published 15 years earlier [3]. The data from the GTH-AH 01/2010 registry reflect an improvement in AHA detection as result of recent educational campaigns that raise awareness of this bleeding disorder. Following these campaigns many centers implemented laboratory tests indispensable for establishing final diagnosis of AHA.

The Clinical picture

In majority of cases, AHA manifests suddenly with spontaneous hemorrhagic diathesis, which, without proper treatment, may lead to death in more than 20% of patients [1, 14]. The most typical symptoms of AHA include extensive subcutaneous hemorrhages (Fig. 1), followed by intramuscular hematomas, mucosal bleeding (from the gastrointestinal tract, urinary tract, genital tract), excessive and prolonged bleeding from postsurgical wounds and tooth extractions (Table 2). In patients with AHA it is difficult to stop bleeding from postoperative wounds even if appropriate treatment is administered (see below). Most experts recommend avoiding invasive diagnostic and therapeutic procedures in patients with AHA [16]. Intracerebral hemorrhage (ICH) is most often fatal, but fortunately uncommon. Bleeding into the anatomical fascia spaces (e.g. into the muscles of the upper and lower extremities) is very dangerous, because the growing hematoma may press on the adjacent nerves and blood vessels, leading to their irreversible damage. Interestingly, in contrast to congenital hemophilia A, there are no spontaneous or traumatic joint bleedings in the course of AHA.

Sometimes AHA manifests by the presence of a hematoma of the retroperitoneal space, unaccompanied by other symptoms of hemorrhagic diathesis. An error of tumor diagnosis can then be made and the patient may be qualified for surgery, which — as already emphasized — is burdened with very high risk of severe, often fatal bleeding complications. It is worth emphasizing that most AHA hematomas are treated conservatively (see below); surgical procedures are performed only when such management is ineffective and failure to perform surgery would result in death.

Table 1. Clinical conditions in course of which acquired hemophilia A may occur (modified from [15])

| Clinical condition or disease                        | Estimated frequency (%) |
|------------------------------------------------------|-------------------------|
| Unrelated to other clinical conditions and diseases — idiopathic form | 51.9                    |
| Malignant neoplasms                                  | 11.8                    |
| • solid tumors                                       | 8                       |
| • hematological malignancies                         | 3.8                     |
| Autoimmune diseases                                  | 11.6                    |
| • rheumatoid arthritis                               | 4                       |
| • other connective tissue diseases                   | 1.6                     |
| • systemic lupus erythematous                        | 1                       |
| • autoimmune thyroid diseases                        | 0.8                     |
| • Sjögren’s syndrome                                 | 0.6                     |
| • antiphospholipid syndrome                          | 0.4                     |
| • other autoimmune diseases                         | 3.8                     |
| Pregnancy and the period of 12 months after childbirth| 8.4                     |
| Infections                                           | 3.8                     |
| Relationship with drugs                              | 3.4                     |
| • beta-lactam antibiotics                            | 0.8                     |
| • clopidogrel                                        | 0.6                     |
| • non-beta-lactam antibiotics                        | 0.4                     |
| • interferon                                         | 0.4                     |
| • non-steroidal anti-inflammatory drugs              | 0.4                     |
| • amiodarone                                         | 0.2                     |
| • rivastigmine                                       | 0.2                     |
| • sunitinib                                          | 0.2                     |
| • heparin                                            | 0.2                     |
| Monoclonal gammopathy of undefined significance      | 2.6                     |
| Rheumatic polymyalgia                                | 2.2                     |
| Dermatological diseases                              | 1.4                     |
| • psoriasis                                          | 0.6                     |
| • pemphigus                                          | 0.6                     |
| • other                                              | 0.2                     |
| Related to blood components transfusion              | 0.8                     |
| Other diseases                                       | 8.2                     |

childbirth [1, 3]. In older age groups, AHA is more often diagnosed in men (57% of cases) [1].

According to the data from the EACH2 registry, approximately 52% of people with anti-FVIII autoantibodies do not have any comorbidities (Table 1) [1]. This form of AHA is called idiopathic. In the remaining cases, AHA coexists with other autoimmune diseases, malignant neoplasms, infections or is associated with drug intake or — as previously mentioned — with pregnancy and puerperium.
Of particular concern is the occurrence of AHA in patients on anticoagulant therapy [17]. This is particularly true for the elderly, at high risk of diseases that require administration of anticoagulants or antiplatelet drugs for e.g. atrial fibrillation, deep vein thrombosis and pulmonary embolism, or ischemic stroke. On the one hand, the coincidence of AHA and anticoagulant therapy may aggravate the symptoms of hemorrhagic diathesis, on the other, the diagnosis of AHA in a person on anticoagulant therapy is difficult, because the symptoms are automatically attributed to the anticoagulants effect. It should be emphasized that AHA diagnosis is practically always an indication for discontinuation of anticoagulant and antiplatelet therapy (see below) [16].

**Laboratory test results and diagnosis of AHA**

AHA patients present with significant APTT prolongation (by > 10 s), normal values of prothrombin time (PT), thrombin time (TT), closure time (CT) in platelet function analyzer PFA-100/200®, as well as platelet counts and fibrinogen levels within the normal range [14, 16, 18, 19]. Similar configuration of test results occurs only in congenital deficiencies of so-called intrinsic coagulation pathway factors (VIII, IX, XI and XII) and in patient with plasma antibodies called lupus anticoagulant (LA), which is directed against phospholipids, rather than clotting factors. LA does not induce bleeding tendencies but predisposes to thrombus formation or is indifferent to the hemostatic system. If APTT prolongation results from the presence of unfractionated heparin in the blood sample, TT is usually undetermined.

