TROMBOCITOPENIJA I KOVID-19: DIFERENCIJALNA DIJAGNOZA I TERAPIJA

PREGLEDNI RAD

REVIEW ARTICLE

THROMBOCYTOPENIA AND COVID-19: DIFFERENTIAL DIAGNOSIS AND THERAPY

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SAŽETAK

Trombocitopenija je česta manifestacija KOVID-19 oboljenja, koja je u pojedinim saopštenjima dostizala učestalost i do 35%. Tromboctopenija predstavlja nepovoljan prognostički faktor tokom lečenja KOVID-19 infekcije. Uprkos velikom broju publikacija o prognostičkom značaju trombocitopenije u KOVID-19 infekciji, podaci o diferencijalnoj dijagnozi i njenoj terapiji su oskudni. U ovom preglednom radu prikazani su sledeći uzroci trombocitopenije kod KOVID-19 oboljenja: trombocitopenija indukovana infekcijom SARS-KoV-2 virusom; diseminovana intravaskularna koagulopatija (DIK); imunološka trombocitopenija; lekovima indukovana trombocitopenija, sa posebnim osvrtom na heparinom indukovanu trombocitopeniju (HIT). Iako je trombocitopenija uglavnom veoma blaga i ne zahteva lečenje, moguć je i razvoj trombocitopenije teškog stepena, koja, zbog krvarenja, može životno ugroziti bolesnika. Sa druge strane, neki oblici trombocitopenije, kao što su HIT ili DIK, nose visok rizik od tromboze, te je neophodna antikoagulantna profilaksa. Na kraju svakog poglavlja ovog rada, date su preporuke za lečenje različitih tipova trombocitopenije nastalih u sklopu KOVID-19 oboljenja.

Ključne reči: trombocitopenija, KOVID-19, SARS-KoV-2, HIT, DIK

ABSTRACT

Thrombocytopenia represents a common manifestation of COVID-19 with a prevalence of up to 35% in certain studies. A low platelet count is an unfavorable prognostic marker in SARS-CoV-2 infected patients. Despite a large number of publications dealing with the prognostic significance of thrombocytopenia in COVID-19, data regarding the differential diagnosis and therapy are scarce. The most common causes of thrombocytopenia in COVID-19 are shown in this review, namely: SARS-CoV-2-induced thrombocytopenia; disseminated intravascular coagulopathy (DIC); immune thrombocytopenia; drug-induced thrombocytopenia, with a special insight into heparin-induced thrombocytopenia (HIT). Although a majority of patients suffer from mild thrombocytopenia and do not require any particular treatment, there are some cases of severe thrombocytopenia which may cause life threatening bleeding. On the other hand, some forms of thrombocytopenia, such as DIC or HIT, carry a high risk of the development of thrombotic events, which is why anticoagulant prophylaxis is required in these patients. At the end of each section of this review, treatment recommendations are given for each aforementioned type of thrombocytopenia developing in COVID-19.

Keywords: thrombocytopenia, COVID-19, SARS-CoV-2, HIT, DIC

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Primljeno • *Received*: December 13, 2022; **Revidirano • *Revised*:** December 22, 2022; **Prihvaćeno • *Accepted*:** December 27, 2022; ***Online first*:** Mach 25, 2022.

DOI: 10.5937/3-35382

UVOD

Tokom prethodne dve godine, teški respiratorni sindrom koronavirus 2 (SARS-KoV-2), koji uzrokuje koronavirusnu bolest 2019 (KOVID-19), doveo je do infekcije miliona ljudi širom planete, i, prema podacima iz novembra 2021. godine, do više od pet miliona smrtnih ishoda [1]. Iako je KOVID-19 primarno infektivna bolest, sistemske manifestacije se posebno često razvijaju kod bolesnika sa teškom kliničkom slikom. Prvi izveštaji iz Vuhana u Kini, kao i velike meta-analize, ukazale su na brojne hematološke abnormalnosti kod obolelih [2,3]. U laboratorijskim analizama, često se uočavaju anemija, leukopenija sa limfopenijom, trombocitopenija, povišeni D-dimer, LDH i feritin. Navedeni poremećaji su posledica citokinske oluje, aktivacije makrofaga i endotela, povećanog oslobađanja tkivnog faktora, aktivacije koagulacije, kao i formiranja mikrotrombova u krvnim sudovima celog tela [2,3]. Pritom su venske i arterijske tromboze najupečatljivije kliničke manifestacije, dok su znatno ređa krvarenja [2,3].

Rezultati meta-analiza, koje su uključile nekoliko hiljada bolesnika sa KOVID-19 oboljenjem, pokazale su da je trombocitopenija veoma česta manifestacija bolesti, koja je u pojedinim grupama dostizala učestalost i do 35% [4,5]. Meta-analiza, sa sistematskim pregledom više od 7.000 bolesnika, pokazala je značajnu udruženost trombocitopenije i teškog oblika KOVID-19 oboljenja (OR = 3,46, 95% CI 1,72 – 6,94, I2 = 91,8%), kao i udruženost trombocitopenije i smrtnog ishoda usled KOVID-19 oboljenja (OR = 11,75, 95% CI 3,51–39,31, I2 = 88,9%) [4].

Uprkos velikom broju publikacija o prognostičkom značaju trombocitopenije u sklopu KOVID-19 oboljenja, podaci o diferencijalnoj dijagnozi i terapiji trombocitopenije su oskudni. Diferencijalna dijagnoza trombocitopenije tokom KOVID-19 infekcije uključuje i preegzistirajuću trombocitopeniju. Takođe se, tokom same infekcije, mogu dijagnostikovati bolesti koje su uzrok trombocitopenije, kao što su mijelodisplastični sindrom, akutna leukemija, ciroza jetre, i drugo. S obzirom da su navedeni uzroci retki, u ovom radu, akcenat će biti na najčešćim uzrocima trombocitopenije kod KOVID-19 oboljenja: SARS-KoV-2 infekcijom indukovana trombocitopenija, diseminovana intravaskularna koagulopatija (DIK), imunološka trombocitopenija (ITP) i lekovima indukovana trombocitopenija (LITP), sa posebnim osvrtom na heparinom indukovanu trombocitopeniju (HIT).

SARS-KOV-2 INFEKCIJOM INDUKOVANA TROMBOCITOPENIJA

Trombocitopenija u sklopu KOVID-19 oboljenja je posredovana nizom kompleksnih patofizioloških procesa,

