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Vaccine-induced immune thrombotic thrombocytopenia: definition, risks with different vaccines, and the regulators' responses

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Abstract

After the vaccination campaign initiation in Europe and the UK, reports of rare cases of atypical thrombosis, including sinus vein thrombosis and splanchnic venous thrombosis, began to appear in association with the use of AstraZeneca (ChAdOx1) and J&J/Janssen adenovirus vector vaccines. The syndrome called VITT (vaccine-induced immune thrombotic thrombocytopenia) is manifested as thrombosis simultaneously with decreased platelet count, significantly increased D-dimer levels and detected anti-factor 4 platelet (PF4) antibodies. We present a detailed review on the epidemiology, pathogenesis, clinical picture, diagnostics and treatment of VITT, which by its nature is an immune complication similar to the processes occurring in heparin-induced thrombocytopenia (HIT). All international and national organizations and regulatory authorities, including experts in the field of thrombosis and hemostasis and the VITT expert council recommend continuing the prompt mass vaccination against COVID-19 as the only method able to reduce the incidence of severe cases, stop the spread of COVID-19 infection and emergence of new dangerous mutations in the viral genome. Failure to vaccinate poses an incomparably greater risk of fatal thrombotic and inflammatory complications associated with infections, compared with the risks of extremely rare adverse events that can occur after vaccination. It should be noted that information on VITT, described as a sporadic phenomenon of abnormal immune response to some variants of vaccines against COVID-19, cannot be translated to other vaccines (including those registered in the Russian Federation) and, moreover, cannot be a reason to refuse their administration.

Keywords: vaccine-induced immune thrombotic thrombocytopenia, VITT, thrombosis, coronavirus, SARS-CoV-2, COVID-19, heparin-induced thrombocytopenia, HIT, vaccination

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Вакцин-индуцированная иммунная тромботическая тромбоцитопения: определение, риски при использовании разных вакцин и реакция регуляторных органов

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Резюме

После запуска массовой вакцинации в Европе и Великобритании стали появляться сообщения о редких случаях тромбозов атипичных локализаций, включая тромбозы синусов головного мозга и висцеральных вен, связанных с применением аденовирусных векторных вакцин AstraZeneca (ChAdOx1) и J&J/Janssen. Синдром, который получил название VITT (англ. vaccine induced immune thrombotic thrombocytopenia) – вакцин-индуцированная иммунная тромботическая тромбоцитопения, сопровождается снижением количества тромбоцитов, значительным повышением уровня Д-димера и выявлением антител к тромбоцитарному фактору 4. В статье представлен детальный обзор вопросов эпидемиологии, рассмотрены клинические симптомы, патогенез, методы диагностики и лечения VITT, которая по своей природе является иммунным осложнением, подобным гепарин-индуцированной тромбоцитопении (ГИТ). В настоящее время все международные и национальные регуляторные организации, сообщества гематологов, включая специальную экспертную комиссию по VITT, рекомендуют продолжение скорейшей массовой вакцинации против COVID-19 как единственного метода, который способен снизить частоту тяжелых случаев инфекции, остановить ее распространение и появление новых опасных мутаций в вирусном геноме. Отказ от вакцинации грозит несравнимо бóльшим риском смертельных тромботических и воспалительных осложнений, связанных с инфекций, по сравнению с рисками крайне редких нежелательных явлений, которые могут возникнуть после вакцинации. Информация по VITT, описанной в качестве крайне редко возникающего феномена аномальной иммунной реакции на некоторые варианты вакцин против COVID-19, не может транслироваться на другие вакцины (в частности, одобренные в Российской Федерации) и тем более не может быть причиной для отказа в их использовании.

Ключевые слова: вакцин-индуцированная тромботическая тромбоцитопения, VITT, тромбоз, коронавирус, SARS-CoV-2, COVID-19, гепарин-индуцированная тромбоцитопения, ГИТ, вакцинация

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Highlights

What is already known about this subject?

- After the vaccination campaign initiation with AstraZeneca (ChAdOx1) and J&J/Janssen adenovirus vector vaccines, the reports on rare cases of thrombosis began to emerge that attracted a strict attention of the regulatory authorities and elicited a vigorous public response.
- The syndrome being fully clinically dissimilar to the "classic" thrombosis was called VITT – a vaccine-induced immune thrombotic thrombocytopenia.
- VITT manifests as atypically localized thrombosis, including sinus vein thrombosis and splanchnic venous thrombosis accompanied with decreased platelet count, markedly increased D-dimer levels and detected anti-factor 4 platelet antibodies.

What are the new findings?

- We present a detailed review on incidence rate for the VITT after using diverse COVID-19 vaccines.
- We present a comprehensive review on clinical symptoms, pathogenesis, diagnostics and treatment of the VITT.
- We outlined a current position of regulatory authorities and medical professional communities on assessing benefit and risk balance related to vaccination.

How might it impact on clinical practice in the foreseeable future?

- Understanding the pathogenesis and clinical picture of VITT will allow medical workers to be alert about this extremely rare adverse event and provide prompt examinations and optimal treatment for patients with suspected VITT.
- We believe that the most relevant information on VITT presented here would become an additional argument in favor of urgent vaccination clearly demonstrating that refusal to vaccinate poses an incomparably greater risk of fatal thrombotic complications associated with COVID-19, compared with the risks of extremely rare adverse events that may occur after vaccination.

Основные моменты

Что уже известно об этой теме?