The presence of circulating anticoagulant is confirmed by prolonged APTT in an equal-volume mixture of patient’s plasma and pooled normal plasma (i.e. mixing study or a correction test) [16, 19]. If prolonged APTT is not corrected as result of adding normal plasma with all the clotting factors (such plasma is commercially available) to patient’s plasma, the test plasma is said to contain a circulating anticoagulant (inhibitor). A positive result of the test for circulating anticoagulant (no APTT correction) is obtained either in the presence of...
FVIII inhibitor or LA, as well as in the presence of an inhibitor directed against coagulation factors other than FVIII of the intrinsic coagulation pathway. Therefore, in order to confirm that the circulating anticoagulant is directed against FVIII, the activity of FVIII should be determined, which is in the range of 50–150 IU/dL (50–150% of the normal) in healthy individuals, while in patients with AHA it is significantly reduced (< 1 IU/dL in 50% of cases; < 5 IU/dL in 75% of cases; < 40 IU/dL in 100% of cases). The last stage of laboratory diagnostics of FVIII inhibitor is the determination of its titer (concentration) expressed in Bethesda units (BU/mL) [19, 20]. Table 3 presents differential diagnosis of prolonged APTT.

Laboratory testing for FVIII inhibitor should be performed on blood samples collected prior to introduction of hemostatic drugs (see below). As a result of the administration of selected hemostatic drugs, in some patients with AHA, APTT is shortened or even normalized, which distorts the results of laboratory tests and may lead to the erroneous exclusion of AHA as the cause of bleeding disorder (Fig. 2).

As already mentioned, in about 80–90% of cases, the suspicion of AHA is based on a clinical picture of hemorrhagic diathesis — often severe, appearing suddenly in a previously healthy individual. It may be accompanied by extensive subcutaneous hemorrhages. However, in some patients with AHA, no symptoms of hemorrhagic disorder are observed, and the only abnormality indicative of AHA is a significant (isolated) prolongation of APTT [1]. It is then important to perform more detailed laboratory tests, and not to wait for exacerbation of the clinical symptoms; AHA detected in time may require no hemostatic therapy but only the implementation of immunosuppressive drugs in order to eliminate FVIII inhibitor (see below).

Since AHA diagnostics includes the analysis of both the clinical features and the results of specialized laboratory tests, the authors of the study point to the need for close cooperation between clinicians and laboratory diagnosticians in order to optimize the process. One of the important elements of this cooperation is the determination of the laboratory testing algorithm for prolonged APTT. An example of such an algorithm is presented in Figure 3.

**Differentiation of AHA and other hemorrhagic disorders in the elderly**

As already mentioned, the aging process significantly affects human hemostasis. Over the years the activity of many coagulation factors increases, the function of fibrinolysis and endothelium weakens, and the content of coagulation inhibitors changes only to a small extent, which in total is responsible for the thrombogenic potential of the human hemostatic system that increases with age [21]. This is reflected, i.a. in in a higher incidence rate of venous and arterial thrombosis in the elderly [22].

This does not mean that the elderly are not at risk of excessive bleeding. Many diseases that are typical of aging process, such as cancers, kidney failure, abnormal liver function, autoimmune diseases, and bone marrow failure, increase the bleeding risk through a variety of mechanisms. The elderly often use anticoagulants, the main side effect of which is bleeding [23].

Particularly important is the use of anticoagulants for prevention of stroke in people with atrial fibrillation. The frequency of this abnormality in the general population in Poland exceeds 22% in people aged 65 years or above, including 41% of cases with silent atrial fibrillation [24]. Among diabetic patients, the frequency of atrial fibrillation is even higher and affects every fourth elderly person [25]. Data from the ChiOTEAF registry indicate that 102 episodes of major bleeding were annually observed in 6,022 patients over 80 years of age who took anticoagulation medication for atrial fibrillation, most of them in the extracranial location (84 cases) [26].

Chronic use of non-steroidal anti-inflammation drugs (NSAIDs) can also lead to bleeding complications. The natural aging process of the skin and connective tissue results in increased fragility of these structures, which may cause senile purpura [27] in more than 10% of people over 70. “Purpura” means subcutaneous blood extravasation. The lesions of senile purpura are located mainly on the hands and forearms, i.e. places where the subcutaneous tissue is thin and does not protect fragile blood vessels from even minor injuries (Fig. 4). Like in other vascular bleeding disorders, the results of laboratory tests for plasma coagulation, as well as the number and function of platelets and the fibrinolytic system remain normal in patients with senile purpura.

