LEKOVIMA UZROKOVANA TROMBOCITOPENIJA

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DRUG-INDUCED THROMBOCYTOPENIA

Nada Suvajdžić-Vuković[1,2], Mirjana Cvetković[1]

[1] Univerzitetski klinički centar Srbije, Klinika za hematologiju, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

[1] *University Clinical Center of Serbia, Clinic for Hematology, Belgrade, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

SAŽETAK

Lekovi predstavljaju čest uzrok trombocitopenije, pogotovo kod hospitalizovanih bolesnika. Učestalost ove neželjene reakcije na lekove kreće se oko 10/1 000 000 stanovnika godišnje i prema mehanizmu nastanka može se klasifikovati kao imunska i neimunska. Lekovi poput citostatika, linezolida, ganciklovira, valaciklovira, Aspirina i vankomicina dovode do neimunskog oblika trombocitopenije, tako što deluju proapoptotički na trombocite ili direktno citotoksično na megakariocite i trombocite. S druge strane, imunski oblik uzrokovan je antitelima specifičnim za lek koja se, u prisustvu leka ili njegovog metabolita, vezuju za trombocitne antigene dovodeći do ubrzane razgradnje trombocita. Osim ovog klasičnog oblika lekom uzrokovane imune trombocitopenije (LITP), koji se odlikuje akutnom trombocitopenijom teškog stepena (nadir broja trombocita < $20x10^9$/L) i krvarenjem, prepoznati su i posebni oblici: heparinom uzrokovana trombocitopenija (HIT), trombocitopenija uzrokovana blokatorima kontrolnih tačaka i vakcinom indukovana trombozna trombocitopenija (VITT). HIT je najčešća LITP u kojoj je nadir broja trombocita najčešće oko $60x10^9$/L, a kliničkom slikom dominiraju tromboze, i to venske i, ređe, arterijske. S druge strane, VITT se odlikuje nastankom tromboze i trombocitopenije 4 do 30 dana od primene adenovirusnih vektorskih vakcina a smrtnost u ovom obliku LITP se kreće između 25% i 60%.

Ključne reči: lek, trombocitopenija, heparin, patofiziološki mehanizmi, algoritmi lečenja

ABSTRACT

Drugs could cause thrombocytopenia, mostly in hospitalized patients. The incidence of this adverse reaction to medicines is around 10/1,000,000 inhabitants/year. Depending on the pathophysiological mechanism, drug-induced thrombocytopenia can be classified into immune and non-immune. Drugs such as cytostatics, linezolid, ganciclovir, valacyclovir, aspirin, and vancomycin can induce a non-immune form of thrombocytopenia. They achieve this by exerting direct cytotoxic effects on megakaryocytes and platelets, or through proapoptotic mechanisms that affect platelets. On the other hand, the immune form is caused by drug-specific antibodies, which, in the presence of the drug or its metabolite, bind to platelet antigens, leading to accelerated destruction of platelets. Apart from this classic form of drug-induced immune thrombocytopenia (DITP), which is characterized by the acute onset of severe thrombocytopenia (nadir platelet counts < 20×10^9/L) and bleeding, special forms such as heparin-induced thrombocytopenia (HIT), thrombocytopenia caused by the use of immune checkpoint inhibitors, and vaccine-induced thrombotic thrombocytopenia (VITT) are identified. HIT is the most common DITP in which nadir platelet count is usually around $60x10^9$/L and the clinical presentation is dominated by thrombosis (venous and less often arterial). Conversely, VITT is characterized by the onset of thrombosis and thrombocytopenia between 4 and 30 days after the administration of adenoviral vector vaccines. The mortality in this form of LITP ranges between 25% and 60%.

Keywords: drug, thrombocytopenia, heparin, pathophysiological mechanisms, treatment algorithms

Autor za korespondenciju:
Nada Suvajdžić-Vuković
Klinika za hematologiju, Univerzitetski klinički centar Srbije
Dr Koste Todorovića 2, 11000 Beograd, Srbija
Elektronska adresa: suvajdzic.nada@gmail.com

Corresponding author:
Nada Suvajdžić-Vuković
Clinic for Hematology, University Clinical Center of Serbia
2 Dr Koste Todorovića Street, 11000 Belgrade, Serbia
E-mail: suvajdzic.nada@gmail.com

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UVOD

Lekovi predstavljaju čest uzrok trombocitopenije, pogotovo kod hospitalizovanih bolesnika. Nastanak trombocitopenije do sada je opisan tokom primene više od 300 lekova, čiji se spisak nalazi na: "Platelets on the web" (https://www.ouhsc.edu/platelets/ditp.html) [1]. Učestalost lekovima uzrokovane trombocitopenije se procenjuje na 10/1.000.000 stanovnika godišnje i značajno je češći kod odraslih u poređenju sa decom [1]. Smatra se da u jedinicama intenzivne nege čak 25% bolesnika ima neki od oblika lekovima uzrokovane trombocitopenije [2]. Prema mehanizmu nastanka, lekovima uzrokovane trombocitopenije se mogu klasifikovati na imunske i neimunske [3-5].

NEIMUNSKE LEKOVIMA UZROKOVANE TROMBOCITOPENIJE

Lekovi poput citostatika, linezolida, ganciklovira, valaciklovira, Aspirina i vankomicina mogu dovesti do trombocitopenije, bilo proapoptotičkim mehanizmima na trombocite ili direktnim citotoksičnim dejstvom na megakariocite i trombocite [1,3,4]. Trombocitopenija u toku primene linezolida registruje se u slučaju primene leka duže od dve nedelje i u slučaju njegovih visokih koncentracija u krvi; posledica je dozno zavisne reverzibilne mijelosupresije u toku koje je trombocitopoeza najviše pogođena [6]. Sa druge strane, citostatici oksaliplatin i irinotekan, osim neimunskim, mogu izazvati trombocitopeniju i imunskim mehanizmom [7,8].