- После запуска массовой вакцинации аденовирусными векторными вакцинами AstraZeneca (ChAdOx1) и J&J/Janssen стали появляться сообщения о редких случаях тромбозов, что потребовало пристального внимания со стороны контролирующих органов и вызвало бурный общественный резонанс.
- Синдром, который по своим клиническим проявлениям абсолютно не похож на «классический» тромбоз, получил название VITT (англ. vaccine induced immune thrombotic thrombocytopenia) – вакцин-индуцированная иммунная тромботическая тромбоцитопения.
- VITT проявляется тромбозами атипичных локализаций, включая тромбозы синусов головного мозга и висцеральных вен, и сопровождается тромбоцитопенией, значительным повышением уровня Д-димера и циркуляцией антител к тромбоцитарному фактору 4.

Что нового дает статья?

- В статье представлен детальный обзор по частоте возникновения VITT при использовании разных вакцин против COVID-19.
- Рассмотрены клинические симптомы, патогенез, методы диагностики и лечения VITT.
- Представлена позиция контролирующих органов и профессиональных сообществ по соотношению пользы и риска вакцинации.

Как это может повлиять на клиническую практику в обозримом будущем?

- Знание патогенеза и клинической картины VITT позволит медицинским работникам проявить настороженность в отношении этого очень редкого нежелательного явления и обеспечить таким пациентам скорейшую диагностику и оптимальную тактику лечения.
- Мы надеемся, что представленная информация по VITT является дополнительным аргументом в пользу скорейшей вакцинации и наглядно демонстрирует, что отказ от вакцинации грозит несравнимо бóльшим риском смертельных тромботических и воспалительных осложнений по сравнению с рисками крайне редких нежелательных явлений после вакцинации.

Introduction / Введение

According to World Health Organization (WHO), at the beginning of September 2021, more than 221 million confirmed cases of COVID-19 including more than 4.5 million deaths were registered [1], whereas in Russia there were reported more than 7 million cases and more than 200 thousand deaths according to official Russian statistics [2]. Despite the lock-downs and strict hygienic measures in different countries, the pandemic continues to claim lives and spread economic, social and psychological consequences. Vaccination is the only way to limit viral transmission, reducing disease severity and controlling the pandemic. According to the WHO, 185 vaccines are currently being in the preclinical phase, 114 vaccines in clinical trials, and 19 of them undergoing the WHO Emergency Use Listing (EUL) and prequalification process (PQ) that has been completed

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for 11 vaccines [3]. Currently, more than 5 billion doses of vaccines have been injected worldwide [1].

After the vaccination campaign initiation in Europe and the UK, the reports on rare cases of severe atypical thrombosis, including cerebral sinus vein thrombosis, splanchnic venous thrombosis and other severe immune reactions, including immune thrombocytopenia and thrombotic microangiopathy, began to emerge related to the use of AstraZeneca (ChAdOx1) and J&J/Janssen vector vaccines. The syndrome occurred 4–22 days after the first dose of the vaccine was inoculated and manifested as thrombosis simultaneously with decreased platelet count and markedly increased D-dimer levels [4]. To describe this phenomenon, the acronyms VITT (vaccine-induced immune thrombotic thrombocytopenia) or TTS (thrombosis with thrombocytopenia syndrome) – thrombosis syndrome with thrombocytopenia have been proposed.

Since March 2021, the use of AstraZeneca vaccine has been halted in some countries (Denmark, Norway, Iceland, Germany). However, on April 7, 2021, the EMA (European Medicines Agency) concluded that the vaccine's benefits outweigh the risks and that the vaccination campaign should be continued [5].

By August 25, 2021, after 24.8 million of the first dose and 23.9 million of the second dose of the AstraZeneca vaccine were administered, 415 cases of thrombosis (including cerebral vein thrombosis in 148 cases) with thrombocytopenia were recorded, causing 72 deaths (17 %). Despite previous reports about higher incidence of such complications in women, they were distributed as follows: 209 cases in women and 202 in men aged 18 to 93 years; with 6 deaths out of 72 cases were recorded after using the second dose. The total VITT incidence was 15 cases per million vaccine doses, with a slightly higher risk found in young adults (20.5 cases per million doses for subjects aged 18–49 compared to 10.9 cases per million doses for subjects aged 50 years and older). After the second dose, the overall incidence of VITT was 1.8 cases per million vaccine doses, with a lower incidence in the younger age group (0.9 cases per million doses aged 18 to 49 years versus 1.8 cases per million doses in age 50 and over). The data on the safety of using the second dose, including young people, are encouraging. Based on this information, the UK Medicines & Health care products Regulatory Agency currently concludes that the benefits from the AstraZeneca vaccine outweigh the risks for most patients [6].

The frequency of VITT cases varies in different geographic regions. For instance, the peak incidence of complications was found in Norway: 1 case per 25,000 doses, whereas in Germany it was 1 per 100,000 as well as total prevalence comprising 1 per 210,000 throughout Europe, and 1 per 500,000 vaccine doses found in the UK [7].

On May 7, 2021, the Joint Committee on Vaccination and Immunization (JCVI) in the UK recommended that people over 40 years of age had the benefits from using the AstraZeneca vaccine that significantly outweighed its risk, whereas for subjects under 40 and especially under 30 years at low risk of complications from novel coronavirus infection, it would be better to choose an alternative vaccine only in case it would not lead to a delay in vaccination [8]. It should be remembered that young patients from risk groups (including patients with cancer, cardiovascular disease, kidney disease, obesity, diabetes mellitus, immunosuppression, etc.) need to receive prompt protection against coronavirus infection. The same may be applied to patients with antiphospholipid syndrome and other patients receiving long-term anticoagulant therapy, when novel coronavirus infection may be associated with greater risk of thrombosis [9].

