

DOSADAŠNJA SAZNANJA O ETIOPATOGENEZI I MOGUĆNOSTIMA TERAPIJE KOVID-19

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SAŽETAK

Trenutno je u svetu od Kovid-19 obolelo preko 35 miliona ljudi, a preko milion je umrlo. Pandemijski karakter bolesti je nametnuo dinamična istraživanja, kako u oblasti razjašnjavanja etiopatogenetskih mehanizama bolesti, tako i u oblasti moguće terapije. Količina naučnih znanja se u poslednjih devet meseci nekoliko desetina puta uvećala, ali i dalje nismo ni blizu definisanju efikasne i sigurne terapije. Saznanje da je Kovid-19 ne samo respiratorno, već i multisistemsko oboljenje, koje zahvata skoro sve organe, dalo nam je mogućnosti za terapijska prilagođavanja. Jak oksidacioni stres, tiha hronična hipoksija, povećana koagulabilnost i povećana agregacija trombocita, samo su neki od mehanizama u razvoju bolesti. Smatra se da su kardiovaskularne posledice i poremećaj funkcije endotela krvnih sudova uglavnom odgovorni za smrtni ishod, uz opasnu citokinsku oluju i akutni respiratorni distres sindrom. Imajući sve ovo u vidu, u terapijskom smislu, kod već obolelih osoba, predložena je primena antibiotika, visokih doza vitamina C zbog antioksidacionog dejstva, transfuzije krvi, imunoglobulina, interferona, anti-IL-6 antitela, malih doza deksametazona ili drugih kortikosteroida, specifičnih antivirusnih lekova, favipiravira i remdesivira. Primena hlorokina isključena je iz terapijskih protokola Svetske zdravstvene organizacije i američkih Centara za kontrolu i prevenciju bolesti. U preventivne i suportivne svrhe savetuju se visoke doze vitamina D, vitamina C, cinka, probiotika, alfalipoinse kiseline i drugih suplemenata. Primena antinflatornih analgo-antipiretika smatra se opravdanom, kao i primena malih doza acetilsalicilne kiseline. Preko 70 drugih lekova se trenutno ispituje u preko 400 kliničkih studija. Kod pacijenata koji već inhalatorno ili intranazalno koriste kortikosteroide zbog astme, hronične opstruktivne bolesti pluća, alergijskog rinitisa, ili biološke lekove zbog imunomodulisanih inflamatornih bolesti, ovu terapiju ne treba menjati i ona nije preduslov za teže oblike bolesti. Moraju se uzeti u obzir i specifičnosti infekcije kod posebnih populacija kakve su deca ili trudnice.

Ključne reči: Kovid-19, etiopatogeneza, terapija

Uvod

Pandemija izazvana novim korona virusom (SARS-CoV-2) pogodila je preko 35 miliona ljudi širom sveta i odnela preko milion ljudskih života. I dok se svet borio sa epidemiološkim problemima i preventivnim merama, dok su se lekari po bolnicima borili za živote ljudi sa teškim oblikom Kovid-19, grupe i pojedinci u svetu nauke i struke pokušavali su da nađu odgovore na brojna pitanja vezana za etiopatogenezu ove bolesti i za terapijske mogućnosti. Nikada u istoriji nauke nije bilo perioda kada je pojavljivanje novih i preispitivanje starih naučnih činjenica imalo ovakvu dinamiku kao u poslednjih 8 ili 9 meseci. I dalje ne znamo mnogo, nemamo specifični antivirusni lek, kao ni klinički verifikovanu i odobrenu vakcinu.

Cilj ovog preglednog rada je da prikaže dosadašnja znanja vezana za etiopatogenezu i terapiju Kovid-19.

Etiopatogeneza Kovid-19

Čini se da je veliki korak ka boljem lečenju i manjem umiranju učinjen kada smo shvatili da Kovid-19 nije samo respiratorno, već multisistemsko oboljenje. Moglo bi se reći da je to pre svega hematološko i kardiovaskularno oboljenje. Izgleda da promene koje se javljaju na plućima, i koje daju karakterističnu sliku na snimku, nisu posledica prave pneumonije, nego pre mikro plućne tromboze, prevashodno venskih krvnih sudova. Mikrotromboza se izgleda dešava i u drugim delovima tela (1).