IMUNSKE LEKOVIMA UZROKOVANE TROMBOCITOPENIJE

Lekovima uzrokovana imunska trombocitopenija (LITP) posredovana je antitelima klase IgG (ređe IgA/M) specifičnim za lek, koja se u prisustvu leka ili njegovih metabolita nekovalentno vezuju za trombocitne antigene putem svog Fab regiona, dovodeći do ubrzane razgradnje trombocita aktivacijom komplementa i/ili fagocitozom. Pritom, glikoproteinski (GP) kompleksi, kao što su GPIIb/IIIa i GPIb/IX, najčešći su trombocitni antigeni u klasičnom obliku LITP (Shema 1A). U zavisnosti od mehanizma vezivanja razlikuje se šest tipova antitela (Tabela 1) [4].

Osim heparina koji najčešće dovodi do LITP, po učestalosti se kao uzročnici ističu: acetaminofen, abciksimab, amjodaron, ampicilin, amlodipin, kotrimoksazol, karbamazepin, hlorpropamid, drospirenon, digitalis, gentamicin, eptifibatid, danazol, moksonidin, etambutol, diklofenak, tirofiban, haloperidol, efalizumab, irinotekan, ibuprofen, piperacilin, preparati zlata, fenitoin, triamteren/hidrohlorotiazid, naproksen, hidrohlorotiazid, oksaliplatin, interferon alfa, metildopa,

INTRODUCTION

Medications are a frequent cause of thrombocytopenia, particularly among hospitalized patients. Thrombocytopenia has been associated with the use of over 300 different medications, a list of which is available at "Platelets on the web" (https://www.ouhsc.edu/platelets/ditp.html) [1]. The incidence of drug-induced thrombocytopenia is estimated at 10 cases per 1,000,000 people per year and is significantly higher in adults than in children [1]. It is believed that in intensive care units as many as 25% of patients have some form of drug-induced thrombocytopenia [2]. Drug-induced thrombocytopenia can be classified into immune and non-immune types based on its underlying mechanism [3-5].

NON-IMMUNE DRUG-INDUCED THROMBOCYTOPENIA

Drugs like cytostatics, linezolid, ganciclovir, valacyclovir, aspirin, and vancomycin can cause thrombocytopenia either through pro-apoptotic mechanisms affecting platelets or by direct cytotoxic effects on megakaryocytes and platelets [1,3,4]. Thrombocytopenia associated with linezolid typically occurs when the drug is administered for more than two weeks or when its blood concentrations are high. This condition results from dose-dependent, reversible myelosuppression, with thrombocytopoiesis being the most affected [6]. Conversely, cytostatics like oxaliplatin and irinotecan can cause thrombocytopenia not only through non-immune mechanisms but also via immune-mediated pathways [7,8].

IMMUNE DRUG-INDUCED THROMBOCYTOPENIA

Drug-induced immune thrombocytopenia (DITP) is mediated by drug-specific IgG antibodies (rarely IgA or IgM), which non-covalently bind to platelet antigens via their Fab region in the presence of the drug or its metabolites. This binding accelerates platelet destruction through complement activation and/or phagocytosis. Additionally, glycoprotein (GP) complexes like GPIIb/IIIa and GPIb/IX are the most common platelet antigens involved in the classic form of drug-induced immune thrombocytopenia (DITP) (Figure 1A). Depending on the binding mechanism, there are six types of antibodies (Table 1) [4].

Besides heparin, which is the most frequent cause of DITP, other common causative agents include acetaminophen, abciximab, amiodarone, ampicillin, amlodipine, co-trimoxazole, carbamazepine, chlorpropamide, drospirenone, digitalis, gentamicin, eptifibatide,

Tabela 1. Lekom uzrokovana imunološka trombocitopenija-mehanizmi (prilagođeno iz Arnold DM, Cuker A. [4])

Table 1. Drug-induced immune thrombocytopenia–mechanisms (adapted from Arnold DM, Cuker A. [4])

	Mehanizam / *Mechanism*	**Primer leka / *Example of drugs***	**Učestalost / *Incidence***
Kininski tip / *Quinine-type*	Lek se vezuje za LZAt i potom za trombocitni integrin / *Drug binds DDAb and subsequently to platelet integrin*	Kinin, kinidin, sulfonamidi, nesteroidni antiinflamatorni lekovi / *Quinine, sulfonamide antibiotics, non-steroidal anti-inflammatory drugs*	26 slučajeva/ 1 000 000 korisnika kinina nedeljno / *26 cases per million quinine users per week*
Hapten-zavisni / *Hapten-dependent*	Lek se kovalentno vezuje za membranski protein i podstiče lek-specifično vezivanje pomoću LZAt / *Drug links covalently to membrane protein and induces drug-specific binding by DDAb*	Penicilin, neki cefalosporinski antibiotic / *Penicillin, some cephalosporin antibiotics*	Veoma retko / *very rare*
Fibanski tip / *Fiban-type*	Lek reaguje sa GPIIb/IIIa i indukuje nove epitope za LZAt / *Drug reacts with GPIIb/IIIa and induces neoepitope for the DDAb*	Tirofiban, Eptifibatid / *Tirofiban, Eptifibatide*	0,2-0,5% / *0.2-0.5%*
Lek-specifični / *Drug-specific*	LZAt prepoznaje mišju komponentu himernog Fab fragmenta specifičnog za GPIIIa / *DDAb recognize murine component of chimeric Fab fragment specific for GPIIIa*	Abciksimab / *Abciximab*	0,5-1% posle prvog i 10-14% posle drugog izlaganja / *0.5-1% after first and 10-14% after second exposure*
Autoantitelo / *Autoantibody*	Lek indukuje stvaranja antitela, koje potom reaguje sa autolognim trombocitims u odsustvu leka / *Drug induces antibody that reacts with autologous platelets in absence of drug*	Soli zlata, prokainamid / *Gold salts, procainamide*	1% za soli zlata, veoma retko kod drugih / *1% with gold salts, very rare with other*
Imunski kompleksi / *Immune complexes*	Antitela sa ciljanim antigenima stvaraju imunske komplekse / *Antibodies form immune complexes with their target antigens*	Heparin, komponente adenovirusne vektorske vakcine protiv COVID-19 / *Heparin, a component of adenoviral vector-based vaccine against COVID-19*	3-6% kod pacijenata lečenih UFH tokom 7 dana, retko kod LMWH / *3-6% in patients treated with UFH, rare with LMWH*

Legenda: LZAt - antitela zavisna od prisustva leka; LMWH - niskomolekularni heparin (engl. *low-molecular-weight heparin*); UFH - nefrakcionisani heparin (engl. *unfractionated heparin*)