As of August 25, 2021, more than 14.2 million Johnson & Johnson's Janssen COVID-19 vaccine doses were administered in the United States, with the CDC (Centers for Disease Control and Prevention) and FDA (Food and Drug Administration) identifying 44 confirmed cases of thrombosis with thrombocytopenia. In most cases, the syndrome developed in women younger than 50 years (reaching 7 cases per 1 million doses at age under 49 years and 0.9 cases per million after 50 years old) [10]. The CDC states that vaccination against COVID-19 is effective and safe, requiring to become vaccinated immediately after an opportunity for this emerges [11].

Currently, VITT is considered as an extremely rare complication that should be taken into account in the context of COVID-19 as well as disproportionately higher risks of complications associated with COVID-19 infection. The EMA and the WHO concluded that the benefits from vaccination far outweigh the risks, and the AstraZeneca and Johnson & Johnson's Janssen COVID-19 vaccines remain to be used without any restrictions in many countries [12].

According to the CDC (last update 02.09.2021), mRNA vaccines do not increase VITT risks. In particular, after administering 346 million doses of Moderna vaccine, only 2 cases of VITT have been confirmed in the United States. As of August 25, 2021, there are the data on 17 cases of VITT after using the Pfizer/BioNTech vaccine (registered in 6 women and 11 men aged 28 to 91 years, with mortality rate 12 %) [3, 10]. Until now, no official reports have been published on thrombotic risks and cases of VITT associated with using the Russian vector vaccine Sputnik V containing adenoviruses other than those within the AstraZeneca and Johnson & Johnson's Janssen COVID-19 vaccines.

Attention should be paid to the risks of thrombosis in the general population: on average, the annual thrombosis incidence is 1–2 cases per 1,000 people, and the incidence of cerebral vein thrombosis is

1–2 cases per 100,000 population, whereas the probability of thrombosis was as high as 1 per 4,600 subjects after at least the four-hour plane flight [13], i. e. about 50–100 times higher than the risk of VITT associated with vaccination [9].

An incredibly high risk of thrombosis accompanies novel coronavirus infection: according to the systematic review analyzing more than 8,000 subjects, the overall incidence of thrombosis was 21 %, including 31 % recorded in the intensive care unit, whereas the autopsy examination data showed that the deep vein thrombosis and pulmonary embolism were detected in 35 % and 22 % cases, respectively. Mortality rate in patients with vs. without thrombosis was 23 % vs. 13 %, respectively. Thus, patients who developed thromboembolic complications, had mortality rate increased by 74 % [14].

Pathogenesis of vaccine-induced immune thrombotic thrombocytopenia and heparin-induced thrombocytopenia / Патогенез вакцин-индуцированной иммунной тромботической тромбоцитопении и гепарин-индуцированной тромбоцитопении

Thrombosis with thrombocytopenia emerging due to COVID-19 adenovirus vaccines is an immune complication in its nature, which pathogenesis is similar to the processes occurring in heparin-induced thrombocytopenia (HIT) and catastrophic antiphospholipid syndrome (CAPS). Because patients with VITT received no heparin preparations, it may imply a so-called "spontaneous HIT" or autoimmune HIT. All patients had a high level of antibodies against platelet factor 4 (PF4) able to activate platelets in the control group samples, but, unlike classical HIT, required no heparin. However, similar to classical HIT, serum-bound platelet activating ability from patients with VITT added to control samples was neutralized by high heparin concentrations, as well as by monoclonal antibodies against surface platelet receptor FcγRIIa (CD32a) [4]. The latter regulates transmembrane signaling, platelet aggregation and secretion, thrombin generation, as well as formation of platelet–neutrophil and platelet–monocyte complexes. The emergence of VITT may be associated with an excessive inflammatory response to vector vaccines and a massive release of platelet-derived PF4. In this case, an uncontrolled generation of thrombin, consumption of platelets, damage to the endothelium, and tissue factor (TF) release as the main trigger for the key coagulation player called thrombin take place. The inflammatory response leads to the release of leukocyte DNA and formation of the neutrophil extracellular traps (NETs) contributing to the microthrombogenesis [9].

Attention should be also paid to controversial issues related to the description of the VITT pathogenesis due to vector vaccine-triggered immune response. The signs of VITT were described to emerge from the day 4 after applying the first vaccine dose, i. e., when seroconversion with the formation of pathological antibodies could not yet occur after vaccine inoculation. In addition, antibodies to PF4/heparin can be detected in 5–7 % of healthy donors [15]. If VITT is suspected, special attention should be paid to exclude concomitant COVID-19 infection and systemic autoimmune diseases able to cause the complement cascade activation, inflammation, and coagulation, including CAPS.

For understanding the pathogenetic mechanisms behind VITT, it is necessary to discuss the more detailed HIT molecular mechanisms. In particular, the heparin-induced thrombocytopenia is a rare but severe antibody-mediated complication coupled to heparin treatment, which leads to catastrophic forms of venous/arterial thrombosis [16]. The emergence of such condition seems paradoxical, because heparin is used to prevent thrombogenesis; however, thrombotic complications and related highly complicated therapy may sometimes occur after using anticoagulant agents.