INTRODUCTION

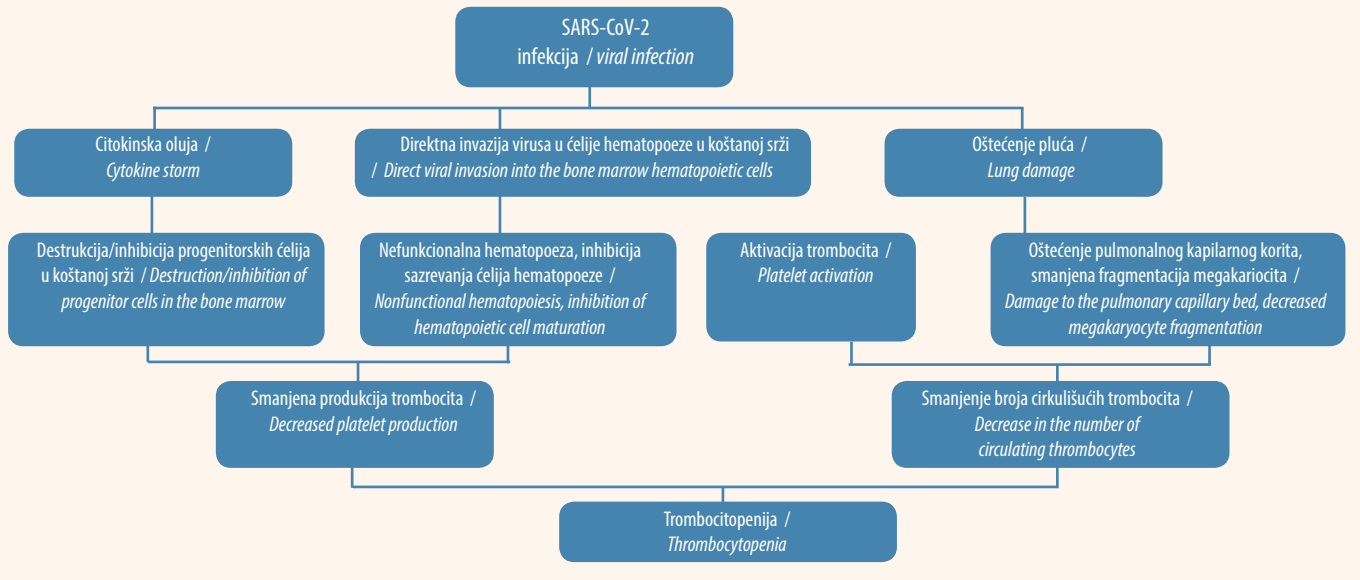
Over the past two years, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has led to the infection of millions of people all over the world, and, according to data from November 2021, it has also led to more than five million deaths worldwide [1]. Although COVID-19 is primarily an infectious disease, systemic manifestations develop particularly frequently in patients with severe clinical presentation. The first reports from Wuhan, China, as well as large meta-analyses, have highlighted numerous hematologic abnormalities in patients suffering from the disease [2,3]. Anemia, leukopenia with lymphopenia, thrombocytopenia, elevated D-dimer, LDH and ferritin are often found in blood test results. The aforementioned disorders are the result of a cytokine storm, macrophage and endothelial activation, increased tissue factor release, coagulation activation, as well as the forming of microthrombi in the blood vessels of the entire body [2,3]. In this process, venous and arterial thromboses are the most prominent clinical manifestations, while bleeding is significantly less frequent [2,3].

The results of meta-analyses, which included several thousand COVID-19 patients, showed thrombocytopenia to be a very frequent manifestation of the disease, which, in certain groups, amounted to as much as 35% [4,5]. A meta-analysis, with a systematic overview of 7,000 patients, showed significant association between thrombocytopenia and the severe from of COVID-19 (OR = 3.46, 95% CI 1.72 – 6.94, I2 = 91.8%), as well as association between thrombocytopenia and the lethal outcome of COVID-19 (OR = 11.75, 95% CI 3.51 – 39.31, I2 = 88.9%) [4].

Despite the large number of publications on the prognostic significance of thrombocytopenia in COVID-19, data on differential diagnosis and the treatment of thrombocytopenia are limited. The differential diagnosis of thrombocytopenia during COVID-19 infection includes preexisting thrombocytopenia. Also, during the infection itself, diseases causing thrombocytopenia, such as myelodysplastic syndrome, acute leukemia, liver cirrhosis, and others, may be diagnosed. Bearing in mind that the aforementioned causes are rare, in this paper, emphasis will be placed on the most frequent causes of thrombocytopenia in COVID-19, which are as follows: SARS-CoV-2-induced thrombocytopenia, disseminated intravascular coagulopathy (DIC), immune thrombocytopenia (ITP), and drug-induced thrombocytopenia (DITP), with a special insight into heparin-induced thrombocytopenia (HIT).

SARS-COV-2-INDUCED THROMBOCYTOPENIA

Thrombocytopenia in COVID-19 is mediated by a series of complex pathophysiological processes, which result



Grafikon 1. SARS-KoV-2 infekcijom indukovana trombocitopenija (prilagođeno iz: *Xu P. et al.* [6])

Figure 1. SARS-CoV-2-induced thrombocytopenia (adapted from: Xu P. et al. [6])

koji za posledicu imaju smanjenu produkciju ili ubrzanu potrošnju cirkulišućih trombocita (Grafikon 1). Ona nastaje kao posledica citokinske oluje, direktne invazije virusa u ćelije hematopoeze, kao i usled oštećenja tkiva pluća [5].

Smanjena produkcija trombocita

Citokinska oluja

Citokinska oluja se definiše kao stanje izrazito povišenog nivoa cirkulišućih citokina, a najčešće se javlja nakon preterane aktivacije imunološkog sistema izazvane akutnom sistemskom infekcijom [7]. Upravo se ovim fenomenom objašnjava trombocitopenija kod jednog broja pacijenata sa infekcijom izazvanom SARS-KoV-2 virusom [8]. Naime, pokazano je da je aktivnost proinflamatornih citokina, kao što su interleukini IL-2R, IL-6, IL-10, kao i faktora tumorske nekroze α, značajno povišena kod obolelih od teškog oblika KOVID-19 infekcije [9]. Povišena koncentracija ovih citokina dovodi do dalje amplifikaciije imunološkog odgovora, oštećenja mikrosredine koštane srži, kao i do supresije hematopoeze [8]. Pored toga, faktor tumorske nekroze α je direktni inhibitor megakariocitopoeze [10].

Direktna invazija virusa u ćelije hematopoeze

Iako ekspresija ACE2 (engl. angiotensin-converting enzyme 2) receptora, koji je označen kao mesto ulaska SARS-KoV-2 virusa u ćelije, nije registrovana na megakariocitima, elektronskom mikroskopijom je detektovan virion ovog virusa u megakariocitima, dok je primenom PCR (engl. polymerase chain reaction) metode dokazano prisustvo genetskog materijala virusa

in decreased production or increased consumption of circulating platelets (Figure 1). It occurs as the result of a cytokine storm, direct viral invasion of hematopoietic cells, as well as the result of pulmonary tissue damage [5].

Decreased platelet production

Cytokine storm

A cytokine storm is defined as the state of an extremely elevated level of circulating cytokines, and it most commonly occurs during excess activation of the immune system, caused by systemic infection [7]. It is this phenomenon that explains thrombocytopenia in a certain number of patients infected by the SARS-CoV-2 virus [8]. Namely, it has been shown that the activity of proinflammatory cytokines, such as interleukins IL-2R, IL-6, IL-10, as well as of tumor necrosis factor α, is significantly increased in patients suffering from the severe form of COVID-19 [9]. An elevated concentration of cytokines leads to further amplification of the immune response, to damage to the bone marrow microenvironment, as well as to the suppression of hematopoiesis [8]. Also, tumor necrosis factor α is a direct inhibitor of megakaryocytopoiesis [10].

Direct viral invasion of hematopoietic cells

Although the expression of the angiotensin-converting enzyme 2 (ACE2) receptor, which has been identified as the point of entry of the SARS-CoV-2 virus into the cells, has not been registered on megakaryocytes, the virion of this virus has been detected with electron microscopy in megakaryocytes, while the application of the polymerase chain reaction (PCR) method has

u trombocitima obolelih [11]. Postoji više mogućih puteva ulaska virusa u megakariocite. Na primer, humani korona virus 229E takođe izaziva trombocitopeniju, koja je objašnjena direktnom invazijom virusa u ćelije koštane srži i trombocite putem CD13 molekula [6]. Imajući u vidu stepen sličnosti ova dva virusa, kao i činjenicu da je prisustvo SARS-KoV-2 virusa dokazano u megakariocitnoj lozi, brojni autori su ovo označili kao jedan od mehanizama supresije megakariopoeze.

Smanjenje broja cirkulišućih trombocita

Oštećenje pluća

Bilateralna pneumonija je česta karakteristika pacijenata hospitalizovanih zbog KOVID-19 oboljenja. Naime, SARS-KoV-2 virus izaziva alveolarno oštećenje, kongestiju pluća, stvaranje hijalinih membrana i fibrozu [10]. Pokazano je da oštećenje plućnog parenhima utiče na smanjenje broja trombocita, putem više mehanizama. Pre svega, u plućima je dokazano prisustvo dve subpopulacije megakariocita: intravaskularni megakariociti, poreklom iz koštane srži, koji stvaraju cirkulišuće trombocite, i sesilni, interticijumski megakariociti, koji su nepoznatog porekla i koji učestvuju u imunološkim reakcijama [12]. Pritom je pokazan povećani broj megakariocita u plućnom tkivu pacijenata obolelih od KOVID-19 oboljenja koji imaju difuzno oštećenje alveolarnih membrana [13]. Kako je za fragmentaciju citoplazme megakariocita i stvaranje trombocita neophodna normalna mikrovaskulatura pluća, koja je u ovom slučaju oštećena, na taj način dolazi i do smanjene produkcije cirkulišućih trombocita [14]. Smanjeni broj trombocita uz povišene zapaljenske faktore, dovodi do porasta nivoa trombopoetina sa posledično povećanom mobilizacijom megakariocita u tkivo pluća [15].