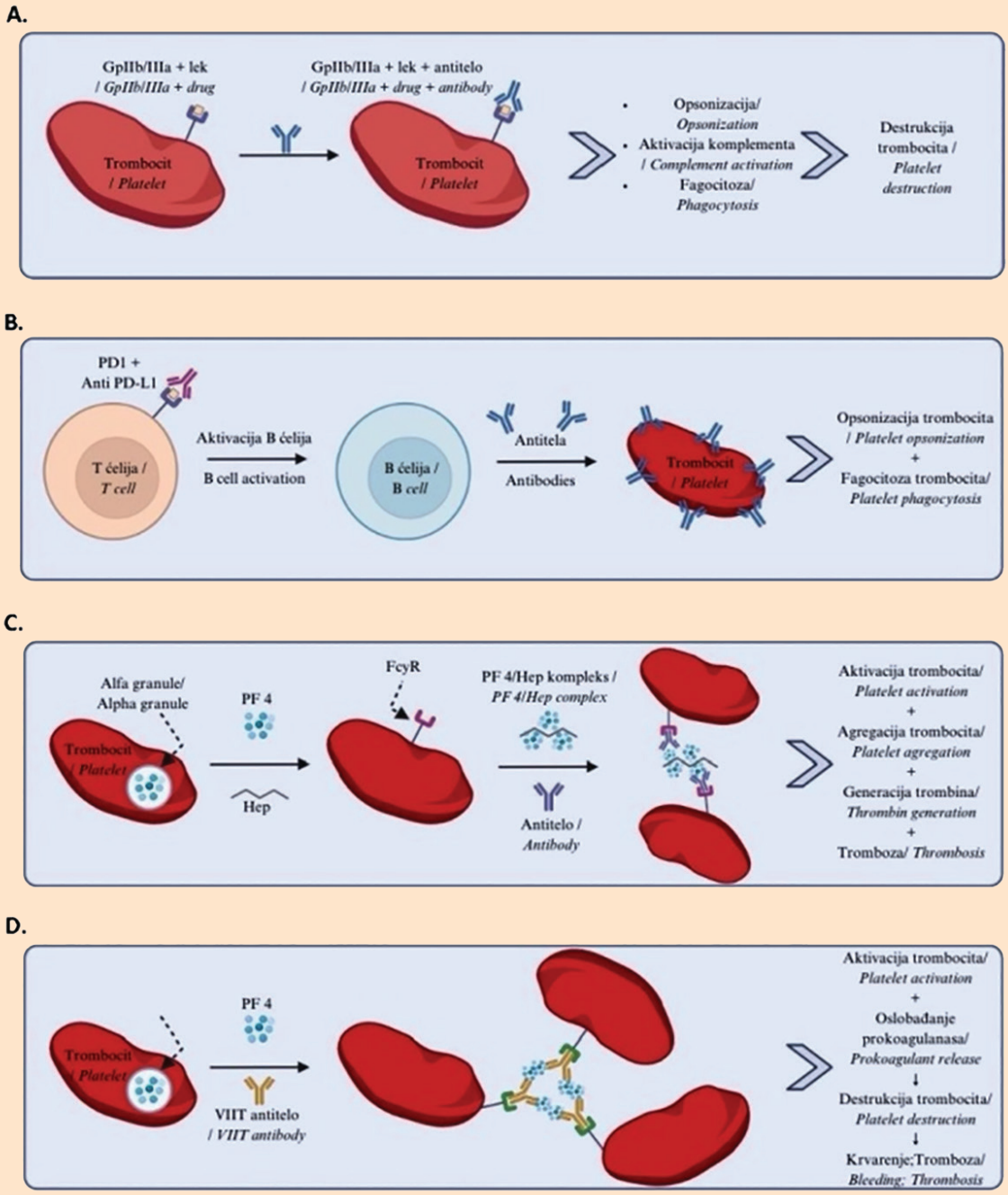
Legend: DDAb - drug dependant antibodies; LMWH - Low-molecular-weight heparin; UFH - unfractionated heparin

nalidiksinska kiselina, kinin, kinidin, rifampin, ranitidin, sulfisoksazol, simvastatin, valproična kiselina i vankomicin [4,9]. Osim lekova, neka hrana i pića kao i biljni preparati, mogu takođe prouzrokovati LITP [10].

Vreme proteklo od uvođenja leka do nastanka trombocitopenije najčešće je jedan do tri dana, ukoliko je lek prethodno korišćen, ili 7-15 dana ako lek nije prethodno primenjivan [1]. Izuzetak su lekovi iz grupe antagonista GPIIb/IIIa (abciximab, tirofiban, eptifibatid) koji dovode do trombocitopenije najčešće nekoliko sati ili čak minuta po započinjanju terapije [4]. Međutim, LITP može da nastane i posle obustave leka ili da perzistira duže vreme posle obustave leka, a primeri su terapija zlatom, alemtuzumabom i lekovima iz grupe blokatora kontrolnih tačaka (engl. *immune check-point inhibitori*) [4]. Naime, u kliničkoj studiji faze 2 u kojoj su ispitivani efikasnost i bezbednost alemtuzumaba u lečenju relapsno-remitentnog oblika multiple skleroze, kod 6/216 pacijenta registrovana je trombocitopenija koja je nastala 1-15 meseci od primene poslednje doze leka a uspešno je lečena standardnom terapijom za primarnu imunološku trombocitopeniju (ITP) [11]. Od interesa je napomenuti da su opisani i slučajevi LITP

danazol, moxonidine, ethambutol, diclofenac, tirofiban, haloperidol, efalizumab, irinotecan, ibuprofen, piperacillin, gold preparations, phenytoin, triamterene/hydrochlorothiazide, naproxen, hydrochlorothiazide, oxaliplatin, interferon alfa, methyldopa, nalidixic acid, quinine, quinidine, rifampin, ranitidine, sulfisoxazole, simvastatin, valproic acid, and vancomycin [4,9]. Along with medications, certain foods, beverages, and herbal preparations can also cause DITP [10].