The elderly are most often diagnosed with acquired hemorrhagic disorder though a mild to moderate congenital hemorrhagic disorder may not manifest until advanced age, e.g. the first symptoms are visible following trauma, surgery, or the use of anticoagulants or NSAIDs. This may include a mild form of von Willebrand disease (VWD),...
Table 3. Differential diagnosis of APTT prolongation (modified from [15])

| Cause/Parameter | Clotting times | Platelets | FIB | Clotting factor activity | Inhibitor assay* | Inhibitor > 0.5 BU/mL | Clinical manifestation |
|----------------|---------------|-----------|-----|-------------------------|-----------------|----------------------|----------------------|
|                | APTT          | PT        | TT  | FVIII | FIX | FXI | FXII | VWF |                          |                  |
| Acquired hemophilia A | ↑ | N | N | N | N | ↓ | N | N | N | Positive | FVIII inhibitor present | Hemorrhagic diathesis of sudden onset |
| Hemophilia A | ↑ | N | N | N | N | ↓ | N | N | N | Negative | Absent | Hemorrhagic diathesis |
| Hemophilia A complicated with inhibitor | ↑ | N | N | N | N | ↓ | N | N | N | Positive | FVIII inhibitor present | Ineffective previous treatment |
| von Willebrand disease | ↑ | N | N | N | N | ↓ | N | N | N | Negative | Absent | Hemorrhagic diathesis |
| Hemophilia B | ↑ | N | N | N | N | ↓ | N | N | N | Negative | Absent | Hemorrhagic diathesis |
| Hemophilia B complicated with inhibitor | ↑ | N | N | N | N | ↓ | N | N | N | Positive | FIX inhibitor present | Ineffective previous treatment |
| FXI deficiency (Hemophilia C) | ↑ | N | N | N | N | N | ↓ | N | N | Negative | Absent | Hemorrhagic diathesis |
| FXII deficiency | ↑ | N | N | N | N | N | N | N | ↓ | Negative | Absent | No hemorrhagic diathesis symptoms |
| Lupus anticoagulant | ↑ | N | N | N | N | N | N | N | N | Positive | Absent# | No hemorrhagic diathesis symptoms/Sometimes thrombosis |
| Heparin presence | ↑ | N or↑ | ↑ | N | N | N | N | N | N | Negative | Absent# | Possible symptoms of hemorrhagic diathesis |
| Deficiency of vitamin K-dependent coagulation factors/VKA overdose | N or↑ | ↑ | N or↑ | N | N | N | N | N | N | Negative | Absent | Possible symptoms of hemorrhagic diathesis |
| Liver diseases | ↑ | ↑ | ↑ | N | ↓ | N | N or↓ | N | N | N | Negative | Absent | Possible symptoms of hemorrhagic diathesis |
| DIC | N or↑ | N or↑ | N | N | N | N | N | N | N | Negative | Absent | Possible symptoms of hemorrhagic diathesis |

APTT — activated partial thromboplastin time; PT — prothrombin time; TT — thrombin time; FIB — fibrinogen; F — factor; VWF — von Willebrand factor; *positive test for the presence of an inhibitor means no APTT correction in the mixture of tested and normal plasma; N — result within reference range; ↑ — result above the reference range; ↓ — result below reference range; **lupus anticoagulant may interfere with the determination of clotting factor activity, giving falsely lowered or elevated results; re-measurement in the patient’s diluted plasma samples eliminates lupus anticoagulant interference; #lupus anticoagulant and heparins (to a much lesser extent) may interfere with inhibitor tests, giving false positive results (inhibitor titre > 0.5 BU/mL); VKA — vitamin K antagonist; DIC — disseminated intravascular coagulation
a slight deficiency of one of the clotting factors, or a mild platelet dysfunction (thrombocytopenia). It is worth recalling that in mild hemorrhagic diathesis, the results of all hemostasis screening tests may be within the normal range [27]. Table 4 presents a summary of selected bleeding disorders that are diagnosed in elderly people and require differentiation with AHA [28].

**Where to treat patients with AHA?**

Patient with AHA should be hospitalized in medical centers with appropriate laboratory facilities and experienced in the treatment of bleeding disorders. These criteria are met primarily by hemophilia treatment centers, which are located in each voivodship in Poland, most often within...
isolated APTT prolongation
(at least 8–10 s above the upper value of the reference range)

Exclusion of preanalytical factors influence

APTT correction test
(mixing test; test for the presence of circulating anticoagulant)

APTT correction

Clotting factor deficiency
(FVIII, FIX, FXI, FXII, PK, HMWK)

Determination of deficient coagulation factor activity in the tested plasma

No APTT correction

Cirulating anticoagulant

LABORATORY-CLINIC consultation

Symptoms of a hemorrhagic diathesis?

NO (YES*)

YES

NO

Pharmacological anticoagulant
(UFH, DOAC)

Specific FVIII inhibitor

Non-specific anticoagulant
(e.g. LA)

Determination of FVIII activity

FVIII ↓ 0–20%

Determination of FVIII inhibitor titer
(Bethesda assay)

> 0.5 BU/mL

AHA

Figure 3. Laboratory diagnostics algorithm for isolated APTT prolongation

selected hematology clinics or departments. If AHA was diagnosed in a center that does not meet the above criteria, and the patient cannot be transported, the treatment strategy should be consulted with a hematologist specializing in hemostatic disorders.

Management

The treatment of AHA patients has two main goals: 1) arrest of bleeding and prophylaxis 2) elimination of the inhibitor, i.e. complete remission and resolving AHA (Fig. 2) [15]. In rare AHA cases with no hemorrhagic disorder, management will be limited to inhibitor elimination. Timely detection and appropriate treatment of comorbidities increases the chance of AHA remission.