Osim toga, patohistološki supstrat plućnog tkiva pacijenata obolelih od KOVID-19 oboljenja predstavlja i oštećenje endotela. Naime, SARS-KoV-2 virus direktno inficira vaskularni endotel preko ACE-2 receptora, izazivajući ćelijsko oštećenje i apoptozu. Na ovaj način dolazi do degranulacije endotelnih ćelija i do oslobađanja Fon Vilebrandovog faktora (vWF) i faktora VIII u cirkulaciju [16]. Oslobođeni vWF aktivira trombocite preko GPIb-IX-V kompleksa, što dovodi do njihove degranulacije. Pritom, što je ćelijsko oštećenje u plućima veće, intenzivnije su i aktivacija i potrošnja trombocita, te je i trombocitopenija većeg stepena [8].

Terapija

U terapiji trombocitopenije indukovane KOVID-19 oboljenjem, najvažnije je lečenje osnovnog uzročnika trombocitopenije. Pre svega, savetuje se lečenje

proven the presence of viral genetic material in the platelets of patients infected with SARS-CoV-2 [11]. There is a number of possible paths of entry of the virus into megakaryocytes. For instance, human coronavirus 229E also causes thrombocytopenia, which is explained by direct viral invasion into bone marrow cells and platelets via CD13 molecules [6]. Bearing in mind the level of similarity between these two viruses, as well as the fact that the presence of SARS-CoV-2 has been proven in the megakaryocyte lineage, numerous authors have marked this as one of the mechanisms of megakaryopoiesis suppression.

Decrease in the number of circulating platelets

Damage to the lungs

Bilateral pneumonia is a frequent characteristic of patients hospitalized for COVID-19. Namely, the SARS-COV-2 virus causes alveolar damage, pulmonary congestion, the formation of hyaline membranes, and fibrosis [10]. It has been shown that the damage to lung parenchyma affects the decrease in the platelet count, which is mediated through a number of mechanisms. Primarily, it has been proven that there are two types of megakaryocyte populations in the lungs: intravascular megakaryocytes, originating from bone marrow, which produce circulating platelets, and sessile, interstitial megakaryocytes of unknown origin, which participate in immunologic reactions [12]. At the same time, an increased number of megakaryocytes has been found in in the pulmonary parenchyma of COVID-19 patients with diffuse damage to alveolar membranes [13]. As normal microvasculature of the lungs, which is in this case damaged, is necessary for megakaryocyte cytoplasm fragmentation and platelet production, thus the production of circulating thrombocytes is reduced [14]. A decreased number of platelets, together with elevated inflammatory factors, leads to the rise in the level of thrombopoietin with consequently elevated mobilization of megakaryocytes into the lung tissue [15].

Additionally, damaged endothelium is also a pathohistological substrate of the pulmonary tissue in COVID-19 patients. Namely, the SARS-CoV-2 virus directly infects the vascular endothelium via the ACE-2 receptors, causing cellular damage and apoptosis. In this way, degranulation of endothelial cells occurs as well as the release of the Von Willebrand factor (vWF) and factor VIII into the circulation [16]. The released vWF activates thrombocytes via the GPIb-IX-V complex, which leads to endothelial cell degranulation. Also, the greater the pulmonary cell damage, the more intensive the activation and consumption of platelets, thus resulting in more severe thrombocytopenia [8].

infekcije u skladu sa Nacionalnim protokolom [17]. Pravovremena primena kortikosteroida, u odgovarajućoj dozi, pokazala se efikasnom u smanjenju sistemskog inflamatornog odgovora. Time se postiže, ne samo povećanje broja trombocita, nego i brža rezolucija oštećenog plućnog parenhima [8].

Druge terapijske mogućnosti, kao što su monoklonska antitela koja antagonizuju dejstvo IL-6 (tocilizumab, sarilumab, siltuksimab), zatim antagonist IL-1 receptora (anakinra), inhibitor komponente komplementa (ekulizumab), inhibitori hemokina i hemokinskih receptora i humanog rekombinantnog solubilnog ACE2, predstavljaju predmet proučavanja brojnih studija čiji je cilj bolja kontrola KOVID-19 oboljenja, a samim tim i uspešnije lečenje trombocitopenije u sklopu KOVID-19 bolesti [8].

Transfuzije trombocita kod ovih pacijenata se savetuju isključivo u slučaju krvarenja, dok se profilaktiče transfuzije ne preporučuju [8].

KOAGULOPATIJA UDRUŽENA SA KOVID-19 OBOLJENJEM (CAC)

Prema definiciji Međunarodnog udruženja za trombozu i hemostazu (engl. International Society on Thrombosis and Haemostasis – ISTH), diseminovana intravaskularna koagulopatija (DIK) je stečeni sindrom koji se odlikuje diseminovanom intravaskularnom aktivacijom koagulacije, koja može nastati zbog različitih uzroka [18]. DIK je istovremeno laboratorijska i klinička dijagnoza koja se odlikuje porastom D-dimera, smanjenom koncetracijom fibrinogena, padom broja trombocita i potrošnjom faktora koagulacije. Osnovna klinička manifestacija DIK-a je multiorganska disfunkcija usled mikroishemija, dok su krvarenja znatno ređa [18]. Kod bolesnika sa KOVID-19 oboljenjem, diseminovana intravaskularna koagulopatija može biti uzrokovana poremećajem hemostaze u okviru virusne infekcije (engl. COVID-19-associated coagulopathy – CAC) ili bakterijskom sepsom koja komplikuje lečenje (SIK – sepsom indukovana koagulopatija) [3,4]. Neophodno je istaći da svaki uzrok koagulopatije ima svoju specifičnu evoluciju i posledičnu dinamiku laboratorijskih parametara. Na primer, CAC se odlikuje višim D-dimerom i većim brojem trombocita, u odnosu na SIK. Dosadašnji podaci ukazuju da se CAC manifestuje aktiviranom koagulacijom i trombozama, pre nego jasnim („overtnim“) DIK-om. Međutim, svi oblici koagulopatija mogu postepeno progredirati do jasnog DIK-a, koji se odlikuje trombocitopenijom, padom koncetracije faktora koagulacije i sklonošću ka krvarenju [3,4].

U prvim fazama infekcije SARS-KoV-2 virusom, bolest je ograničena na pluća. Naime, usled oštećenja alveola, dolazi do ekstravazacije i ekstravaskularne ak-