CURRENT KNOWLEDGE ABOUT THE ETIOPATHOGENESIS AND THERAPY OPTIONS FOR COVID-19

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SUMMARY

Currently, over 35 million people in the world are infected with the COVID-19 and over a million have died. The pandemic character of the disease has imposed dynamic research both in the field of clarification of the etiopathogenetic mechanisms of the disease and in the field of possible therapy. The amount of scientific knowledge has increased dozens of times in the last nine months, but we are still not even close to define an effective and safe therapy. The knowledge that COVID-19 is not only a respiratory but also a multisystem disease, which affects almost all organs, gave us opportunities for therapeutic adjustments. Strong oxidative stress, silent chronic hypoxia, increased coagulability, and increased platelet aggregation are just some of the mechanisms in the development of the disease. Cardiovascular consequences and vascular endothelial dysfunction are thought to be mainly responsible for death with a dangerous cytokine storm and acute respiratory distress syndrome. Having all this in mind in the therapeutic sense, it is proposed to use antibiotics, high doses of vitamin C, blood transfusion, immunoglobulin, interferon, anti-IL-6 antibodies, small doses of dexamethasone or other corticosteroids, specific antiviral drugs such as favipiravir and remdesivir. The use of chloroquine is excluded from the therapeutic protocols of the World Health Organization and the Centers for Disease Control and Prevention (United States of America). For preventive and supportive purposes, high doses of vitamin D, vitamin C, zinc, probiotics, alpha-lipoic acid, and other supplements are recommended. The use of anti-inflammatory, analgo-antipyretics drugs is considered justified, as well as the use of small doses of acetylsalicylic acid. Over 70 other drugs are currently being tested in over 400 clinical studies. In patients who already use corticosteroids by inhalation or intranasally due to asthma, chronic obstructive pulmonary disease, allergic rhinitis, or biological drugs due to immunomodulatory inflammatory diseases, this therapy should not be changed and it is not a prerequisite condition for more severe forms of the disease. The specifics of the infection in special populations such as children or pregnant women must also be taken into consideration.

Key words: COVID-19, etiopathogenesis, therapy

Introduction

The pandemic caused by the novel corona virus (SARS-CoV-2) has affected over 35 million people around the world and taken more than million lives. While the world struggled with epidemiological problems and preventive measures, and doctors fought against the severe forms of Covid-19 infection in hospitals, some groups and individuals from the scientific and professional world tried to find answers to numerous questions connected with the etiopathogenesis of this disease and possible therapy. There have been no periods in the history of science when the appearance of new

and re-examination of old scientific facts had such dynamics as during the last 8 or 9 months. We still do not know much, we do not have a specific antiviral medicine, or clinically verified and approved vaccine.

The aim of this review article was to present the current knowledge about the etiopathogenesis and therapy of Covid-19.

The etiopathogenesis of Covid-19 infection

It seemed that a big step was made towards better treatment and smaller mortality when we realized that Covid-19 infection is not only a respiratory, but a multisystem disease, as well.

Obdukcionu nalaz nemačkih patologa objavljen u avgustu 2020. godine pokazao je da pacijenti inficirani SARS-CoV-2 virusom umiru uglavnom od koagulopatija, poremećaja funkcije endotela krvnih sudova ili poremećaja funkcije ćelija srčanog mišića. Virus utiče na funkciju endotela, on gubi svoja antiadhezivna, antiagregaciona i antiinflamatorna svojstva, manje se luči azot monoksid (NO) i nastaje *endotelitis* praćen povećanom sintezom protrombotičnih alfa defenzin proteina, što je najčešće glavni uzrok smrtnih ishoda kod Kovid-19 bolesti. Ovo je i razlog promena na bubrezima i drugim vitalnim organima i njihovog akutnog otkazivanja (2).

Sa druge strane, virus se svojim „spike” proteinima vezuje za angiotenzin-konvertujući enzim 2 (ACE2) receptore u epitelu respiratornog trakta, ali i drugim delovima tela, i ulazi u ćelije. Ekspresija ovih receptora je najveća u nosnoj sluzokoži i opada ka donjim partijama respiratornog sistema, te se nos smatra glavnim mestom ulaska virusa u naše telo (3). Osim pluća, virus na ovakav način ulazi i u druge ćelije, ali se naročito važnim smatra način na koji on napada eritrocite. Postavljena je hipoteza da se virus zahvaljujući specifičnim proteinima vezuje za beta lanac hemoglobina i iz njega istiskuje gvožđe (Fe) (4). Posledica toga je visok nivo slobodnog Fe^{2+} u krvi, kada ono ima toksičnu ulogu, i svojim snažnim oksidativnim kapacitetom dovodi do sistemskog oksidativnog stresa i oštećenja skoro svih organa. Sa druge strane, hemoglobin nema vezano gvožđe koje bi prenosilo kiseonik, pa nastaje tiha hronična hipoksija sa posledičnim hipoksičnim oštećenjima čitavog organizma. Druga važna komplikacija Kovid-19 bolesti se objašnjava hiperimunim odgovorom, tzv. citokinska oluja, koju karakteriše povišen nivo i hiperaktivnost primarno interleukina 6 (IL-6), interleukina 1b (IL-1b) i faktor nekroze tumora alfa (TNF-alfa) i citokina (5,6), zbog čega sam imunski odgovor obolele osobe vrši destrukciju plućnog tkiva, a nagomilane i aktivirane ćelije imunskog sistema dodatno oslobađaju inflamatorne medijatore i oštećuju krvne sudove, što se dešava u najtežim kliničkim slučajevima akutnog respiratornog distres sindroma (5,6).