Hemostatic drugs

Unlike in congenital hemophilia A, in AHA there is no close relationship between plasma FVIII activity and the severity of the bleeding disorder. Even with a very low inhibitor titer and a residual plasma FVIII activity (several percent), the best way to inhibit AHA-related bleeding is not infusion of human factor VIII (hFVIII) concentrate, but administration of one of the two by-passing agents (BPIAs), i.e. recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). Recombinant porcine factor VIII (rpFVIII) can also be used (Table 5).

BPA-drugs activate the coagulation process while bypassing the FVIII-dependent stage (hence the term — bypassing drugs). The advantage of
rFVIIa boluses administered with infusion pump [35]. aPCC is administered at a dose of 50–100 U/kg every 8–12 h (not exceeding the maximum dose of 200 U/kg/day) by intravenous injection or intravenous infusion at a maximum rate of 2 U/kg/min [36].

Once the inhibitor has been eliminated, rFVIIa and aPCC should be immediately discontinued to avoid thromboembolic complications. Administration of aPCC is also contraindicated in patients with disseminated intravascular coagulation (DIC). In patients with AHA, anticoagulants are contraindicated, but can be safely administered if required, after the inhibitor is eliminated and FVIII activity ≥ 50 IU/dL achieved [16].

If rFVIIa and aPCC do not prove clinically effective in monotherapy, sequential therapy may be considered, i.e. alternating rFVIIa and aPCC. Sequential therapy is associated with a higher risk of thromboembolic episodes than rFVIIa or aPCC in monotherapy and should therefore be used only by hematologists experienced in treating patients with AHA [37, 38].

In 2014, recombinant porcine factor VIII was implemented in clinical practice as still another drug for arresting bleeding in AHA patients. Initially it was introduced in the United States and then in the countries of the European Union [39, 40]. The coagulant activity of this drug is almost identical with that of hFVIII, and in more than 50% of cases it is not neutralized by anti-hFVIII antibodies [41].

The great advantage of rpFVIII as compared to rFVIIa and aPCC is the laboratory monitoring of plasma FVIII activity and thus the possibility of selection of appropriate rpFVIII doses (individualization of therapy). Prior to launching rpFVII therapy it is necessary to determine cross-reacting antibodies that neutralize both hF-VIII and rpFVIII in plasma of AHA patient. In the presence of such antibodies high doses of rpFVIII (200 IU/kg initially) must be used and hemostatic plasma FVIII activity, i.e. — depending on the clinical situation — must be maintained at > 50 or > 80 IU/dL, respectively. If no anti-FVIII antibodies are detected at baseline, the initial rpFVIII dose is 50–100 IU/kg) [40, 41, 43, 45]. The size and frequency of subsequent rpFVIII doses are based on patient clinical condition and plasma FVIII activity [44].

Anti-rpFVIII antibodies may appear de novo during rpFVIII therapy and lead to decreased plasma FVIII activity. The drug may be ineffective if the titer of anti-rpFVIII antibodies is high.
Table 4. Selected bleeding disorders with which AHA should be differentiated in the elderly (modified from [27, 28])

| Hemorrhagic diathesis                        | Brief characteristics                                                                                                                                                                                                 |
|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Senile purpura (see Fig. 4)                  | • Subcutaneous blood extravasation mainly on the back of the hand and forearms and on the lower limbs; morphology of lesions similar to AHA<br>• Lesions occur after minor injuries and may be spontaneous<br>• The most important risk factor is the aging process (natural remodeling of the vascular wall)<br>• Results of laboratory hemostasis remain normal<br>• More severe in people taking anticoagulants and corticosteroids<br>• No specific treatment, preventing injuries is recommended<br>• Not related to a predisposition to severe and life-threatening hemorrhages                                                                 |
| Purpura simplex                               | • Bruising from repetitive injuries related to daily activities such as regular bumps against a bed, chair, table etc.; morphology of lesions similar to AHA<br>• No tendency to excessive bleeding<br>• More frequently reported by women                                                                                                                                       |
| Immune thrombocytopenic purpura (ITP)        | • Minor petechiae and larger bruises on the skin<br>• Mucosal bleeding (nose, gums when brushing teeth)<br>• Post-traumatic and post-procedural bleedings (invasive procedures, e.g. tooth extraction)<br>• Isolated thrombocytopenia in complete blood count (CBC), with no abnormalities in plasma coagulation tests (normal clotting time)<br>• Risk of life-threatening bleeding, including spontaneous and traumatic intracerebral bleeding with platelet count < 10 G/L<br>• With the number of platelets > 50 G/L, no symptoms of hemorrhagic diathesis in majority of cases                                                                 |
| Acquired thrombocytopenies (platelets disfunction) | • Clinical symptoms similar to ITP<br>• The platelet count is normal or minimally decreased<br>• No abnormalities in plasma coagulation tests (normal clotting time)<br>• Prolonged occlusion time in the PFA-100/200®<br>• Most often associated with the chronic use of antiplatelet drugs (acetylsalicylic acid, clopidogrel, etc.), e.g. due to ischemic heart disease or after ischemic stroke; less frequently congenital (e.g. Bernard-Soulier syndrome, Glanzmann’s thrombasthenia); thrombocytopathy may accompany chronic kidney disease; non-steroidal anti-inflammatory drugs also impair platelet function |
| Amyloidosis                                   | • Subcutaneous blood extravasation, both large bruises and minor ecchymoses; morphology of lesions similar to AHA<br>• Characteristic periorbital location<br>• Acquired, isolated factor X deficiency may coexist (isolated PT prolongation in screening tests)                                                                 |
| Hemorrhagic diathesis associated with the use of dietary supplements | • Ginkgo biloba — reduced platelet aggregation<br>• Ginseng — reduced platelet aggregation<br>• Ginger — inhibiting of platelet activation<br>• Vitamin E — reduced adhesion and aggregation of platelets<br>• Fish oil — reduced platelet aggregation<br>These dietary supplements increase the risk of bleeding in people who use them in large quantities, especially in combination with anticoagulants or non-steroidal anti-inflammatory drugs. |
| Hemorrhagic diathesis associated with the use of anticoagulants, most often with overdosage | VKAs • Inhibit the synthesis of vitamin K-dependent coagulation factors (II, VII, IX and X) in the liver<br>• PT prolongation (therapeutic INR usually in the range 2.0–3.0)<br>• Antidote: vitamin K and PCC or FFP<br>UFH and LMWH • UFH mainly inhibits factor IIa (thrombin) in the bloodstream (antithrombin is a cofactor)<br>• The use of UFH at therapeutic doses is monitored by APTT measurement<br>• Antidote to UFH: protamine sulfate
In exceptional cases of AHA with low FVIII inhibitor titer and minor bleeding, the use of hF-VIII concentrate or desmopressin may be effective under the control of plasma FVIII activity (at least 50 IU/dL). The data from the EACH2 registry show that inhibition of bleeding with rFVIIa and aPCC is much more effective compared to the use of hFVIII concentrate or desmopressin [16, 32]. The authors of 2020 international recommendations [16] advise against the use of desmopressin in elderly patients with AHA due to the fluid retention caused by this drug, which may lead to exacerbation of heart failure and dangerous hyponatremia.