Treatment

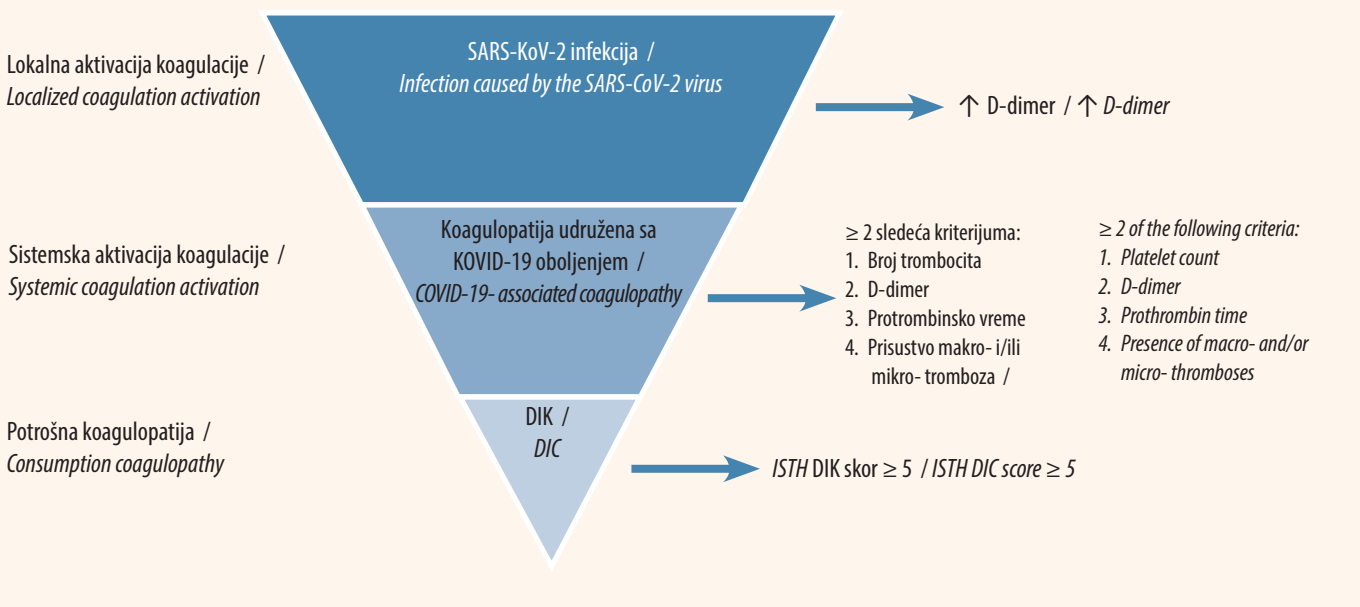
In the treatment of COVID-19-induced thrombocytopenia, it is most important to treat the main source of the thrombocytopenia. It is primarily advised to treat the infection itself according to the National Protocol [17]. Timely administration of corticosteroids, in the appropriate dose, has proven effective in reducing systemic inflammatory response. Thereby, not only is the platelet count increased, but a faster resolution of the damaged pulmonary parenchyma is achieved [8].

Other treatment options, such as monoclonal antibodies which antagonize the effect of IL-6 (tocilizumab, sarilumab, siltuximab), also the IL-1 receptor antagonist (anakinra), the complement component inhibitor (eculizumab), as well as the chemokine and chemokine receptor inhibitors and the human recombinant soluble ACE2 inhibitor, are the object of research in numerous studies, whose aim is better control of COVID-19, and, consequently, more effective treatment of thrombocytopenia in COVID-19 [8].

Platelet transfusions in these patients are recommended only in case of hemorrhage, while prophylactic transfusions are not recommended [8].

COVID-19-ASSOCIATED COAGULOPATHY (CAC)

According to the definition of the International Society on Thrombosis and Haemostasis (ISTH), disseminated intravascular coagulopathy (DIC) is an acquired syndrome, characterized by disseminated intravascular coagulation activation, which may occur due to different causes [18]. DIC is, at the same time, both a laboratory and a clinical diagnosis, characterized by D-dimer elevation, a reduced concentration of fibrinogen, a fall in the platelet count and the consumption of the clotting factor. The main clinical manifestation of DIC is multiorgan dysfunction resulting from microischemias, while bleeding is significantly rarer [18]. In COVID-19 patients, disseminated intravascular coagulopathy may be caused by hemostatic disturbance occurring as a part of the viral infection (COVID-19-associated coagulopathy – CAC) or by bacterial sepsis, which complicates treatment (SIC – sepsis-induced coagulopathy) [3,4]. It is necessary to stress that every cause of coagulopathy has its own particular evolution and consequent laboratory parameter dynamics. For instance, CAC is characterized by a higher D-dimer and a higher platelet count, as compared to SIC. Data up to date indicate that CAC manifests through activated coagulation and thromboses, rather than as overt DIC. However, all forms of coagulopathy may gradually progress towards overt DIC, which is characterized by thrombocytopenia, a fall in the concentration of the clotting factor and a tendency towards bleeding [3,4].



Grafikon 2. Progresija od koagulopatije indukovane KOVID-19 infekcijom (CAC) do diseminovane intravaskularne koagulopatije (DIK) (prilagođeno iz: *Ida T. et al.* [37])

Figure 2. Progression from COVID-19-associated coagulopathy (CAC) to disseminated intravascular coagulopathy (DIC) (adapted from: Ida T. et al. [37])

tivacije koagulacije, sa pretvaranjem fibrinogena u fibrin i ograničavanjem bolesti [3,4]. Ova inicijalna faza se odlikuje porastom D-dimera [3,4]. Povećana inflamacija i aktivacija bolesti u samim plućima sa oštećenjem vaskularnog endotela uzrok su in situ tromboza tipičnih za KOVID-19 oboljenje. U slučaju progresije bolesti i nastanka citokinske oluje, dolazi do intravaskularne aktivacije koagulacije u celom organizmu, pre svega putem aktivacije makrofaga, kao i do oštećenja endotela i povećane ekspresije tkivnog faktora (Grafikon 2) [3,4].

Prema definiciji koju su ponudili Iba i saradnici, CAC se dijagnostikuje ako postoji dokazana infekcija SARS-KoV-2 virusom i jedan od sledećih kriterijuma: (1) broj trombocita < 150 $\times 10^9$/L; (2) porast D-dimera > dva puta iznad normale; (3) produženo protrombinsko vreme (engl. prothrombin time – PT) za > 1 sekunde ili INR (engl. international normalized ratio) > 1,2; (4) smanjenje fibrinogena; (5) tromboza. Rizik za razvoj CAC-a imaju bolesnici sa: (1) povišenim nivoom fibrinogena;

In the first stages of the SARS-CoV-2 viral infection, the disease is limited to the lungs. Namely, due to alveolar damage, extravasation and extravascular coagulation activation occur, with the conversion of fibrinogen into fibrin and disease containment [3,4]. This initial phase is characterized by D-dimer elevation [3,4]. Increased inflammation and disease activation in the lungs themselves with vascular endothelial damage are the cause of in situ thromboses, typical for COVID-19. In case of disease progression and the occurrence of a cytokine storm, intravascular coagulation activation occurs in the whole body, primarily through macrophage activation, as well as through endothelial damage and increased expression of tissue factor (Figure 2) [3,4].

According to the definition by Iba et al, CAC is diagnosed if there is proven SARS-CoV-2 infection, as well as one of the following criteria: (1) platelet count < 150 $\times 10^9$/L; (2) D-dimer increase > twice above the normal value; (3) prolonged prothrombin time (PT) by > 1 second or international normalized ratio (INR) > 1.2; (4) fibrinogen

Tabela 1. *ISTH* DIK skor [19]

Table 1. ISTH DIC score [19]

	0	1	2	3
Trombociti (x 10^9/L)	*> 100*	*50 – 100*	*< 50*	/
Produženje PT (s)	*< 3*	*3 – 6*	*> 6*	/
Fibrinogen (g/L)	*> 1*	*< 1*	/	/
D-dimer	/	/	*> 2 – 4 x*	*> 4 x*

ISTH - International Society on Thrombosis and Haemostasis; DIK – diseminovana intravaskularna koagulopatija; PT – protrombinsko vreme

ISTH - International Society on Thrombosis and Haemostasis; DIC – disseminated intravascular coagulopathy; PT – prothrombin time

Tabela 2. SIK skor [3]

Kategorija / *Category*	Parametar / *Parameter*	0 poena / *0 points*	1 poen / *1 point*	2 poena /*2 points*
PT / *PT*	PT/INR / *PT/INR*	≤ 1,2	> 1,2	> 1,4
Koagulacija / *Coagulation*	Trombociti (x 10^9/L) / *Platelets (x 10^9/L)*	≥ 150	< 150	< 100
Ukupni SOFA skor / *Total SOFA*	SOFA skor (četiri komponente) / *SOFA score (four components)*	0	1	≥ 2

SIK – sepsom indukovana koagulopatija; PT – protrombinsko vreme; *INR - international normalized ratio; SOFA - sequential organ failure assessment score*

Table 2. SIC score [3]

ISTH - International Society on Thrombosis and Haemostasis; DIC – disseminated intravascular coagulopathy; PT – prothrombin time

(2) povišenim vWF-om (više od dva puta iznad normale); (3) prisustvom antifosfolipidnih antitela [3].