In June 1, 1957, R.E. Weismann and his resident R.W. Tobin at the V scientific meeting of the International Society of Vascular Surgeons (ISVS) held in New York presented the 3-year report on ten patients, six of which died, who had thrombosis while using heparin anticoagulant therapy. The first reported case was femoral artery embolic occlusion observed in the heparin-treated 62-year-old woman with a history of deep vein thrombosis. Three days after successful embolectomy and continued heparin therapy, the patient developed aorta occlusion, requiring embolectomy and bilateral iliac embolectomy [17]. Upon that, the clots were described as "pale, unusually long, soft", consisted primarily of fibrin and platelets, which differed significantly from the appearance and composition of heart clots. After analyzing personal data, it was hypothesized that peripheral arterial embolism occurred 7–15 days after the onset of heparin treatment that later stopped after the drug was discontinued. However, none of the ISVS members supported such conclusions, because they had no similar personal observations in clinical practice. Several years later, B. Roberts and his colleagues also noted the paradox of "unexplained arterial embolization" that arose while receiving antithrombotic therapy. Examining the pathogenesis of this condition, it was concluded that taking into consideration the delayed timeframe for such thromboembolic complications, an antigen-antibody-based immune response took place [18]. In 1973, G.R. Rhodes et al. for the first time described the major clinical and laboratory signs of HIT developed due to a link between thrombocytopenia, heparin therapy, and thromboembolism. They also noted

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in their studies that the platelet count was restored after the heparin therapy was discontinued [19].

Until 1982, no treatment for HIT other than surgical intervention existed: thrombectomy as well as limb amputation was performed in case of developing gangrene. In 1982, J. Harenberg et al. for the first time successfully used the experimental drug danaparoid* to treat a 48-year-old patient with a history of deep vein thrombosis and pulmonary embolism, which resulted in progression of venous thrombosis. Over the next six years, this patient had successfully stopped episodes of recurrent thrombosis due to the drug applied [20]. In 1989, the Platelet Immunobiology Workshop accepted the HIT classification [21].

The early non-immune thrombocytopenia emerging after heparin therapy was designated as HIT-1, whereas immune thrombocytopenia with a relatively late onset was referred to as HIT-2 (**Table 1**) [22].

HIT is a relatively rare complication of heparin therapy. However, the close attention to this pathology is due to extremely severe consequences: thrombocytopenia concomitant with thrombosis developed in 35–70 % of cases, 20 % of patients require amputation, whereas lethal outcome was found in 30 % of cases [23].

The main paradox related to HIT is development of thrombosis, rather than hemorrhage. HIT is a thrombophilic condition accompanied by thrombocytopenia along with platelet activation and aggregation. It was shown that 95 % of patients had platelet count lower than 150×10^9/L, but HIT cannot be diagnosed solely assessing thrombocytopenia [24]. Due to the circulating antibodies, patients with isolated thrombocytopenia remain at high risk for thrombosis (20 % to 50 %). Thrombosis underlies developing HIT, but the reason of why thrombosis emerges in some vessels still remains unclear. Today, it may be noted that venous vs. arterial thrombosis is much more common. Atypical manifestations such as bilateral adrenal hemorrhage, limb gangrene, and skin necrosis should motivate to conduct HIT diagnostics (**Table 2**) [16]. It must be remembered that unusual HIT manifestations may occur even without thrombocytopenia.

T.E. Warkentin et al. proposed a scoring system for assessing likelihood of developing HIT – a scale of four "T" for helping clinicians in diagnostics (**Table 3**) [25].

The role of immunoglobulins in the pathogenesis of HIT-2 was experimentally obtained as early as 1973 [18]. The pathogenesis of HIT is currently described as follows: heparin, a large anionic polysaccharide, binds to the cationic protein PF4 (platelet factor 4). PF4 exists in the form of positively charged tetramers; however, when interacting with the anionic molecule of heparin, the tetramers merge, and their conformational changes occur [26]. As a result, a neoepitope is formed, and B-cells of the spleen marginal zone produced specific pathological antibodies. Immune complexes consisting of antibody-PF4/heparin bind to platelet receptors FcγRII (CD32), resulting in signal transduction followed by platelet activation with further release of PF4 and microparticles with high procoagulant activity. Both platelets and endothelial cells are involved in the pathogenesis of HIT. Surface of the endothelial cells bears proteoglycans with side chain glycosaminoglycans, particularly heparan sulfate, which recognizes heparin-dependent antibodies in the presence of PF4. The latter is capable of binding heparan sulfate, resulting in the heparan sulfate/PF4 complex [27]. Immune complexes can also activate monocytes and endothelial cells, resulting in tissue factor expression, activation of the external coagulation pathway, and production of inflammatory cytokines [28]. Platelet activation, further enhanced by damage to endothelial

Table 1. Comparative characteristics of heparin-induced thrombocytopenia type 1 (HIT-1) and type 2 (HIT-2) [22].

Таблица 1. Сравнительная характеристика гепарин-индуцированной тромбоцитопении 1-го (ГИТ-1) и 2-го (ГИТ-2) типа [22].