The onset of thrombocytopenia typically occurs within one to three days after starting the drug if it has been used before, or within 7 to 15 days if the drug is being administered for the first time [1]. Exceptions include GPIIb/IIIa antagonists (such as abciximab, tirofiban, and eptifibatide), which can cause thrombocytopenia within hours or even minutes after starting therapy [4]. However, DITP can occur even after discontinuing the drug or persist for an extended period. Examples include therapy with gold, alemtuzumab, and immune checkpoint inhibitors [4]. In a Phase 2 clinical study evaluating the efficacy and safety of alemtuzumab for treating relapsing-remitting multiple sclerosis, thrombocytopenia was observed in 6 out of 216 pa-



Shema 1. Shematski prikaz patofiziologije A. Lekovima uzrokovane trombocitopenije (LITP) – klasične; B. Trombocitopenije indukovane lekovima blokatorima kontrolnih tačaka; C. Heparinom-indukovane trombocitopenije (HIT); D. Vakcinom indukovane trombozne trombocitopenije (VITT). (Prilagođeno iz Marini et al. [3])

Figure 1. Schematic representation of the pathophysiology of A. Drug-induced thrombocytopenia (DITP) - classic; B. Immune-checkpoint inhibitor (ICI) induced thrombocytopenia; C. Heparin-induced thrombocytopenia (HIT); D. Vaccine-induced immune thrombotic thrombocytopenia (VITT). (Adapted from Marini et al. [3])

koji su nastali posle dužeg vremena od uvođenja leka – pet meseci od uvođenja dabigatrana kod pacijentkinje sa atrijalnom fibrilacijom [12] ili čak 10 godina od uvođenja interferona beta-1a pacijentkinji sa dijagnozom multiple skleroze [13]. Sa druge strane, učestalost LITP u sklopu lečenja blokatorima kontrolnih tačaka kreće se od 0,2-2,8% i veoma retko je teškog stepena i sa fatalnim ishodom. Najveći broj opisanih slučajeva uzro-

tients. This condition emerged 1 to 15 months after the last dose of the drug and was effectively managed with standard treatment for primary immune thrombocytopenia (ITP) [11]. It is of interest to note that cases of drug-induced immune thrombocytopenia (DITP) have also been reported long after the drug was introduced—such as five months after starting dabigatran in a patient with atrial fibrillation [12], or even ten

kovan je nivolumabom i pembrolizumabom. Smatra se da je posledica oporavka T limfocita u sklopu imunološke terapije sa posledičnim stvaranjem autoantitela na trombocitne antigene, kao u ITP [14] (Shema 1B).

KLINIČKA SLIKA LEKOM UZROKOVANE IMUNSKE TROMBOCITOPENIJE

Trombocitopenija u sklopu LITP nastaje akutno, može biti teškog stepena (nadir broja trombocita < 20x10^9/L), uz životno ugrožavajuće krvarenje [1,3,4]. Naime, pokazano je da čak 67% bolesnika krvari, da njih 9% ima masivno krvarenje, a da čak 0,8% egzitira [15]. Međutim, kod heparinom uzrokovane trombocitopenije (HIT), nadir broja trombocita je oko 60x10^9/L, retko se registruje trombocitopenija < 20x10^9/L, a umesto krvarenja kliničkom slikom dominiraju tromboze [16]. Životno ugrožavajuće tromboze se takođe javljaju i u vakcinom indukovanoj tromboznoj trombocitopeniji (VITT). U LITP mogu se javiti i febrilnost, hipotenzija, sinkopa, mučnina i povraćanje [3,4].

PROCENA VEROVATNOĆE NASTANKA LEKOM UZROKOVANE TROMBOCITOPENIJE

Algoritam za procenu verovatnoće nastanka LITP je prikazan Shemom 2**.** S obzirom na to da u rutinskoj praksi nisu dostupni specifični dijagnostički testovi/ili biomarkeri za LITP, prvi korak u lečenju LITP je posumnjati na lek kao uzrok trombocitopenije da bi potom lek koji je sumnjiv odmah bio obustavljen i zamenjen lekom drugačije hemijske strukture. Ukoliko bolesnik koristi veći broj lekova koji su istovremeno uvedeni, savetuje se korekcija celokupne terapije [4]. S obzirom da se oporavak broja trombocita očekuje u proseku za 7 dana (opseg: 1-15), a prisutan je hemoragijski sindrom, preporučuju se primena kortikosteroida, intravenskih imunoglobulina i terapijske izmene plazme, a samo u slučaju intenzivnog krvarenja transfuzija trombocita. Međutim, tek po isteku 4-5 poluživota uzročnika LITP ili njegovog metabolita može se očekivati porast broja trombocita. Takođe, transfuzija trombocita biće neefikasna dokle god su prisutni bilo lek bilo njegovi metaboliti u plazmi pacijenta [4]. S druge strane, ukoliko su blokatori kontrolnih tačaka uzrokovali LITP, modifikacija doze ovih lekova u zavisnosti od broja trombocita regulisana je preporukama Američkog udruženja onkologa [17,18]. U diferencijalnoj dijagnozi LITP treba razmatrati ITP, trombocitopeniju u sklopu sepse, diseminovanu intravaskularnu koagulaciju (DIK), trombotičnu trombocitopenijsku purpuru (TTP), i posttransfuzionu purpuru [4]. Neophodno je pacijenta posavetovati da doživotno izbegava osumnjičeni lek.