Pacijenti sa CAC-om, ili pod rizikom od razvoja CAC-a, mogu progredirati do jasnog DIK-a. Kako ne postoji pouzdani dijagnostički test za DIK, preporučuje se dinamičko praćenje parametara koagulacije i primena sistema bodovanja. Najčešće primenjivani sistemi bodovanja za dijagnozu DIK-a su ISTH kriterijumi (Tabela 1), dok se u jedinicama intenzivnog lečenja koristi i SIK skor (Tabela 2). Kriterijumi za jasni DIK su vrednost ISTH DIK skora ≥ 5 ili vrednost SIK skora ≥ 4. Neophodno je istaći da sa porastom skora za 1 poen dolazi do značajnog porasta smrtnosti pacijenta. Naime, smrtni ishod pacijenata sa jasnim DIK-om i oboljenjem KOVID-19 iznosi više od 70%. Takođe, u uslovima jasnog DIK-a, raste verovatnoća krvarenja, te se, uz lečenje osnovne bolesti, preporučuje i nadoknada faktora koagulacije i trombocita transfuzijama derivata i komponenata krvi [18,19].

Imajući u vidu visoku učestalost tromboznih komplikacija, kao osnovne manifestacije CAC-a, obustava antikoagulantne terapije se preporučuje samo ako su trombociti < 25 x 10^9/L i u slučaju krvarenja. Trombocite je potrebno održavati > 25 x 10^9/L, transfuzijama trombocita. Sa druge strane, ako bolesnik krvari, potrebno je transfuzijama održavati nivo fibrinogena > 1,5 g/L, broj trombocita > 50 x 10^9/L, a PT odnos (nije isto što i INR) < 1,5 [20].

IMUNOLOŠKA TROMBOCITOPENIJA

Imunološka trombocitopenija (ITP) je difinisana kao izolovani broj trombocita < 100 x 10^9/L, u odsustvu drugih potencijalnih uzročnika trombocitopenije [21]. Dijagnoza ITP-a se postavlja isključivanjem drugih uzroka trombocitopenije (negativne virusološke i imunološke analize, normalan CRP i IL-6, odsustvo znakova potrošne koagulopatije, isključivanje lekova kao uzročnika trombocitopenije). U grupi pacijenata sa KOVID-19 oboljenjem i ITP-om razlikujemo dve podgrupe: pacijenti sa novodijagnostikovanom imunološkom trombocitopenijom i pacijenti sa prethodno dijagnostikovanom imunološkom trombocitopenijom.

depletion; (5) thrombosis. Risk of developing CAC is present in patients with the following: (1) elevated fibrinogen level; (2) increased vWF (more than twice above the normal level); (3) presence of antiphospholipid antibodies [3].

Patients with CAC, or those at risk of developing CAC, may progress to overt DIC. As there is no reliable diagnostic test for DIC, dynamic monitoring of coagulation parameters and the application of a scoring system is advised. The most frequently applied scoring system for the diagnosis of DIC are the ISTH criteria (Table 1), while in intensive care units, the SIC score is also used (Table 2). The criteria for overt DIC are the value of the ISTH DIC score of ≥ 5 or the value of the SIC score of ≥ 4. It is necessary to point out that with each rise of the score by 1 point, patient mortality significantly rises. Namely, the lethal outcome for patients with overt DIC and COVID-19 is more than 70%. Also, in the conditions of overt DIC, the possibility of bleeding increases, which is why, in addition to treatment for the underlying disease, replacement of the clotting factor and platelets through the transfusion of blood derivatives and components is recommended [18,19].

Bearing in mind the high frequency of thrombotic complications, as the main manifestation of CAC, discontinuation of anticoagulant therapy is recommended only if the platelet count is < 25 x 10^9/L and in case of bleeding. Platelets should be kept at > 25 x 10^9/L, with platelet transfusions. On the other hand, if the patient is bleeding, it is necessary to maintain fibrinogen at > 1.5 g/L, the platelet count at > 50 x 10^9/L, and the PT ratio (not the same as INR) at < 1.5, with transfusions [20].

IMMUNE THROMBOCYTOPENIA

Immune thrombocytopenia (ITP) is defined as isolated platelet count of < 100 x 10^9/L, in the absence of other potential causes of thrombocytopenia [21]. The diagnosis of ITP is established through excluding other causes of thrombocytopenia (negative virological and immunological analyses, normal values of CRP and IL-6, absence of signs of consumption coagulopathy, exclusion of drugs as the cause of thrombocytopenia). In the group of patients with COVID-19 and ITP, there are two subgroups: patients with newly diagnosed immune

Novodijagnostikovana imunološka trombocitopenija

Infekcije virusima su poznati okidač za nastanak ITP-a. Ipak, iako je broj objavljenih slučajeva ili manjih serija slučajeva ITP-a posle KOVID-19 infekcije značajan, podataka o učestalosti ITP-a posle KOVID-19 bolesti, za sada nema. Iz do sada publikovanih slučajeva, može se zaključiti da je ovaj tip ITP-a češći kod pacijenata starijih od 60 godina. Može da se javi kao težak stepen trombocitopenije (< 20 x 10^9/L), gde su zabeležena životno ugrožavajuća krvarenja (intracerebralna hemoragija, gastrointestinalno krvarenje), te ovo stanje nikada ne treba zanemariti. Najčešće se trombocitopenija javlja tokom druge ili treće nedelje KOVID-19 bolesti (kada počinje sinteza anti-KOVID-19 antitela) [22].

Prethodno dijagnostikovana imunološka trombocitopenija

Različite infekcije često dovode do relapsa primarne imunološke trombocitopenije. Prema rezultatima španske grupe autora, infekcija SARS-KoV-2 virusom povećava učestalost relapsa pacijenata sa već postojećom dijagnozom ITP-a [23]. Takođe, pokazano je da je stopa relapsa veća kod pacijenata sa težom inicijalnom kliničkom slikom [23]. Sa druge strane, kod pacijenata kod kojih je, primenom agonista trombopoetinskih receptora (engl. thrombopoietin receptor agonists – TPO-RA), postignuta stabilna remisija pre-KOVID-19 infekcije, tokom bolesti je uočena trombocitoza [24–26].

Terapija

Kao prva linija terapije u lečenju ITP-a, savetuje se primena kortikosteroida i intravenskih imunoglobulina. Standardno, terapija prve linije je prednizolon u dozi od 1 mg/kg t.m. (maksimalno 80 mg), tokom dve nedelje, a potom je potrebno započeti postepenu obustavu [27]. Međutim, prema nekim vodičima, u slučaju KOVID-19 oboljenja, ukoliko je broj trombocita < 20 x 10^9/L, kod pacijenata koji ne krvare, treba otpočeti terapiju prednizolonom u nižim dozama (20 mg/dan), uz povećavanje doze, ukoliko izostane terapijski odgovor [28,29]. Ukoliko pacijent krvari, potrebno je odmah primeniti intravenske imunoglobuline (ukupna doza 2 g/kg t.m. tokom dva ili pet dana) i/ili kortikosteroide (deksametazon 40 mg/dan, tokom četiri dana, ili prednizolon 1 mg/kg t.m.) [28,29]. Objavljeni su slučajevi ITP-a u KOVID-19 oboljenju, koji nisu reagovali na prethodno navedenu terapiju, a kod kojih je uspostavljena kontrola krvarenja tek primenom agonista trombopoetinskih receptora (TPO-RA) [30,31]. Primena rituksimaba se ne preporučuje tokom KOVID-19 infekcije [28,29].

Ukoliko dođe do relapsa kod pacijenata sa prethodno dijagnostikovanim ITP-om, treba razmotriti

thrombocytopenia and patients with previously diagnosed immune thrombocytopenia.

Newly diagnosed immune thrombocytopenia

Viral infections are a known trigger for the development of ITP. However, although the number of published cases or smaller series of cases of ITP following COVID-19 is significant, so far there are no data on the frequency of ITP after COVID-19. From reports on cases published so far, it may be concluded that this type of ITP is more frequent in patients older than 60 years. It can present as severe thrombocytopenia (< 20 x 10^9/L), wherein life-threatening bleeding has been recorded (intracerebral hemorrhage, gastrointestinal bleeding), which is why this state must never be overlooked. Thrombocytopenia most commonly occurs during the second or third week of COVID-19 (when synthesis of anti-COVID-19 antibodies begins) [22].