Tranexamic acid (TXA) is an antifibrinolytic drug effective in stopping mucosal bleeding. In adults, TXA is used at a dose of 1.0 g every 8 hours, most often orally or intravenously, much less locally. TXA is contraindicated in patients with an active thrombotic process, as well as those with active bleeding from the urinary tract due to the increased risk of developing blood clots that block urine flow. In AHA patients, TXA has the status of supportive drug. It can be used simultaneously with BPAs and FVIII concentrates. In EACH2 study, 17% of patients treated with rFVIIa and 5% of patients treated with aPCC received concurrent TXA [32]. The previously signaled concerns about the increased risk of thromboembolic complications in patients receiving concurrently aPCC and TXA have been largely dispelled in recent years, after several publications presenting positive experience in the concomitant use of aPCC and TXA [45, 46].

A good therapeutic option for AHA patients may be immunoadsorption combined with immunosuppression and intravenous infusion of large doses of hFVIII concentrate under control of plasma FVIII activity. The strategy is known as the modified Bonn-Malmö protocol [16]. To the best of our knowledge in Poland, as in many other European countries and the United States, immunoadsorption procedures are not performed, and literature data do not clearly indicate that it is more effective in eliminating FVIII inhibitor than immunosuppressive drugs [2, 16]. The authors of 2020 international recommendations [16] recommend the implementation of the Bonn-Malmö protocol only in patients with AHA and severe bleeding resistant to the above-mentioned therapeutic options.

### Invasive procedures in patients with acquired hemophilia A

Each invasive procedure in a patient with AHA (insertion of catheters into large blood vessels included), and even more so, major surgery may be complicated by severe bleeding despite the use of recommended hemostatic drugs. Most experts...
Table 5. Drugs used to inhibit bleeding in acquired hemophilia A (modified from [15, 35, 36, 44]):

| Drug                        | Dosage                                                                 |
|-----------------------------|------------------------------------------------------------------------|
| rFVIIa                      | ≥ 90 mg/kg in an intravenous bolus lasting 2–5 minutes at intervals of 2 to 24 hours (with the possibility of automatic boluses administration using an infusion pump) |
| aPCC                        | 50–100 U/kg every 8–12 h (maximum 200 U/kg/day) by intravenous injection or intravenous infusion at a maximum rate of 2 U/kg for a minute |
| rpFVIII                     | If anti-rpFVIII antibodies are absent: initially 50–100 U/kg, then under control of plasma FVIII activity* |
|                            | If anti-rpFVIII antibodies are present: initially 200 U/kg if the bleeding is heavy, or 50–100 U/kg if the bleeding is milder; then under the control of plasma FVIII activity* |
| Human factor VIII concentrate** | 50–100 U/kg intravenously every 8–12 hours or by continuous intravenous infusion under the control of plasma FVIII activity |
| Desmopressin**              | 0.3–0.4 mg/kg (in 100 ml 0.9% NaCl) in an intravenous infusion lasting min. 30 min, repeated as needed every 24 h under the control of plasma FVIII activity |
| Tranexamic acid             | 1.0 g every 8 hours orally or intravenously (supportive therapy)*** |

rFVIIa — recombinant activated factor VII; aPCC — activated prothrombin complex concentrate; rpFVIII — recombinant porcine factor VIII; *determination of porcine FVIII activity in the recipient’s plasma should be performed frequently, i.e. every 2–3 hours, especially in the initial phase of treatment and when bleeding is severe; **drugs with uncertain efficacy and limited use in acquired hemophilia A.; ***tranexamic acid is contraindicated in patients with hematuria and in patients with active thromboembolism

Where are clotting factor concentrates available for AHA patients in Poland?