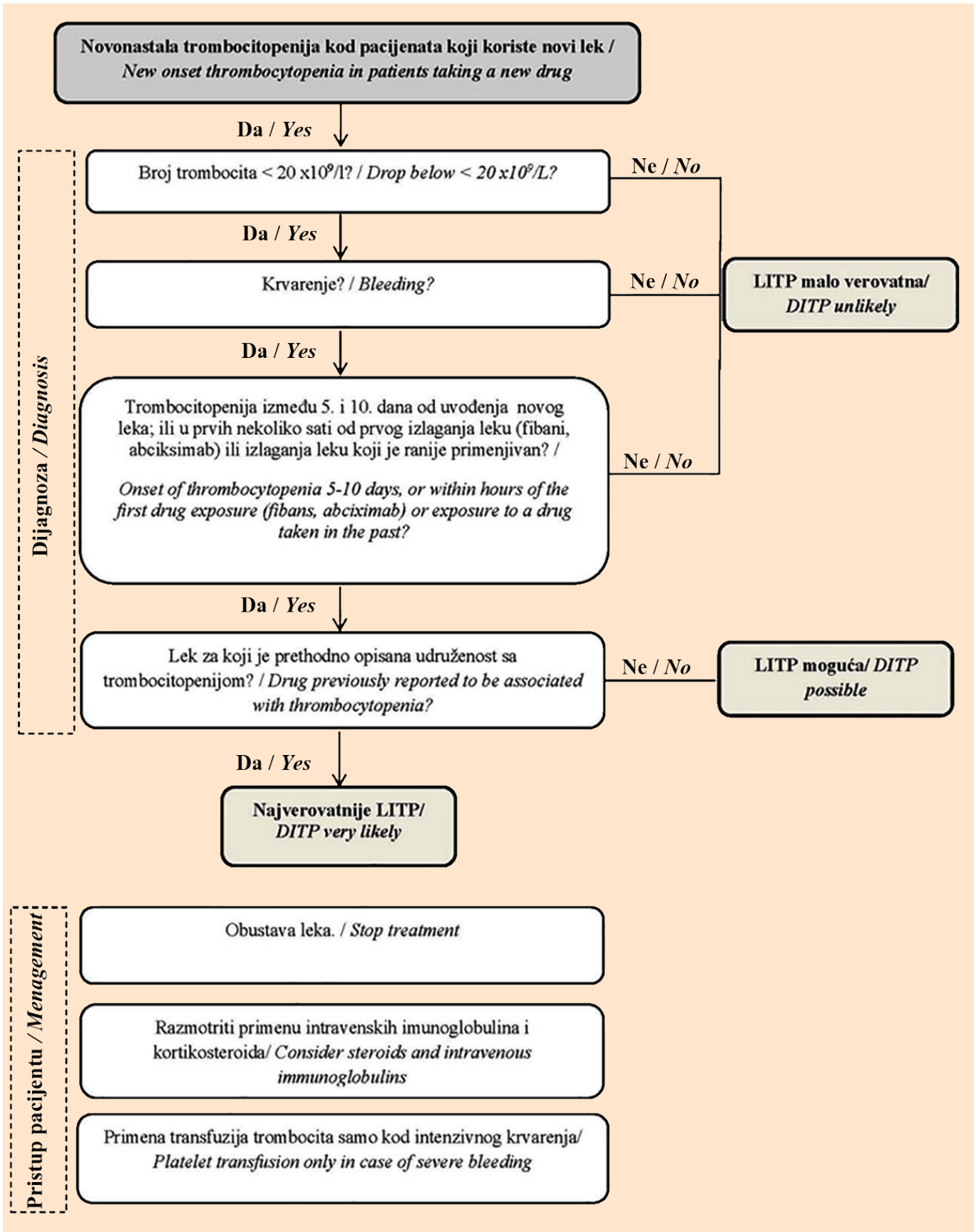
years after beginning interferon beta-1a treatment in a patient with multiple sclerosis [13]. Conversely, the incidence of DITP associated with checkpoint blockers ranges from 0.2% to 2.8%. Severe or fatal cases are extremely rare. Most of the reported cases were associated by nivolumab and pembrolizumab. It is believed that this condition arises from the recovery of T lymphocytes during immunotherapy, which leads to the formation of autoantibodies against platelet antigens, similar to what occurs in immune thrombocytopenia (ITP) [14] (Figure1B).

CLINICAL PRESENTATION OF DRUG-INDUCED THROMBOCYTOPENIA

In drug-induced immune thrombocytopenia (DITP), thrombocytopenia typically presents acutely and can be severe, with nadir platelet counts dropping below 20 × 10^9/L and potentially leading to life-threatening bleeding [1,3,4]. Studies have shown that 67% of patients with DITP experience bleeding, with 9% of these cases being classified as massive bleeding. Additionally, 0.8% of patients may experience fatal outcomes [15]. In heparin-induced thrombocytopenia (HIT), the lowest nadir platelet count typically reaches around 60 × 10^9/L, with counts below 20 × 10^9/L being rare. Instead of bleeding, HIT is primarily characterized by thromboses [16]. Life-threatening thromboses also occur in vaccine-induced thrombotic thrombocytopenia (VITT). In DITP, symptoms such as fever, hypotension, syncope, nausea, and vomiting may also occur [3,4].

EVALUATION OF THE LIKELIHOOD OF DRUG-INDUCED THROMBOCYTOPENIA

Figure 2 illustrates the algorithm for estimating the likelihood of DITP. Since specific diagnostic tests or biomarkers for drug-induced thrombocytopenia (DITP) are not routinely available, the initial step in managing DITP is to identify a suspected drug as the cause. The suspected drug should be promptly discontinued and replaced with an alternative medication of a different chemical structure. If the patient is taking multiple medications introduced simultaneously, it is advisable to adjust the entire therapy regimen [4]. Since platelet count recovery typically occurs within an average of 7 days (range: 1-15 days), and if hemorrhagic symptoms are present, the use of corticosteroids, intravenous immunoglobulins, and therapeutic plasma exchange is recommended. Platelet transfusion should be considered only in cases of severe bleeding. However, an increase in platelet count is typically expected only after the causative agent of DITP or its metabolite has been cleared from the body, which usually occurs after 4-5 half-lives of the drug. Platelet transfusion will be inef-



Shema 2. Pristup dijagnozi i lečenju pacijenta sa novonastalom trombocitopenijom kod kojih se sumnja na lekovima uzrokovanu trombocitopeniju (LITP) (prilagođeno iz Arnold DM, Cuker A. [4])

Figure 2. Diagnostic approach and management of a patient with new-onset thrombocytopenia in whom drug-induced immune thrombocytopenia (DITP) is suspected (adapted from Arnold DM, Cuker A. [4])