Previously diagnosed immune thrombocytopenia

Different infections often lead to the relapse of primary immune thrombocytopenia. According to the results of a Spanish group of authors, SARS-CoV-2 viral infection increases the frequency of relapse in patients with a preexisting ITP diagnosis [23]. Also, it has been shown that the relapse rate is greater in patients with more severe initial clinical presentation [23]. On the other hand, in patients in whom, through the application of thrombopoietin receptor agonists (TPO-RA), stable remission has been achieved prior to COVID-19, thrombocytosis has been recorded, during the illness [24–26].

Treatment

As first-line therapy in treating ITP, application of corticosteroids and intravenous immunoglobulins is recommended. Normally, first-line therapy is prednisolone in the dose of 1 mg/kg bw (maximum 80 mg), for two weeks, and then it is necessary to start with gradual discontinuation of treatment [27]. However, according to some guidelines, in case of COVID-19, if the platelet count is < 20 x 10^9/L, in patients who are not bleeding, prednisolone treatment should be started in lower doses (20 mg/day), with an increase of the dose, if therapeutic response is lacking [28,29]. If the patient is bleeding, it is necessary to administer intravenous immunoglobulins immediately (total dose 2 g/kg bw for two or five days) and/or corticosteroids (dexamethasone 40 mg/day, for four days, or prednisolone 1 mg/kg bw) [28,29]. Cases of ITP in COVID-19 have been reported, which did not respond to the previously described therapy and where control of bleeding was established only after thrombopoietin receptor

primenu TPO-RA. U slučaju akutnog krvarenja, kod ovih pacijenata može biti primenjena terapija prve linije – kortikosteroidi i intravenski imunoglobulini. Kod pacijenata koji već primaju TPO-RA, dozu treba prilagoditi aktuelnom broju trombocita uz češću kontrolu njihovog broja. Primena rituksimaba se ne preporučuje u ovoj grupi pacijenata [28,29].

Transfuzije trombocita kod pacijenata sa ITP-om savetuju se isključivo u slučaju životno ugrožavajućih krvarenja [27].

LEKOVIMA UZROKOVANA TROMBOCITOPENIJA

Lekovi su jedan od najčešćih uzroka trombocitopenije, posebno kod hospitalizovanih bolesnika. Do sada je opisana pojava trombocitopenije tokom primene više od 1.300 lekova [30]. Precizan spisak ovih lekova se može pronaći na linku: www.ouhsc.edu/platelets. Učestalost lekovima uzrokovane trombocitopenije se procenjuje na 10/1.000.000 stanovnika godišnje [30]. U jedinicama intenzivne nege, 30% bolesnika ima neki stepen lekovima uzrokovane trombocitopenije [31].

Na osnovu mehanizma nastanka, lekovima indukovana trombocitopenija može se podeliti na imunološke i neimunološke (citotoksične).

Citotoksične lekovima uzrokovane trombocitopenije

Lekovi kao što su citostatici i antineoplastici – linezolid, ganciklovir, aspirin, vankomicin i etanol mogu da uzrokuju trombocitopeniju direktnim citotoksičnim ili proapoptotičkim dejstvom na megakariocite [31].

Imunološke lekovima uzrokovane trombocitopenije

Lekovima uzrokovana imunološka trombocitopenija (LITP) je najčešće uzrokovana antitelima specifičnim za lek, koja se u prisustvu leka vezuju za trombocite, dovodeći do njihovog ubrzanog klirensa. Lekovi koji najčešće dovode do LITP-a su: abciksimab, acetaminofen, amlodipin, amjodaron, ampicilin, karbamazepin, kotrimoksazol, hlorpropamid, cimetidin, digitalis, drospirenon, gentamicin, eptifibatid, danazol, moksonidin, etambutol, diklofenak, tirofiban, haloperidol, efalizumab, ibuprofen, irinotekan, preparati zlata, fenitoin, triamteren/hidrohlorotiazid, naproksen, hidrohlorotiazid, oksaliplatina, interferon A, metildopa, nalidiksinska kiselina, kvinidin, kinin, ranitidin, rifampin, simvastatin, tirofiban, sulfisoksazol, vankomicin, valproična kiselina [30,31].

Vreme od početka terapije do nastanka trombocitopenije varira od nekoliko sati do nekoliko meseci (najčešće 10 - 15 dana). Trombocitopenija nastaje akutno i može biti teškog stepena, praćena životno

agonists had been administered (TPO-RA) [30,31]. The application of rituximab is not recommended during COVID-19 infection [28,29].

If relapse occurs in patients with previously diagnosed ITP, the application of TPO-RA should be considered. In case of acute bleeding in these patients, first-line therapy may be applied – corticosteroids and intravenous immunoglobulins. In patients already receiving TPO-RA, the dose should be adjusted to the current platelet count with more frequent control of the number of thrombocytes. The application of rituximab is not recommended in this patient group [28,29].

Platelet transfusions in patients with ITP are recommended only in case of life-threatening bleeding [27].

DRUG-INDUCED THROMBOCYTOPENIA

Drugs are one of the most common causes of thrombocytopenia, especially in hospitalized patients. So far, thrombocytopenia has been registered during the application of more than 1,300 different drugs [30]. A precise list of these drugs can be found on the following website: www.ouhsc.edu/platelets. The frequency of drug-induced thrombocytopenia is estimated at 10/1,000,000 per capita a year [30]. In intensive care units, 30% of patients suffer from some level of drug-induced thrombocytopenia [31].

Based on the mechanism of development, drug-induced thrombocytopenia can be categorized as immune and non-immune (cytotoxic).

Cytotoxic drug-induced thrombocytopenia

Drugs such as cytostatics and antineoplastics – linezolid, ganciclovir, aspirin, vancomycin, and ethanol, may cause thrombocytopenia through direct cytotoxic or proapoptotic effect on megakaryocytes [31].

Immune drug-induced thrombocytopenia

Drug-induced immune thrombocytopenia (DIIT) is most commonly caused by antibodies specific to the particular drug, which, in the presence of the drug, bind to platelets, leading to their accelerated clearance. Drugs most commonly leading to DIIT are the following: abciximab, acetaminophen, amlodipine, amiodarone, ampicillin, carbamazepine, cotrimoxazole, chlorpropamide, cimetidine, digitalis, drospirenone, gentamicin, eptifibatide, danazol, moxonidine, ethambutol, diclofenac, tirofiban, haloperidol, efalizumab, ibuprofen, irinotecan, gold-based drugs, phenytoin, triamterene/hydrochlorothiazide, naproxen, hydrochlorothiazide, oxaliplatin, interferon A, methyldopa, nalidixic acid, quinidine, quinine ranitidine, rifampin, simvastatin, tirofiban, sulfisoxazole, vancomycin, valproic acid [30,31].

ugrožavajućim krvarenjem. Zapravo, čak 67% bolesnika krvari, a kod čak 9% pacijenata je u pitanju životno ugrožavajuće krvarenje. Povremeno se mogu pojaviti i febrilnost, mučnina, povraćanje, hipotenzija i sinkopa [30,31].

Terapija

Najvažniji korak u lečenju ovog stanja je razmatranje mogućnosti da je do trombocitopenije doveo lek. Potrebno je „sumnjivi lek" odmah obustaviti i zameniti ga lekom drugačije hemijske strukture. Kako je, u toku lečenja KOVID-19 oboljenja, bolesnik izložen istovremeno velikom broju lekova, koji su uvedeni konkomitantno, savetuje se promena celokupne terapije. Kako se oporavak očekuje za prosečno 7 dana (u opsegu od 1 - 15), ako bolesnik krvari, savetuje se primena transfuzija trombocita, kortikosteroida, intravenskih imunoglobulina i terapijske izmene plazme [30,31].