Teorijski gledano, ovakav patogenetski mehanizam zahteva da pacijent dobije trans-

fuziju sveže krvi (nadokanada kiseonika), visoke doze vitamina C intravenski (1,5 do 2 g dnevno) kao antioksidansa, te antikoagulanse (prednost se daje niskomolekularnom heparinu). Visoke doze vitamina D se daju pacijentima starije životne dobi sa utvrđenim deficitom, a cilj je da nivo 25-hidroksi vitamina D bude u okviru referentni vrednosti (40-60 ng/ml) (7).

Imajući u vidu da pacijenti sa hipertenzijom, dijabetesom ili oni koji su gojazni imaju već bazalno nizak nivo NO, smatra se da je to razlog njihove povećane sklonosti ka obolevanju i težim oblicima Kovid-19 bolesti (8). Moguća inhalatorna primena NO ili tadalafil (inhibitora fosfodiesteraze tipa V), u manjim dozama, može predstavljati terapijsku opciju u budućnosti (9).

Kod pacijenta u biohemijskim analizama dominira visoko serumsko gvožđe, feritin, transaminaze, laktat dehidrogenaza, monociti, limfopenija, trombocitopenija i povišen nivo D dimera.

Terapijske mogućnosti u lečenju Kovid-19

Kako se donekle rasvetljavala etiopatogeneza, tako se i nametala moguća terapija. U početku nije bilo nikakve terapije koja bi se mogla smatrati specifičnom. Bilo je pokušaja sa preparatima interferona alfa u obliku nebulizatora ili spreja kod dece sa relativno slabim terapijskim uspehom. Prva antivirusna terapija koja se koristila bio je anti-influenca lek oseltamivir, koji skoro da nije dao nikakve rezultate, kao ni antivirusni lek za HIV ribavirin. Neki početni uspesi su se javili posle primene fiksne anti-HIV kombinacije lopinavir/ritonavir. Ubrzo se posle početka primene pojavila studija koja je pokazala da ovaj lek nema željeni terapijski uspeh te je napušten, osim kod trudnica gde se drugi antivirusni lekovi ne mogu davati (10).

Hlorokin u lečenju Kovid-19

Prvi lek koji nam je dao nadu u stvari je stari antimalarik hlorokin i njegov sintetski derivat hidroksihlorokin. Ovi lekovi su dugo u upotrebi, ali kao antiinflamatorni lekovi kod pacijenata sa sistemskim lupusom ili reumatoidnim artritismom, kao i u terapiji malarije. Od prvih terapijskih protokola u Vuhanu, do nesmotrene izjave američkog predsednika Trampa da se radi o, takoreći, čudotvornom leku, preko studije

It could be said that it is, first of all, hematologic and cardiovascular disease. It seems that the changes that appear on the lungs and which give a characteristic picture on an X-ray are not just a consequence of real pneumonia, but more of micro pulmonary thrombosis, primarily of venous blood vessels. Micro thrombosis appears in other parts of the body, as well (1).

The autopsy finding of German pathologists, which was published in August 2020, showed that patients infected with SARS-CoV-2 virus died mainly of coagulopathy, endothelial dysfunctions of blood vessels or heart muscle cell dysfunction. The virus affects endothelial function, and it loses its anti-adhesive, anti-aggregation and anti-inflammatory characteristics, the secretion of Nitric Oxide is smaller and endotheliitis appears followed by the increased synthesis of prothrombin alpha defensin proteins, which is most frequently the main cause of deadly disorders in Covid-19 infection. This is the reason of changes that appear on kidneys and other vital organs and their acute failure (2).