Characteristic **Характеристика**	**HIT-1** **ГИТ-1**	**HIT-2** **ГИТ-2**
Mechanism Механизм возникновения	Non-immune platelet aggregation Неиммунная агрегация тромбоцитов	Immune-mediated platelet aggregation Иммунообусловленная агрегация тромбоцитов
Onset Время возникновения	First days/hours Первые дни/часы	In 4–14 days На 4–14 день
Platelet count Количество тромбоцитов	"Mild" thrombocytopenia, platelet reduction by 10–30 % «Мягкая» тромбоцитопения, снижение тромбоцитов на 10–30 %	"Severe" thrombocytopenia, platelet reduction by > 50 % «Тяжелая» тромбоцитопения, снижение тромбоцитов на > 50 %
Clinical manifestations Клинические проявления	Absent Отсутствуют	"Catastrophic" thrombosis «Катастрофический» тромбоз
Therapy Терапия	Heparin withdrawal Отмена гепарина	Heparin withdrawal, other anticoagulants prescribed Отмена гепарина, назначение других антикоагулянтов

*Danaparoid is not registered in the Russian Federation.

Table 2. Thrombotic manifestations of heparin-induced thrombocytopenia [adapted from 16].

Таблица 2. Тромботические проявления гепарин-индуцированной тромбоцитопении [адаптировано из 16].

Thrombotic manifestations of heparin-induced thrombocytopenia **Тромботические проявления гепарин-индуцированной тромбоцитопении**	
Venous thrombosis Венозные тромбозы	• deep vein thrombosis of the lower extremities (50 %) • pulmonary embolism (25 %) • adrenal infarction (3 %) • cerebral sinus thrombosis (< 3 %) • mesenteric thrombosis (< 3 %) • тромбоз глубоких вен нижних конечностей (50 %) • тромбоэмболия легочной артерии (25 %) • инфаркты надпочечников (3 %) • тромбозы синусов головного мозга (< 3 %) • мезентериальный тромбоз (< 3 %)
Arterial thrombosis Артериальные тромбозы	• thrombosis of the aorta, iliac and femoral arteries (5–10 %) • myocardial infarction (5 %) • thrombotic stroke (3–5 %) • arterial thrombosis of other localizations (< 3 %) • тромбоз аорты, подвздошных, бедренных артерий (5–10 %) • инфаркт миокарда (5 %) • тромботический инсульт (3–5 %) • артериальные тромбозы других локализаций (< 3 %)
Skin lesions at the site of subcutaneous heparin injections Поражения кожи на месте подкожных инъекций гепарина	• erythematous and necrotic lesions (5–10 %) • эритематозные и некротические повреждения (5–10 %)
"Pseudo-thromboembolic syndrome" 5–30 minutes after heparin bolus «Псевдотромбоэмболический синдром» через 5–30 мин после струйного введения гепарина	• inflammatory: fever, flushing, chills • cardiorespiratory: tachycardia, tachypnea, dyspnea, hypertension • neurological: headache • gastrointestinal: diarrhea • воспалительные: лихорадка, гиперемия, озноб • кардиореспираторные: тахикардия, тахипноэ, диспноэ, гипертензия • неврологические: головная боль • гастроинтестинальные: диарея

cells, increases thrombin synthesis, which influences developing main clinical picture of this condition (**Fig. 1**). Antibodies in HIT are not typical: unlike the classical immune response, when IgM antibodies are initially formed, in case of HIT IgG antibodies are usually formed able to disappear few months later. Pharmaceutical drugs capable of causing a syndrome mimicking HIT include polyanions such as dextran sulfate, pentosan polysulfate, and polysulfated chondroitin sulfate [29].

In 2008, the phenomenon of "spontaneous HIT" was described in the absence of exposure to heparin or other polyanionic drugs, which can develop in surgical patients (mainly after orthopedic operations) and therapeutic patients (mainly after infections) [30]. The development of HIT can also be triggered by bacterial or viral agents, and nucleic acids [28, 31]. This type of HIT is characterized as "autoimmune" or arising in the presence of heparin-independent antibodies that activate PF4. VITT appears to be a variant of autoimmune HIT. Anti-PF4 antibodies have been identified in VITT patients, which bind to the same limited region of the PF4 molecule as heparin. These antibodies are capable of forming platelet-activating immune complexes involving no heparin. Platelet activation in patients with VITT was completely blocked by adding monoclonal antibodies against FcγRII [32].

Heparin-induced thrombocytopenia in COVID-19 / Гепарин-индуцированная тромбоцитопения при COVID-19

Data from China reported about impaired blood coagulation parameters in patients with COVID-19. The most common was an elevated level of D-dimer, which correlated with the disease severity [33]. Hypercytokinemia, increased markers of the inflammatory response – C-reactive protein, ferritin, interleukin-6 are also considered as unfavorable predictors of developing severe condition [33–36]. In addition, critically ill patients have had severe thrombocytopenia [37, 38]. Low platelet count/thrombocytopenia is associated with an increased risk of death in patients with SARS-CoV-2, but the causes for this condition are not fully understood [39]. HIT is prothrombotic disease, which usually manifests as a thrombocytopenia, is one of the most severe complications of heparin therapy. However, HIT in some cases may develop regardless using heparin preparations [40–42]. HIT is caused by Ig G-specific antibodies targeting PF4, forming immune complexes, and inducing platelet activation via FcγRII receptor [43]. X. Liu et al. concluded that some patients with laboratory-confirmed COVID-19 developed HIT

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Table 3. Scale of the probability of developing heparin-induced thrombocytopenia (HIT) [25].

Таблица 3. Шкала вероятности развития гепарин-индуцированной тромбоцитопении (ГИТ) [25].