HEPARINOM UZROKOVANA TROMBOCITOPENIJA

HIT je stečeni protrombotični poremećaj izazvan primenom heparina, nefrakcionisanog ili niskomolekularnog. Učastalost HIT-a posle primene niskomolekularnog heparina je 10 puta ređa nego posle upotrebe nefrakcionisanog oblika [16]. Patofiziološki mehanizam HIT-a se zasniva na sintezi antitela, najčešće klase IgG, na imunogeni kompleks sastavljen od trombocitnog faktora 4 (PF4) i heparina. Vezivanje ovog trojnog kompleksa za trombocite dovodi do ubrzanog klirensa trombocita i nastanka trombocitopenije sa jedne strane, i aktivacije i agregacije trombocita i generacije trombina sa druge strane. Istovremena aktivacija endotela i monocita, sa posledičnom ekspresijom tkivnog faktora na njihovoj površini, dodatno potencira stvaranje trombina (Shema 1C). HIT nastaje 5-10 dana od uvođenja heparina a izuzetno ranije kod pacijenata lečenih heparinom u prethodna tri meseca. Retko, HIT može da se ispolji i po obustavi heparina [16,19]. Kod 5-10% pacijenata sa HIT-om koji ispolje DIK može nastati teži stepen trombocitopenije < 20x10^9/L [16]. Osim smanjenja broja trombocita za 50% od najvećeg registrovanog broja trombocita pre uvođenja heparina, u 20-50% slučajeva nastaju venske, a ređe i arterijske tromboze u narednih 30 dana. Pored toga, HIT se može ispoljiti i bolnim kožnim eritematoznim i nekrotičnim promenama, naročito na mestu injekcija, intrakardijalnim trombima i mezenterijalnim infarktima. Opisuju se i pojava febrilnosti, eritema lica i prolazne amnezije nastale 30 minuta posle primene intravenskog bolusa heparina [16]. Obustava heparina kod bolesnika sa HIT-om je nedovoljna mera te se mora primeniti alternativna antikoagulantna terapija. Pritom, težak stepen trombocitopenije nije kontraindikacija za primenu ove antikoagulantne terapije [16].

PRISTUP PACIJENTU SA SUMNJOM NA HIT

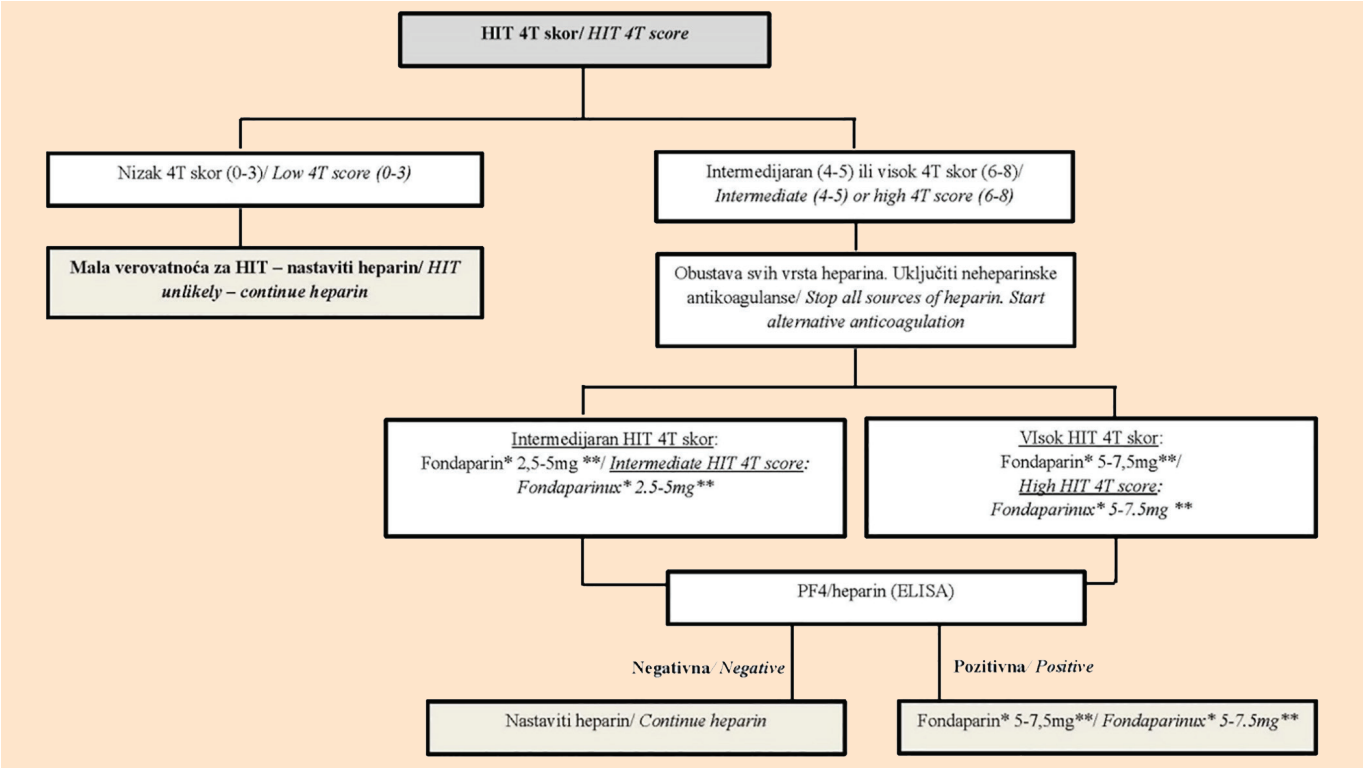
Ukoliko se registruje trombocitopenija kod bolesnika koji je na terapiji heparinom izračunavanjem 4Ts skora procenjuje se verovatnoća za nastanak HIT-a (Tabela 2) [16,19].

Ovaj bodovni sistem ima umereno pozitivnu prediktivnu i visoko negativnu prediktivnu vrednost. S druge strane, laboratorijska potvrda HIT-a bazira se na dokazu antitela uperenih na kompleks PF4-heparin. U rutinskoj upotrebi je nekoliko enzimskih imunosorbentnih (ELISA) testova koji imaju visoku negativnu prediktivnu vrednost što ih čini korisnim u isključivanju HIT-a. Međutim, usled njihove niske specifičnosti pozitivan test nema veliku vrednost u potvrdi kliničke sumnje na HIT. Pristup pacijentu sa sumnjom na HIT prikazan je Shemom 3.

fective as long as the drug or its metabolites remain present in the patient's plasma [4]. On the other hand, if checkpoint blockers are the cause of DITP, dose adjustments based on platelet counts should follow the guidelines provided by the American Society of Clinical Oncology [17,18]. In the differential diagnosis of DITP, it is important to consider immune thrombocytopenia (ITP), thrombocytopenia due to sepsis, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), and post-transfusion purpura [4]. The patient should be advised to avoid the suspected drug for life.