HEPARINOM INDUKOVANA (IZAZVANA) TROMBOCITOPENIJA

Heparinom indukovana trombocitopenija (HIT) je stečeni protrombotički poremećaj izazvan primenom antikoagulansa heparina [32,33]. Patofiziologija HIT-a se zasniva na stvaranju IgG antitela na kompleks trombocitnog faktora 4 (engl. platelet factor 4 – PF4) i heparina. Vezivanjem ovog kompleksa za trombocite dolazi do njihovog ubrzanog klirensa i trombocitopenije, sa jedne strane, ali i aktivacije trombocita i generacije trombina, sa druge strane [32,33]. Stoga je obustava antikoagulantne terapije kod bolesnika sa HIT-om stručna greška.

Prema meta-analizi koja je obuhvatila 7 studija sa 5.849 pacijenata, ukupna incidencija HIT-a u KOVID-19 oboljenju je iznosila 0,8% (95%-tni interval poverenja (engl. confidence interval – CI) = 0,2 – 3,2%; I2 = 89%). Procenjena incidencija za grupu pacijenata na terapijskoj dozi niskomolekularnog heparina (engl. low-molecular-weight heparin – LMWH) iznosila je 1,2% (95% CI, 0,3 – 3,9%; I2 = 65%), nasuprot 0,1% (95% CI, 0,0 – 0,4%; I2 = 0%) u profilaktičkoj grupi. Incidencija HIT-a je bila znatno viša kod kritično bolesnih pacijenata (2,2%, 95% CI, 0,6 – 8,3%; I2 = 72,5%), u poređenju sa pacijentima koji nisu bili kritično bolesni (0,1%, 95% CI, 0,0 – 0,4%; I2 = 0%). Iako učestalost HIT-a u KOVID-19 oboljenju nije prevelika, apsolutni broj bolesnika, imajući u vidu razmere pandemije, jeste ogroman [34].

U slučaju razvoja trombocitopenije kod bolesnika na terapiji heparinom, potrebno je izracunati 4T HIT skor (Tabela 3) [17,35,36]. Naime, ako je 4T HIT skor nizak (≤ 3), verovatnoća HIT-a je mala, te ne treba obustavljati heparin. Međutim, ako je vrednost skora intermedijarna ili visoka (≥ 4) neophodno je prekinuti izlaganje bolesnika svim vrstama heparina, uključujući i propiranje

The time from the beginning of treatment until the development of thrombocytopenia varies from several hours to several months (most commonly 10 - 15 days). Thrombocytopenia occurs acutely and may be severe, accompanied by life-threatening bleeding. In fact, as many as 67% of patients hemorrhage, and as many as 9% experience life-threatening bleeding. Occasionally, febrility, nausea, vomiting, hypotension, and syncope may occur [30,31].

Treatment

The most important step in treating this condition is considering the possibility of drug-induced thrombocytopenia. It is necessary to immediately discontinue the drug suspected of causing the condition and replace it with a drug of different chemical structure. Since, in COVID-19 treatment, the patient is exposed to a large number of drugs at the same time, which are introduced concomitantly, it is recommended that the entire drug regimen is changed. As recovery is expected within an average of 7 days (range: 1 – 15 days), if the patient is bleeding, it is recommended to apply platelet transfusion, corticosteroids, intravenous immunoglobulins, and therapeutic plasma exchange [30,31].

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is an acquired prothrombotic disorder caused by the administration of the anticoagulant heparin [32,33]. The pathophysiology of HIT is based on the production of IgG antibodies to the platelet factor 4 (PF4)/heparin complex. The binding of this complex to thrombocytes leads to their accelerated clearance and to thrombocytopenia, one the one hand, but also to platelet activation and thrombin production, on the other [32,33]. Thus, discontinuation of anticoagulant therapy in patients with HIT is a professional error.

According to the meta-analysis including 7 studies with 5,849 patients, the overall incidence of HIT in COVID-19 was 0.8% (95% confidence interval (CI) = 0.2 – 3.2%; I2 = 89%). The estimated incidence for the group of patients receiving a therapeutic dose of low-molecular-weight heparin (LMWH) was 1.2% (95% CI, 0.3 – 3.9%; I2 = 65%), as opposed to 0.1% (95% CI, 0.0 – 0.4%; I2 = 0%) in the prophylaxis group. The incidence of HIT was significantly higher in critically ill patients (2.2%, 95% CI; 0.6 – 8.3%; I2 = 72.5%), as compared to patients who were not critically ill (0.1%, 95% CI, 0.0 – 0.4%; I2 = 0%). Although, the frequency of HIT in COVID-19 patients is not too high, the absolute number of patients, when the scale of the pandemic is taken into consideration, is massive [34].

Tabela 3. 4T HIT skor (prilagođeno iz: Linkins LA i saradnici [36])

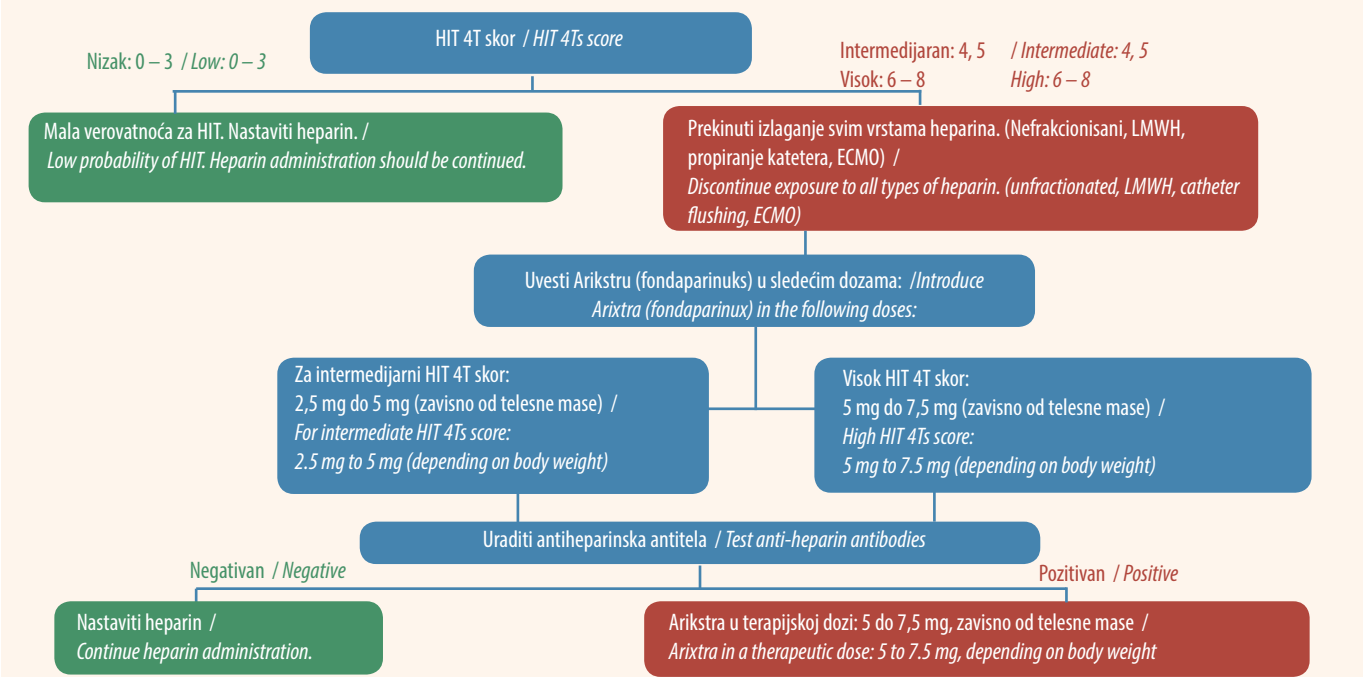
Parametar	Broj poena
Trombocitopenija	
Broj trombocita u padu za > 50% od inicijalne vrednosti i minimalni broj Tr > 20 x 10^9/L	2
Broj trombocita u padu za 30% – 50% od inicijalne vrednosti ili minimalni broj Tr 10 – 19 x 10^9/L	1
Broj trombocita u padu < 30% od inicijalne vrednosti ili minimalni broj Tr < 10 x 10^9/L	0
Vreme od uvođenja heparina do nastanka trombocitopenije	
Pojava trombocitopenije između 5. i 10. dana terapije, ili ≤ 1 dana, u slučaju prethodne terapije heparinom unutar 30 dana	2
Nejasna pojava trombocitopenije između 5. i 10. dana terapije; pojava > 10 dana ili ≤ 1 dana, u slučaju prethodne primene heparina unutar 30 do 100 dana	1
Pojava trombocitopenije ≤ 4 dana od početka terapije, u odsustvu prethodne primene heparina	0
Tromboze i ostale komplikacije	
Potvrđena akutna tromboza, nekroza kože ili akutna sistemska reakcija posle intravenskog bolusa nefrakcionisanog heparina	2
Progresivna ili ponovna tromboza, kožne lezije (eritem bez nekroze), sumnja na trombozu koja nije dokazana	1
Ništa od navedenog	0
Trombocitopenija - drugi uzroci	
Nema dokaza	2
Mogući drugi uzroci	1
Dokazani drugi uzroci	0