According to the provisions of the National Program for the Treatment of Patients with Hemophilia and Related Hemorrhagic Diseases for 2019–2023, rFVIIa, aPCC, and rpFVIII concentrates are available free of charge to patients with strong suspicion of AHA and a confirmed diagnosis of AHA at Regional Blood Transfusion Centers (RCKiK) [49]. The list of RCKiK is presented in the Attachment.

Elimination of FVIII inhibitor

Immunosuppression is used to eliminate FVIII inhibitor [16, 39, 47, 50]. Immunosuppressive drugs are administered immediately after AHA diagnosis unless contraindicated. The risk of adverse reactions (including myelosuppression and infections) is high and reactions may be severe in the elderly which account for the majority of AHA patients. In GTH-AH 01/2010 registry [51], the most common cause of death among AHA patients was infection (47% of all deaths), followed by cardiovascular disease (18%), underlying disease (9%) and bleeding (9%). As many as 41% of all deaths were directly related to immunosuppressive treatment.

Complete remission in AHA is defined as normal FVIII activity and undetectable FVIII inhibitor without immunosuppression [3]. Partial remission is defined as FVIII activity > 50 IU/dL and no evidence of bleeding at least 24 hours after discontinuation of hemostatic drugs [51]. In GTH-AH 01/2010 registry, 83% of patients achieved partial remission after a median of 5 weeks (range: 1–52 weeks) [51]. German authors demonstrated that the most important prognostic factor for a response to immunosuppressive drugs is the activity of FVIII at AHA diagnosis; in patients with FVIII < 1 IU/dL, the chance of remission is lower and the time to remission is longer compared to patients with FVIII activity > 1 IU/dL [51]. Moreover, the authors observed that monotherapy with corticosteroids is highly effective in eliminating FVIII inhibitor in AHA patients, as long as the baseline FVIII activity is ≥ 1 IU/dL and inhibitor titer is ≤ 20 IU/mL. In AHA patients with baseline FVIII activity < 1 IU/dL and inhibitor titer > 20 IU/mL, the chance of eliminating the inhibitor with corticosteroids alone is relatively small but can be increased by combining with a second immunosuppressant, most often rituximab or cyclophosphamide [16, 51].
Table 6. Immunosuppressants used in eradication of anti-factor VIII autoantibodies (modified from [15])

| Drug                          | Suggested dosage                                                                 |
|-------------------------------|----------------------------------------------------------------------------------|
| Prednisone/prednisolone*      | 1 mg/kg/day orally for max. 4–6 weeks                                             |
| Cyclophosphamide*             | 1.5–2.0 mg/kg/day orally for max. 4–6 weeks                                       |
| Rituximab*                    | 375 mg/m² intravenously once a week (for ≥ 4 consecutive weeks) (lower doses may be effective) |
| Azathioprine                  | 2 mg/kg/day orally (max. daily dose — 150 mg)                                     |
| Cyclosporine                  | 5 mg/kg/day orally for 6 days, then 2.5–3 mg/kg/day orally under the control of serum level, which should be 100–200 ng/mL |
| IVIg**                        | 0.3–0.4 g/kg/day intravenously for 5 days or 1 g/kg/day intravenously for 2 days |
| Vincristine***                | 1 mg/m² intravenously (max. single dose of 2 mg), 4–6 administrations at 7-day intervals (max. total dose 6 mg) |
| 2-CDA                         | 0.1 mg/kg as a 24-hour intravenous infusion for 7 days or 0.14 mg/kg as a 2-hour intravenous infusion for 5 days |
| Mycophenolate mofetil         | 1000 mg every 12 hours orally for at least 3–4 weeks                             |
| Immunotolerance (Budapest Program) | FVIII (intravenous) 30 IU/kg every 24 h for the first week, 20 IU/kg every 24 hours for the second week and 15 IU/kg every 24 hours for the third week + cyclophosphamide (intravenously) 200 mg/day up to a total dose of 2–3 g + methylprednisolone (intravenously) 100 mg/day for the first week and in gradually decreasing doses for the next 2 weeks |

Other immunosuppressants mentioned in the literature in this indication: tacrolimus, sirolimus, bortezomib

*In first-line treatment, it is recommended to use prednisolone/prednisone or simultaneous use of prednisolone/prednisone and rituximab or prednisolone/prednisone and cyclophosphamide in the doses indicated in the table; **not recommended as monotherapy; ***most often with cyclophosphamide and/or prednisolone/prednisone; IVIg — intravenous immunoglobulins; 2-CDA — 2-chlorodeoxyadenosine — cladribine; FVIII — factor VIII

Table 6 presents the immunosuppressive drugs that are used in AHA [1, 15, 16, 18, 47, 50, 52–60]. Among the corticosteroids, prednisone/prednisolone is administered orally at a dose of 1 mg/kg/day for 4–6 weeks. Rituximab is not approved for treatment of patients with AHA, but according to expert opinions this drug, used together with corticosteroids, plays a major role in eliminating anti-FVIII autoantibodies. In the 2020 international guidelines, rituximab is indicated as a drug that should be: 1) used with corticosteroids in patients with unfavorable prognostic factors for achieving remission with corticosteroids only (see above), 2) used in patients with contraindications to corticosteroids and 3) introduced as a second-line therapy in patients after failure of FVIII inhibitor eradication during first line therapy [16]. Rituximab widely replaced cyclophosphamide, which was designated as a second-line drug a decade ago and was often combined with corticosteroids even in first-line treatment [47, 52].