HEPARIN-INDUCED THROMBOCYTOPENIA

HIT is an acquired prothrombotic disorder triggered by the use of heparin, whether unfractionated or low molecular weight. The incidence of HIT with low molecular weight heparin is about ten times lower compared to unfractionated heparin [16]. The pathophysiological mechanism of HIT involves the formation of antibodies, typically of the IgG class, against an immunogenic complex composed of platelet factor 4 (PF4) and heparin. The binding of this ternary complex to platelets results in their accelerated clearance, leading to thrombocytopenia. Simultaneously, it triggers platelet activation and aggregation, as well as thrombin generation. Simultaneous activation of endothelial cells and monocytes, along with the expression of tissue factor on their surfaces, further enhances thrombin generation (Figure 1C). HIT typically occurs 5-10 days after starting heparin therapy, but it can develop much earlier in patients who have received heparin within the previous three months. Rarely, HIT can also occur after stopping heparin [16,19]. In 5-10% of patients with HIT who develop disseminated intravascular coagulation (DIC), thrombocytopenia may be more severe, with platelet counts dropping below 20 × 10^9/L [16]. In addition to a 50% reduction in the highest recorded platelet count before starting heparin, 20-50% of patients may develop venous, and less frequently arterial, thrombosis within the following 30 days. HIT can also present with painful erythematous and necrotic skin changes, particularly at injection sites, as well as intracardiac thrombi and mesenteric infarcts. Symptoms such as fever, facial erythema, and transient amnesia can occur within 30 minutes after administering an intravenous bolus of heparin [16]. Merely suspending heparin in patients with HIT is inadequate; alternative anticoagulant therapy must be implemented. At the same time, severe thrombocytopenia is not a contraindication for using alternative anticoagulant therapy in HIT [16].



Shema 3. Protokol postupanja kod sumnje na heparinom uzrokovanu trombocitopeniju (HIT) (prilagođeno iz Crowther M, Pishko A. [16])
*fondaparinuks je za sada jedini dostupan neheparinski antikogulans u Republici Srbiji
**u zavisnosti od telesne mase

Figure 3. SHIT protocol (adapted from Crowther M, Pishko A. [16])
*fondaparinuks is the only non-heparin antivoagulans in Serbia currently
** depending on body weight

Naime, ukoliko je 4Ts skor ≤ 3, verovatnoća HIT-a je mala, zbog čega se ne savetuje obustava heparina, ali ukoliko je skor intermedijaran ili visok (≥ 4), neophodna je obustava svih vrsta heparina, što podrazumeva i propiranje venskih linija i upotrebu ekstrakorporalnih membranskih oksigenatora, a potom uvođenje neheparinskih antikoagulansa (NHA). Takođe je neophodno određivanje titra antiheparinskih antitela. Ukoliko su antiheparinska antitela odsutna treba obustaviti NHA i nastaviti primenu heparina, a u slučaju pozitivnog testa, lečenje se nastavlja sa NHA [16,19]. Izbor NHA zavisi od karakteristika i dostupnosti pojedinih NHA sa jedne strane, i karakteristika pacijenta sa druge [16].-

Varfarin i ostali oralni antikoagulansi ne koriste se u lečenju pacijenata sa aktivnim HIT jer u HIT-u sa dubokom venskom trombozom, pogotovo sa vrednošću INR > 4, smanjenim nivoom proteina C i povišenim trombin-antitrombin kompleksima može nastati gangrena ekstremiteta. Međutim, ovi lekovi se mogu primeniti kod klinički stabilnih pacijenata čije je stvaranje trombina kontrolisano sa NHA i koji su normalizovali broj trombocita [16]. Ukoliko se kod pacijenta sa HIT-om razvila tromboza, antikoagulantnu terapiju treba sprovoditi tokom najmanje tri meseca. S druge strane, ukoliko je HIT kod pacijenta protekao bez tromboze,

APPROACH TO A PATIENT WITH SUSPECTED HIT

If a patient on heparin therapy develops thrombocytopenia, the likelihood of HIT is assessed using the 4Ts score (Table 2) [16,19].

This scoring system has a moderate positive predictive value and a high negative predictive value. On the other hand, laboratory confirmation of HIT relies on detecting antibodies specific to the PF4-heparin complex. Several enzyme-linked immunosorbent assay (ELISA) tests are routinely used and have a high negative predictive value, making them effective for ruling out HIT. However, due to their low specificity, a positive test result has limited value in confirming the clinical suspicion of HIT. The approach to a patient with suspected HIT is outlined in Figure 3.

If the 4Ts score is ≤ 3, the probability of HIT is considered low, so discontinuing heparin is not necessary. However, if the score is intermediate or high (≥ 4), all forms of heparin should be stopped, which includes removing venous lines and discontinuing the use of extracorporeal membrane oxygenators. In such cases, non-heparin anticoagulants (NHAs) should be introduced. It is also important to measure the titer of

Tabela 2. 4Ts bodovni sistem za procenu rizika od nastanka heparinom indukovane trombocitopenije (HIT) (prilagođeno iz Crowther M, Pishko A. [16])

Table 2. 4Ts score for heparin-induced thrombocytopenia (HIT) (adapted from Crowther M, Pishko A. [16])