Table 3. 4Ts HIT score (adapted from: Linkins LA et al. [36])]

Parameter	No. points
Thrombocytopenia	
> 50% platelet count (PC) fall, as compared to the initial level, and minimal PC > 20 x 10^9/L	2
PC fall by 30% – 50% of the initial level or minimal PC 10 – 19 x 10^9/L	1
PC fall by < 30% of the initial level or minimal PC < 10^9/L	0
Time elapsed from heparin introduction to the development of thrombocytopenia	
Thrombocytopenia onset 5 – 10 days after start of therapy, or within ≤ 1 day of start of therapy, in case of previous heparin application within 30 days	2
Unexplained thrombocytopenia between 5th and 10 th day of therapy, onset of thrombocytopenia within > 10 days or ≤ 1 day, in case of previous heparin application within 30 to 100 days	1
Thrombocytopenia onset ≤ 4 days after the start of therapy, in case of no previous heparin application	0
Thromboses and other complications	
Confirmed acute thrombosis, skin necrosis, or acute systemic reaction following an intravenous bolus of unfractionated heparin	2
Progressive or recurrent thrombosis, skin lesions (erythema without necrosis), suspicion of unconfirmed thrombosis	1
None of the above	0
Thrombocytopenia - other causes	
No evidence	2
Possibility of other causes	1
Other causes confirmed	0

venskih linija i upotrebu ekstrakorporalnih membranskih oksigenatora, te uvesti fondaparinuks (Arixtra®) i odrediti antiheparinska antitela. Ako su antiheparisnka antitela negativna, savetuje se obustava fondaparinuksa i nastavak primene heparina. Sa druge strane, u slučaju pozitivnog titra antiheparinskih antitela, lečenje se nastavlja fondaparinuksom [17,35,36]. Pregled

In case of the development of thrombocytopenia in patients treated with heparin, it is important to calculate the 4Ts HIT score (Table 3) [17,35,36]. Namely, if the 4Ts HIT score is low (≤ 3), the probability of HIT is small, which is why heparin need not be discontinued. However, if the score is intermediate or high (≥ 4), it is necessary to discontinue patient exposure to



Grafikon 3. Protokol pri sumnji na heparinom indukovanu trombocitopeniju

Figure 3. Protocol applied when heparin-induced thrombocytopenia is suspected

dijagnostike i lečenja HIT-a u KOVID bolnici „Batajnica" prikazan je u Grafikonu 3. Osim fondaparinuksa, moguća je primena i sledećih antikoagulanasa: (1) argatroban: 1 – 2 mcg/kg/min, uz postizanje produženja aktiviranog parcijalnog tromboplastinskog vremena (engl. activated partial thromboplastin time – aPTT) 1,5 do 3 puta iznad normale; (2) danaparoid: bolus 2.250 jedinica, 400 jed/h tokom 4 sata, zatim 300 jed/h naredna 4 sata, potom 200 jed/h; (3) bivalirudin 0,15 mg/kg na sat, (aPTT 1,5 do 2,5 puta veći od normale); (4) rivaroksaban (Xarelto®, Rivaroksaban SK®): 2 x 15 mg 21 dan, potom 20 mg/dan; (5) apiksaban (Eliquis®): 2 x 10 mg/dan 7 dana, potom 2 x 5 mg na dan; (6) dabigatran (Pradaxa®): 2 x 150 mg/dan (posle perioda parenteralne antikoagulacije, u trajanju od 5 – 10 dana). Varfarin je moguće započeti po normalizaciji broja trombocita [17,35,36].

Ako je pacijent sa HIT-om imao trombozni događaj, antikoagulantna terapija mora da se sprovodi tokom najmanje tri meseca. Sa druge strane, ako je HIT kod pacijenta protekao bez tromboznih događaja, lečenje se sprovodi tokom četiri nedelje [17,35,36].

Pacijent kome je jednom dijagnostikovana heparinom indukovana trombocitopenija više ne sme biti izložen heparinu, osim pod kontrolom hematologa [17,35,36].

ZAKLJUČAK

Razvoj trombocitopenije predstavlja nepovoljan prognostički faktor tokom lečenja KOVID-19 oboljenja. Iako je trombocitopenija uglavnom veoma blaga i ne zahteva lečenje, moguć je razvoj trombocitopenija teškog stepena, koje zbog krvarenja mogu životno ugroziti bolesnika. Sa druge strane, neki oblici trombocitopenija, kao sto su HIT ili CAC, nose visok rizik od tromboza, te je neophodno nastaviti antikoagulantnu profilasku. Od izuzetne je važnosti poznavanje algoritma dijagnostike i lečenja ovih stanja.

Sukob interesa: Nije prijavljen.

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any type of heparin, including the flushing of venous catheters and the use of extracorporeal membrane oxygenators, and to introduce fondaparinux (Arixtra®) as well as determine anti-heparin antibodies. If anti-heparin antibodies are negative, discontinuation of fondaparinux and the continuation of heparin application are advised. On the other hand, in case of a positive titer of anti-heparin antibodies, treatment with fondaparinux is continued [17,35,36]. The overview of the diagnostics and treatment of HIT in the COVID-19 hospital Batajnica, is presented in Figure 3. Apart from fondaparinux, the application of the following anticoagulants is possible: (1) argatroban: 1 – 2 mcg/kg/min, with the achievement of the prolongation of activated partial thromboplastin time (aPTT) 1.5 to 3 times the normal value; (2) danaparoid: bolus 2.250 units, 400 units/h for 4 h, followed by 300 units/h for 4 h, then 200 units/h; (3) bivalirudin: 0.15 mg/kg per hour, (aPTT 1.5 to 2.5 times the normal value); (4) rivaroxaban (Xarelto®, Rivaroksaban SK®): 2 x 15 mg for 21 day, then 20 mg/day; (5) apixaban (Eliquis®): 2 x 10 mg/day for 7 days, then 2 x 5 mg per day; (6) dabigatran (Pradaxa®): 2 x 150 mg/day (after the period of parenteral anticoagulation, for 5 – 10 days). It is possible to start Warfarin upon the reestablishing of the normal platelet count [17,35,36].

If the patient with HIT has had a thrombotic event, anticoagulant therapy must be applied for a minimum of three months. On the other hand, if HIT in a patient passes without thrombotic events, treatment is carried out for a period of four weeks [17,35,36].

A patient diagnosed with heparin-induced thrombocytopenia must not be exposed to heparin again, unless monitored by a hematologist [17,35,36].

CONCLUSION

The development of thrombocytopenia is an unfavorable prognostic factor in COVID-19 treatment. Although thrombocytopenia is mainly mild and does not require treatment, the development of severe forms of thrombocytopenia is possible, which, due to bleeding, may be life-threatening for the patient. On the other hand, some forms of thrombocytopenia, such as HIT and CAC, carry a high risk of thrombosis, which is why it is necessary to continue anticoagulant prophylaxis. The understanding of the algorithm of diagnostics and treatment of these conditions is essential.

Conflict of interest: None declared.

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