Other treatment options include cyclosporine, tacrolimus, azathioprine, vincristine, and mycophenolate mofetil, and combination therapy including several immunosuppressive drugs, e.g. cyclophosphamide + vincristine + prednisone/prednisolone. Monotherapy with intravenous immunoglobulins (IVIg) is not recommended in patients with AHA [16]. According to some authors, concomitant use of immunosuppressants and intravenous injections of hFVIII concentrate contributes to shortening the time necessary for inhibitor eradication. The treatment regimen, based on immunotolerance programs used in congenital hemophilia A complicated with anti-FVIII alloantibodies, is known as the Budapest Program [60]. However, the authors of the 2020 international guidelines expressed skepticism about such a treatment regimen, and thought there was insufficient evidence that adding FVIII concentrate to immunosuppressive drugs would increase the chance of eliminating anti-FVIII autoantibodies [16]. Table 7 presents a simplified scheme for selecting immunosuppressants for patients with AHA.

What follows after remission is achieved?

After remission is achieved, the patient is monitored for 2 years for possible disease recurrence [2, 28–30]. FVIII activity is determined once a month for the first six months after achieving remission, then every 2–3 months for the next six months, and then every 6 months for the next year. The EACH2 registry, reports AHA recurrences in 12–18% of patients after a median of 138 days.
In the case of AHA relapse, another attempt at eliminating autoantibodies should be made usually with the same immunosuppressive drugs that provided the first remission. If immunosuppression proves completely unsuccessful, the next step is monitoring and management of bleeding episodes. In the case of severe hemorrhagic diathesis, prolonged prophylaxis with the use of concentrates bypassing the inhibitor may be considered [33]. Perhaps in the future it will be possible to use emicizumab in the prophylaxis of bleeding in patients with AHA, but so far this drug has not been approved for this indication [61, 62].

### Prognosis in acquired hemophilia A

The prognosis in AHA depends on the course of comorbidities, the severity of bleeding, as well as timely diagnosis and the initiation of appropriate antihemorrhagic and immunosuppressive treatment [15, 16, 47]. If bleeding is timely controlled and immunosuppressive therapy is commenced properly, the chance of achieving complete remission is approximately 80% [51].

In the EACH2 registry, a group of 331 AHA patients was analyzed for survival. After the median follow-up of 258 days [interquartile range (IQR): 74–685] 61.2% of patients survived, 27.9% died [median time between AHA diagnosis and death was 75 days (IQR: 25–240 days)], and the fate of 10.9% was unknown [1]. In the EACH2 registry, independent risk factors for mortality in AHA patients were as follows: older age, lower hemoglobin concentration at diagnosis, coexistence of neoplastic disease and failure to eradicate FVIII inhibitor [1]. Gender as well as baseline FVIII activity and FVIII inhibitor titer had no statistically significant effect on survival [1]. For comparison, in the GTH-AH 01/2010 registry, the percentage of deaths after 12 months of follow-up was 32% [51].

Death due to bleeding occurred in 3% of patients under observation in the EACH2 registry, which means that excessive bleeding accounted for only 16% of all deaths in the analyzed group [1]. This confirms the effectiveness of antihemorrhagic treatment in AHA patients. It should be emphasized however that the EACH2 registry includes only centers specializing in the treatment of hemorrhagic disorders. The most common cause of death among patients of the EACH2 registry was the underlying disease (45% of all deaths and 9% of patients included in the survival analysis) [1]. Among the patients analyzed for survival in the EACH2 registry, immunosuppression-related complications accounted for 3% of all deaths, as did hemorrhages [1].

### Final comments

The most important principles of AHA management in the elderly are presented below:

1. Acquired hemophilia A is to be suspected in the case of hemorrhagic diathesis with sudden onset accompanied by an isolated prolongation of APTT in a person with no previous bleeding tendency.
2. Acquired hemophilia A develops primarily in people aged over 60.
3. In approximately 20–30% of cases, AHA is initially asymptomatic, and the only diagnostic indication is isolated prolongation of APTT.
4. A diagnostic algorithm for isolated APTT prolongation should be developed in hemostasis-testing laboratories and applied in everyday practice.
5. It is recommended to avoid elective invasive procedures in AHA patients until eradication of FVIII inhibitor. If the invasive procedure cannot be postponed, a hematologist experienced in treating patients with bleeding
disorders should decide how to proceed with antihemorrhagic management.

6. The three main strategic goals in AHA management are: control of bleeding, elimination of FVIII inhibitor, and treatment of comorbidities that may have contributed to the development of the FVIII inhibitor.

7. The first-choice hemostatic drugs for AHA patients are rFVIIa, aPCC and rpFVIII. TXA is a supportive drug.

8. Immunosuppressive treatment to eliminate the FVIII inhibitor should be commenced as soon as possible after AHA diagnosis, provided there are no contraindications.