Sign Признак	2 points 2 балла	1 point 1 балл	0 points 0 баллов
Thrombocytopenia Тромбоцитопения	Decreased platelets > 50 % or platelets > 20×10^9/L Снижение тромбоцитов > 50 % или тромбоциты > 20×10^9/л	Decrease in platelets by 30–50 % or platelets $10–19\times10^9$/L Снижение тромбоцитов на 30–50 % или тромбоциты $10–19\times10^9$/л	Decreased platelets < 30 % or platelets < 10×10^9/L Снижение тромбоцитов < 30 % или тромбоциты < 10×10^9/л
Time interval between starting heparin use and developing thrombocytopenia Временной интервал между началом использования гепарина и развитием тромбоцитопении	After 5–14 days, or on day 1 (with repeated heparin use for 30 days) Через 5–14 дней или в 1-е сутки (при повторном применении гепарина в течение 30 дней)	After more than 14 days or on day 1 (with repeated heparin use for 30–100 days) Более чем через 14 дней или в 1-е сутки (при повторном применении гепарина в течение 30–100 дней)	After < 4 days without prior heparin use Через < 4 дней без предшествующего применения гепарина
Clinical manifestations Клинические проявления	New confirmed thrombosis; skin necrosis at the sites of heparin injections; acute systemic reaction after intravenous heparin injection; adrenal hemorrhage Вновь возникший подтверждённый тромбоз; кожные некрозы в местах инъекций гепарина; острая системная реакция после внутривенного введения гепарина; кровоизлияние в надпочечники	Progressive or recurrent thrombosis; erythematous (non-necrotic) skin lesions; suspected thrombosis (not confirmed) Прогрессирующий или рецидивирующий тромбоз; эритематозные (не некротические) поражения кожи; подозрение на тромбоз (не подтвержденный)	Absent Отсутствуют
Other causes of thrombocytopenia Другие причины тромбоцитопении	Нет очевидных причин No obvious reasons	Возможны Possible	Присутствуют Present
Likelihood score for HIT development Оценка вероятности развития ГИТ	0–3 points: low (< 5 %) 0–3 балла: низкая (< 5 %)	4–5 points: middle 4–5 баллов: средняя	6–8 points: high (> 80 %) 6–8 баллов: высокая (> 80 %)

while receiving heparin preparations, which significantly aggravated course of the disease. However, it was also shown that HIT developed in association with a novel coronavirus or secondary bacterial infection in patients previously receiving no heparin therapy [44]. The heparin-related adverse effects share much similarity with the mechanisms of host anti-bacterial defense. While binding to heparin, PF4 is able to link to polyanions on bacterial surface, which leads to formation of the PF4-bacterial immune complex. R. Palankar et al. showed that anti-PF4/polyanionic IgG opsonizes Gram-positive and Gram-negative bacteria particularly killing *Escherichia coli* opsonized with PF4 [45]. B-lymphocytes from the splenic marginal zone produce IgG antibodies, which can bind to PF4–heparin complexes, forming primary immunocomplexes [46]. Thus, the infection is capable of independently causing "spontaneous HIT," which clinically resembles heparin-induced thrombocytopenia but has a different serological profile and develops without prior exposure to heparin. In reports of "spontaneous HIT" complications an unexplained thrombocytopenia and/or thrombosis are accompanied by laboratory data on high titers anti-PF4/heparin antibodies [30, 47]. Although rare, antibodies against PF4/heparin are also found in healthy people (from 0.3 % to 0.5 %) [48], which may be accounted for by effects of dominating amount of microbial antigens. The so-called "primary immunization" emerges, that can be described is a misdirected, evolutionarily ancient antimicrobial response [49].

Management of suspected vaccine-induced immune thrombotic thrombocytopenia / Тактика при подозрении на вакцин-индуцированную иммунную тромботическую тромбоцитопению

The VITT expert council currently proposes the following recommendations [9]:

1. Systemic flu-like events (such as muscle pain, fever, headache, general weakness) usually resolve within 48–

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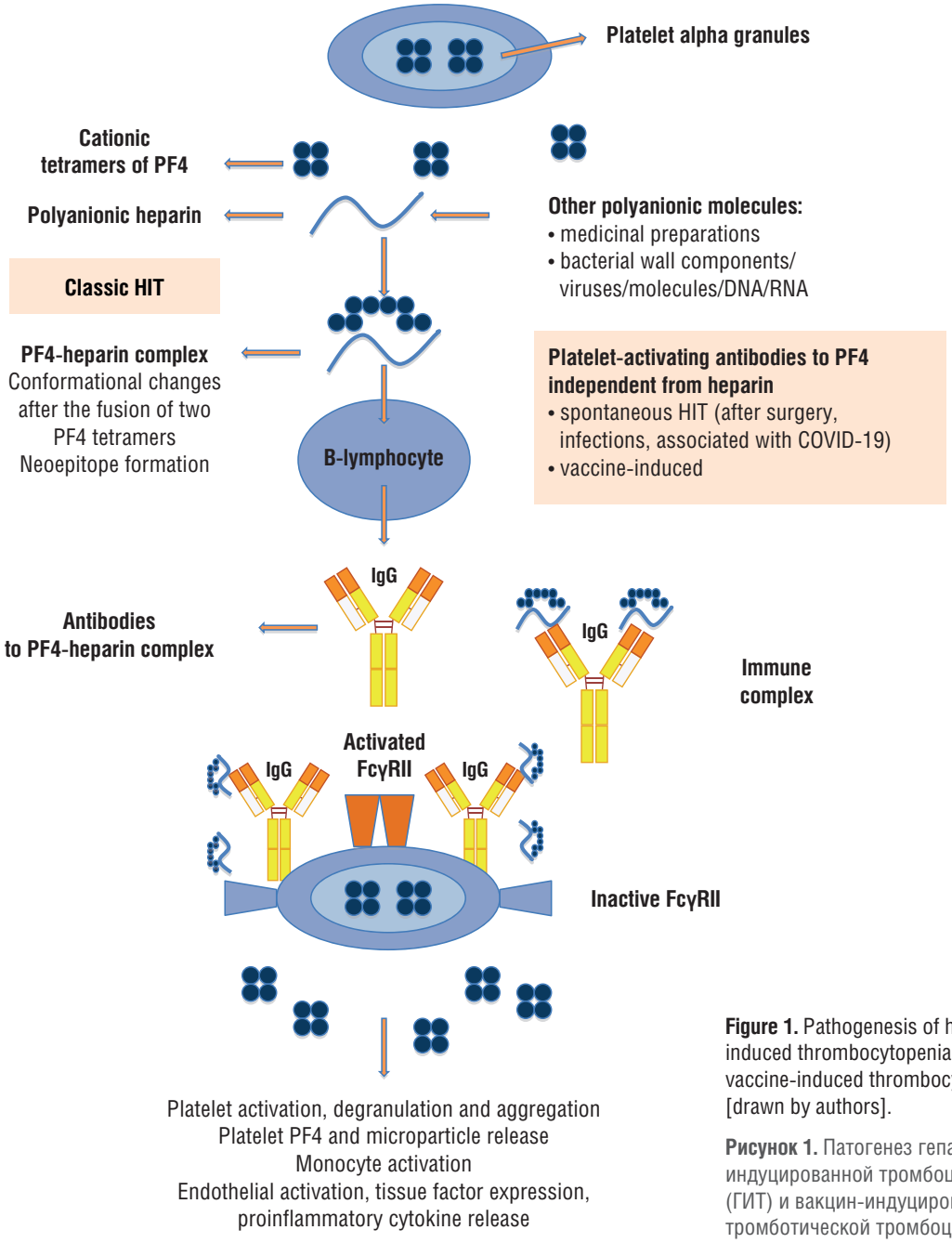

Figure 1. Pathogenesis of heparin-induced thrombocytopenia (HIT) and vaccine-induced thrombocytopenia [drawn by authors].

Рисунок 1. Патогенез гепарин-индуцированной тромбоцитопении (ГИТ) и вакцин-индуцированной тромботической тромбоцитопении [рисунок авторов].

72 hours. Treatment is symptomatic – increased fluid intake and paracetamol.

2. Symptoms that appear or aggravate 4 days or more after vaccination should alert. Emergent medical attention is necessary in case of severe persistent headache, dizziness, confusion, visual disturbances, seizures, shortness of breath, chest pain, abdominal pain, back pain, nausea, vomiting, unusual bruising and petechiae, thrombophlebitis, sudden tachycardia.

3. Laboratory examination should include a complete blood count with microscopy of a blood smear (to exclude platelet aggregates and pseudothrombocytopenia), measuring D-dimer level, and coagulogram. Attention should be paid to decline in platelet level ower than 120×10^9/L, D-dimer exceeding more than 1000 ng/ml, and fibrinogen decreased lower than 2 g/L.

4. Additionally, C-reactive protein can be assessed, schizocytes serve as a sign of microangiopathy, lupus anticoagulant, antiphospholipid antibodies (antibodies to cardiolipin, to β_2-glycoprotein 1), antinuclear antibodies, ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). Determine antibodies against heparin–PF4 (a marker of HIT) by ELISA at platelet count lower 120×10^9/L.

5. Instrumental studies to exclude thrombosis – Doppler ultrasound, MRI (magnetic resonance imaging), CT angiography (computed tomographic angiography).

6. Start anticoagulant therapy depending on drug availability and experience with fondaparinux, danaparoid, or argatroban* followed by switching to direct oral anticoagulants (dabigatran, rivaroxaban, or apixaban). Do not prescribe any heparin preparations.

7. If thrombosis is detected, inject intravenous immunoglobulin (IVIG) at a dose of 1 mg/kg for 48 hours in combination with anticoagulant therapy. The mechanism of IVIG action is based on binding to and blockade of platelet CD32 surface receptors that prevents them from binding to pathological antibodies and inhibits platelet activation, inflammatory and prothrombotic responses. IVIG used more than for 2 days may be accompanied by increased thrombotic risks [50]. Thrombosis has previously been described in patients receiving IVIG. Therefore, it is necessary to carefully monitor the IVIG therapy and simultaneously prescribe anticoagulant therapy. It is also possible to use steroids and plasmapheresis.

8. Platelet transfusion and acetylsalicylic acid use are not recommended (as acetylsalicylic acid does not block the effects of anti-PF4 antibodies but increases a risk of hemorrhagic complications).

9. Low fibrinogen and thrombocytopenia in case of VITT are not absolute contraindications to anticoagulant therapy, especially with thrombocytopenia more than 20×10^9/L, positive dynamics in platelet count as well as after onset of IVIG therapy.

10. The duration of anticoagulant therapy for VITT has not been determined, but in case of thrombosis, most likely it should last for at least 3 months, as in case of any provoked thrombosis.

On August 12, 2021, the American Society of Hematology (ASH) issued the TTS/VITT guidelines [51].