Parametar / *Category*	Broj poena / *Points*
Trombocitopenija / *Thrombocytopenia*	
Broj Tr snižen za > 50% od inicijalne vrednosti i minimalan broj Tr > $20x10^9$/L / *Platelet count fall > 50% and platelet nadir > $20x10^9$/L*	2
Broj Tr snižen za 30-50% od inicijalne vrednosti ili minimalan broj Tr 10-$19x10^9$/L / *Platelet count fall 30-50% or platelet nadir 10-$19x10^9$/L*	1
Broj Tr snižen < 30% od inicijalne vrednosti ili minimalni broj Tr < 10^9/L / *Platelet count fall < 30% or platelet nadir <10^9/L*	0
Vreme proteklo od uvođenja heparina do pojave trombocitopenije / *Timing of platelet count fall*	
Između 5. i 10. dana terapije ili ≤ 1 dana u slučaju primene heparina tokom prethodnih 30 dana / *Clear onset between days 5 - 10 or falls ≤1 day in case of prior heparin exposure during the last 30 days*	2
> 10. dana ili ≤ 1 dana u slučaju primene heparina tokom prethodnih 30-100 dana / *Onset > 10 day or falls ≤ 1 day in case of prior heparin exposure within prior 30-100 days*	1
≤ 4 dana od početka terapije ili > 14 dana po izlaganju / *Platelet count falls < 4 days or >14 days after exposure*	0
Tromboze i ostale komplikacije / *Thrombosis or other sequelae*	
Nova potvrđena tromboza i: nekroza kože, akutna sistemska reakcija posle intravenskog bolusa nefrakcionisanog heparina, progresivna ili rekurentna tromboza, eritem kože, bez nekroze / *New thrombosis (confirmed); necrotizing and non-necrotizing skin lesions; acute systemic reaction post-intravenous UFH bolus; progressive or recurrent thrombosis*	2
Sumnja na trombozu (nedokazana) / *Suspected thrombosis (not proven)*	1
Nijedno od navedenog / *None of the above*	0
Trombocitopenija, drugi uzroci / *Other causes of thrombocytopenia*	
Nema / *None apparent*	2
Mogući drugi uzroci / *Possible*	1
Dokazani drugi uzroci / *Definite*	0

Legenda: Tr- trombociti

Legend: UFH - unfractionated heparin

lečenje se sprovodi tokom četiri nedelje [16,19]. Pacijent kome je jednom dijagnostikovan HIT više se ne sme izlagati heparinu, osim pod kontrolom specijalizovanog tima [20].

VAKCINOM INDUKOVANA TROMBOZNA TROMBOCITOPENIJA

VITT se odlikuje nastankom tromboze i trombocitopenije 4 do 30 dana od primene adenovirusne vektorske vakcine. Naime, učestalost VITT je 2.5-38/milion primenjenih prvih doza ChadOx1 nCov19 i 1.9/ milion drugih doza [21]. S druge strane, saopštena je učestalost VITT od 3.5/milion primenjenih doza Ad26.CoV2.S [22]. Smatra se da je ključni događaj u nastanku VITT stvaranje antitela klase IgG na PF4 usled formiranja neoantigena na PF4 prilikom njegovog vezivanja za komponentu vakcine. Naime, anti-PF4 antitelo vezuje se za PF4 na površini trombocita što prouzrokuje aktivaciju

anti-heparin antibodies. If anti-heparin antibodies are absent, NHAs should be discontinued, and heparin administration can be resumed. If the test is positive, continue treatment with NHA [16,19]. The choice of NHA depends on both the specific characteristics and availability of each NHA and the individual patient's clinical condition [16].

Warfarin and other oral anticoagulants are not used in the treatment of patients with active HIT. In cases of HIT with deep vein thrombosis, particularly with an INR value > 4, there is a risk of limb gangrene due to reduced levels of protein C and elevated thrombin-antithrombin complexes. However, these drugs can be used in clinically stable patients whose thrombin generation is controlled with NHA and whose platelet count has normalized [16]. If a patient with HIT develops thrombosis, anticoagulant therapy should be continued for at least three months. Conversely, if the

trombocita uz oslobađanje prokoagulantnih supstanci (Shema 1D). Oko dve nedelje posle vakcinacije, javljaju se krvarenje usled teškog stepena trombocitopenije i tromboza, najčešće u cerebralnim venskim sinusima, kojoj prethodi intenzivna glavobolja. Dokazano je da anti-PF4 antitela perzistiraju u organizmu obolelih od VITT čak 12 do 15 meseci od vakcinacije [23]. Kod 30% pacijenata javlja se intrakranijalno krvarenje koje je često fatalno. Smrtnost u VITT se kreće od 20- 60% [24-25]. Po svom kliničkom ispoljavanju VITT veoma liči na HIT, a jedina razlika je što pacijent nije prethodno bio izložen heparinu. U lečenju VITT koriste se neheparinski antikoagulansi, intravenski imunoglobulini i kortikosteroidi ukoliko je broj trombocita < 50x10^9/L, dok transfuzije trombocita treba izbegavati zbog rizika od tromboze.

Sukob interesa: Nije prijavljen.

patient's HIT resolves without thrombosis, treatment should be continued for four weeks [16,19]. A patient who has been diagnosed with HIT should avoid re-exposure to heparin, unless under the supervision of a specialized medical team [20].

VACCINE-INDUCED THROMBOTIC THROMBOCYTOPENIA

VITT is characterized by the onset of thrombosis and thrombocytopenia occurring 4 to 30 days after administration of an adenoviral vector vaccine. The frequency of VITT is approximately 2.5 to 38 cases per million doses administered for the first dose of the ChAdOx1 nCoV-19 vaccine and about 1.9 cases per million for the second dose [21]. Conversely, the frequency of VITT with the Ad26.CoV2.S vaccine has been reported as 3.5 cases per million doses administered [22]. The development of VITT is believed to be primarily triggered by the generation of IgG antibodies against platelet factor 4 (PF4). This occurs due to the formation of a neoantigen on PF4 when it binds to the vaccine component. Namely, the anti-PF4 antibodies bind to PF4 on the surface of platelets, leading to platelet activation and the release of procoagulant substances (Figure 1D). Approximately two weeks after vaccination, bleeding may occur due to severe thrombocytopenia and thrombosis, commonly affecting the cerebral venous sinuses and often preceded by intense headaches. It has been proven that anti-PF4 antibodiespersist in the body of VITT patients even 12 to 15 months after vaccination [23]. Intracranial bleeding occurs in about 30% of patients, and it is often fatal. Mortality in VITT ranges from 20-60% [24-25]. Clinically, VITT closely resembles HIT, the only difference being that the patient has not previously been exposed to heparin. In the treatment of VITT, non-heparin anticoagulants, intravenous immunoglobulins, and corticosteroids are used if the platelet count is < 50 × 10^9/L. Platelet transfusions should be avoided due to the risk of exacerbating thrombosis.

Conflict of interest: None declared.

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