9. Corticosteroids are used in the first line of immunosuppressive therapy, either in monotherapy or in combination with rituximab or cyclophosphamide.

10. AHA may relapse, therefore following FVIII inhibitor eradication, APTT and FVIII activity should be monitored monthly for the first 6 months, every 2–3 months for the next 6 months, and then every 6 months for the second year of follow-up.

11. At AHA recurrence, immunosuppressive medication successful in the first remission can be used once more.

12. Anticoagulants are contraindicated for patients with AHA, but following AHA remission, anticoagulants may be used in accordance with the generally accepted principles of thromboembolic therapy.

Potential conflict of interest

J.W. — participated in clinical trials and received lecture fees from Alfasigma, Baxalta, Bayer, CSL Behring, Novartis, Novo Nordisk, Octapharma, Pfizer, Rigel Pharmaceuticals, Roche, Sanofi, Shire/Takeda, SOBI, Swixx BioPharma, Werfen.

B.B. — participated in clinical trials and received lecture fees from Baxalta, Baxter, Biogen Idec, Bio-Ksel, Biomedica, CSL Behring, Grifols, Kselmed, Novo Nordisk, Octapharma, Roche, Shire/Takeda, Siemens, Takeda, Siemen, SOBI, Werfen.

E.O. — participated in clinical trials and received lecture fees from Baxalta, Baxter, Bayer, Bio-Ksel, Biomedica, CSL Behring, Grifols, Kselmed, Novo Nordisk, Octapharma, Roche, Shire/Takeda, Siemens, SOBI, Werfen.

T.G. — received lecture fees from Abbott, CSL Behring, Novo Nordisk, Pfizer, Servier.

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Attachment

List of Regional Blood Transfusion Centers (RCKiK) in Poland that dispose of clotting factor concentrates for the treatment of patients with congenital bleeding disorders and acquired hemophilia A

| Name                                      | Address                                      | Telephone no |
|-------------------------------------------|----------------------------------------------|--------------|
| Regional Blood Transfusion Center in Białystok | ul. Marii Skłodowskiej-Curie 23, 15–950 Białystok | 85 744 70 02 |
| Regional Blood Transfusion Center in Bydgoszcz | ul. ks. Markwarta 8, 85–015 Bydgoszcz         | 52 322 18 71 |
| Regional Blood Transfusion Center in Gdańsk | ul. J. Hoene-Wrońskiego 4, 80–210 Gdańsk      | 58 520 40 20 |
| Regional Blood Transfusion Center in Kalisz  | ul. Kaszubska 9, 62–800 Kalisz               | 62 767 66 63 |
| Regional Blood Transfusion Center in Katowice | ul. Raciborska 15, 40–074 Katowice           | 32 208 73 00 |
| Regional Blood Transfusion Center in Kielce  | ul. Jagiellońska 66, 25–734 Kielce           | 41 335 94 00 |
| Regional Blood Transfusion Center in Kraków  | ul. Rzeźnicza 11, 31–540 Kraków              | 12 261 88 20 |
| Regional Blood Transfusion Center in Lublin  | ul. Żołnierzy Niepodległej 8, 20–078 Lublin    | 81 532 62 75 |
| Regional Blood Transfusion Center in Łódź    | ul. Franciszkańska 17/25, 91–433 Łódź         | 42 616 14 00 |
| Regional Blood Transfusion Center in Olsztyn | ul. Małborska 2, 10–255 Olsztyn               | 89 526 01 56 |
| Regional Blood Transfusion Center in Opole    | ul. Końskiego 55, 45–372 Opole               | 77 441 06 00 |
| Regional Blood Transfusion Center in Poznań   | ul. Marcelińska 44, 60–354 Poznań            | 61 886 33 00 |
| Regional Blood Transfusion Center in Racibórz | ul. Sienkiewicza 3 A, 47–400 Racibórz         | 32 418 15 92 |
| Regional Blood Transfusion Center in Radom    | ul. Limanowskiego 42, 26–600 Radom           | 48 340 05 20 |
| Regional Blood Transfusion Center in Rzeszów  | ul. Wierzbowa 14, 35–310 Rzeszów             | 17 867 20 30 |
| Regional Blood Transfusion Center in Słupsk    | ul. Szarych Szeregów 21, 76–200 Słupsk        | 59 842 20 21 |
| Regional Blood Transfusion Center in Szczecin | al. Wojska Polskiego 80/82, 70–482 Szczecin   | 91 424 36 00 |
| Regional Blood Transfusion Center in Wałbrzych| ul. Chrobrego 31, 58–303 Wałbrzych           | 74 664 63 10 |
| Regional Blood Transfusion Center in Warsaw   | ul. Saska 63/75, 03–948 Warszawa             | 22 514 60 00 |
| Regional Blood Transfusion Center in Wrocław  | ul. Czerwonego Krzyża 5–9, 50–345 Wrocław     | 71 371 58 10 |
| Regional Blood Transfusion Center in Zielona Góra | ul. Zaty 21, 65–046 Zielona Góra             | 68 329 83 60 |
| Blood Transfusion Center of the Ministry of Internal Affairs and Administration | ul. Wołoska 137, 02–507 Warszawa | 22 508 13 12 |
| Military Blood Transfusion Center            | ul. Koszykowa 78, 00–671 Warszawa            | 26 184 50 66 |