TTS is considered in case of concomitant all 5 criteria:

- vaccination against COVID-19 4-42 days before symptoms develop;
- any venous or arterial thrombosis (often cerebral or abdominal);
- thrombocytopenia (less than < 150×10^9/L) ;
- positive test result for HIT – antibodies against PF4 measured by ELISA;
- significantly increased D-dimer level (> 4-fold higher than the upper limit of normal range).

Immediate initiation of IVIG and anticoagulant therapy is recommended before receiving test results for anti-PF4 antibodies in case of of thrombosis combined with thrombocytopenia and/or markedly increased D-dimer. In the case of normal platelet count and thrombosis, the likelihood of delayed development of thrombocytopenia and VITT should be considered, and anticoagulants other than heparin should be preferably used.

At present, the expert council for VITT does not recommend [9]:

- systematic use of antithrombotic drugs – low molecular weight heparins (LMWH), direct oral anticoagulants to "cover" vaccination;
- systematic testing for thrombophilia before vaccination;
- systematic ultrasound screening for thrombosis before and after vaccination;
- routine screening for PF4 antibodies after vaccination;
- routine analysis for D-dimer before and after vaccination;
- refusal of vaccination in patients with former thromboembolic complications and patients with autoimmune diseases, including immune thrombocytopenia;
- refusal to vaccinate patients with a history of allergic reactions;
- patients with a history of HIT should be considered to choose in favor of mRNA vaccines.

Currently, the risk factors for VITT remain unknown and to what extent traditional risk factors of thrombosis, such as pregnancy, combined hormonal contraceptive use, obesity, acquired or congenital thrombophilia, affect the risk of its development still has not been elucidated. Hence, this is why no data to restrain vaccination in such patients are currently available. Moreover, the vaccine refusal in such patients may avoid them from being protected against novel coronavirus infection, wherein they could have profoundly higher risk of thromboembolic complications and lethal outcome due to COVID-19 compared with the general population.

Current position regarding a balance between vaccination-related benefits and risks / Современная позиция в отношении соотношения пользы и рисков вакцинации

At present, all international and national organizations and communities (WHO, CDC, Ministry of Health of the Russian Federation), including experts in the field of thrombosis and hemostasis, recommend continuing the prompt mass vaccination against COVID-19 as the only means able to reduce the incidence of severe disease cases, stop spreading of COVID-19 infection and the emergence of new dangerous mutations in the viral genome. During repeated virus transmission in human population, continuous mutations take place with the selection of more contagious and deadly SARS-CoV-2 variants, as it occurred, e. g., with the Delta variant. Refusal to vaccinate poses an incomparably greater risk of fatal thrombotic and inflammatory complications associated with COVID-19, compared with the risks of extremely rare adverse events that can arising after vaccination.

It should be noted that the data on VITT, described as a sporadic phenomenon of extremely rare abnormal immune

*Danaparoid and argatroban are not registered in the Russian Federation.

response to some variants of COVID-19 vaccines, cannot be translated to other vaccines nor even be a reason to refuse their application. Until now, no official reports regarding thrombotic risks related to COVID-19 vaccines registered in the Russian Federation are currently available. Provided that potential adverse events associated with vaccination have been objectively recorded, the risk/benefit ratio for the Sputnik V vaccine appears to be very encouraging, including it compared with foreign adenovirus vaccines. In particular, according to the phase III study that enrolled 14,964 subjects inoculated with the Sputnik V vaccine and 4,902 placebo-treated persons, the vaccination efficiency against symptomatic and severe COVID-19 was 91.6 % and 100.0 %, respectively. The study results were published in one of the most respected international journals, the Lancet [52]. The data obtained after using the Sputnik V vaccine in real-life clinical practice in Argentina suggest about its high efficacy and safety. It was revealed that the first dose of the Sputnik V vaccine was effective in preventing symptomatic COVID-19 in more than 78.0 % cases, hospitalization – in 87.6 %, and deaths – in 87.4 % cases. Moreover, there were recorded as few as 2 cases of immune thrombocytopenia per applied total 6,964,344 doses of the Sputnik V vaccine [53]. Among the hospitalized patients diagnosed with COVID-19, 92.0 % were not vaccinated [54]. In connection with this, the refusal to vaccinate based upon data on rare cases of atypical thrombosis described for other vaccines at present leaves patients without any chance for protection against severe, potentially fatal complications related to COVID-19, including thrombosis.

The risk of emerging potentially fatal complication HIT comprises 0.1 % after using LMWH compared with up to 7.0 % by using conventional, unfractionated heparin in surgery [55]. However, taking into account potential benefits of heparin preparations, not a single country in the world abandons such drugs. Moreover, heparins remain the most frequently prescribed drugs in medical practice that, no doubt, does not exclude platelet monitoring during heparin therapy in high-risk groups. All cases of potentially dangerous vaccine-associated adverse events should be carefully recorded and analyzed. Such an analysis will help to understand which patients are at risk for developing post-vaccination complications, propose optimal diagnostic and treatment tactics, and bring it to primary care specialists potentially first encountering adverse events associated with vaccination. Medical workers should be alert regarding potential development of VITT after vaccination, whereas patients with suspected VITT should be provided with prompt hospitalization, hematologist consultation, as well as laboratory and instrumental examinations. The only way providing better insight into pathogenesis of such thrombosis and giving a momentum to further development of efficient and safe COVID-19 vaccines may result from objectively analyzed thrombotic events related to the novel coronavirus infection per se and vaccination within the framework of clinical studies and real-life clinical settings.

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