On the other hand, the virus with its "spike" proteins creates a bond with angiotensin, converting the enzyme 2 (ACE2) receptors in the epithelium of respiratory tract, as well as in other body parts, and it enters the cells. The expression of these receptors is highest in the nasal mucosa and it decreases towards the lower parts of respiratory tract, and therefore, nose is deemed to be the main place of the entry of this virus into our body (3). In addition to lungs, the virus enters in this way into other cells, but what is of great importance is the way in which it attacks erythrocytes. It has been hypothesized that the virus binds to the beta chain of hemoglobin thanks to specific proteins and displaces iron from it (4). The consequence of that is the high level of "free" iron, when it becomes toxic, and with its oxidative capacity it leads to the systemic oxidative stress and damage of almost all organs. On the other hand, hemoglobin does not have bound Fe which would transfer oxygen, and therefore quiet chronic hypoxia appears with the consequent hypoxic damages of the whole organism. The other important complication of Covid-19 is explained by the hyper-immune response, the so-called cytokine storm, which is characterized

by the increased level and hyperactivity primarily of interleukin 6 (II-6), interleukin 1b (IL-1b) and tumor-necrotizing factor alpha (TNF-a) and cytokine (5,6), due to which the immune response of the patient destroys the lung tissue, and accumulated and activated cells of the immune system additionally liberate inflammatory mediators and damage blood vessels, which happens in the most difficult clinical cases of acute respiratory distress syndrome (5,6).

Theoretically speaking, such pathogenetic mechanism demands that the patient gets transfusion of fresh blood (compensation of oxygen), high doses of vitamin C intravenously (1.5 to 2 g daily) as the antioxidant, and then anticoagulants (low molecular weight heparin is preferred). High doses of vitamin D are given to elderly patients with established deficiency and the goal is to keep the level of 25-hydroxy vitamin D within the reference values (40-60 ng/ml) (7). Having in mind that patients with hypertension, diabetes and obese patients have a low level of basal NO, it is considered to be the reason of their increased tendency to get the disease and more severe forms of Covid-19 (8). A possible application of NO and tadalafil in inhalation (inhibitors of phosphodiesterase type V) in smaller doses, can present a therapy option in the future (9).

In patients, high serum iron, ferritin, transaminase, lactate dehydrogenase, monocytes, lymphopenia, thrombocytopenia and increased level of D dimer are dominant in biochemical analyses.

Therapy options for Covid-19

As the etiopathogenesis was slowly cleared up, the possible therapy was accepted. At the beginning there was no specific therapy. There were attempts to use the preparation of interferon in the form of nebulizers or spray in children with relatively weak therapeutic success. The first antiviral therapy was the anti-influenza medicine oseltamivir, which did not give any results, as well as the antiviral medicine for AIDS ribavirin. Some success was achieved after the administration of fixed anti AIDS combination of lopinavir/ritonavir. Soon after the beginning of administration, a study appeared which showed that this medicine

marsejskih virusologa sa skoro 100% uspehom u kombinaciji sa azitromicinom, do otrežnjenja vezanog za njegova neželjena dejstva i predloga francuskog ministra zdravlja da se ovaj lek više ne daje. Ono što nam nedostaje su dobro planirane randomizovane kliničke studije koje bi pokazale njegovu delotvornost i sigurnost. Ovaj stari lek ima mnogobrojne mehanizme dejstva, on sprečava da virus istisne gvožđe iz hemoglobina, sprečava ulazak virusa u ćelije domaćina, njihovu replikaciju i izlazak iz ćelija, smanjuje sintezu proinflamatornih citokina važnih u citokinskoj oluji, pre svih IL-6 i TNF-alfa i deluje proimunski (11,12). Po ranijim verzijama nacionalnog protokola bilo je predloženo da se hidroksihlorokin daje na sledeći način: tbl. 2×400 mg p.o. prvi dan (2×600 mg ukoliko pacijent ima nazogastričnu sondu), zatim 400 mg p.o. još 7 dana, u zavisnosti od kliničke slike. Pedijatrijske doze su: početna doza 2×6.5 mg/kg (maksimalno 400 mg) prvi dan, zatim 2×3.5 mg/kg na dan (maksimalno 200 mg) 4 dana. Osim toga, postoji velika mogućnost da ovaj lek izazove srčane aritmije, naročito kod predisponiranih pacijenata sa komorbiditetima, pa je od početne euforije došlo do velikog otrežnjenja da se lek mora davati samo uz velike mere predostrožnosti i posebnu pažnju (13). Na osnovu mnogobrojnih studija koje su pokazale neefikasnost hlorokina (14), Svetska zdravstvena organizacija (SZO) je predložila da se dalje ne daju dozvole za kliničke studije sa njim, Agencija za hranu i lekove (FDA) je to podržala, a mnoge zemlje su ga izbacile iz svojih protokola uključujući i Srbiju. Sa druge strane, grupe istraživača i dalje veruju i pokušavaju da daju dokaze da hidroksihlorokin sam, ili u kombinaciji sa azitromicinom, naročito ako se pravovremeno primeni, i dalje predstavlja jedan od ključnih lekova u terapiji Kovid-19. Da li je hidroksihlorokin zaista bezvredan, ili je žrtva igara i intriga velikih igrača na farmaceutskom svetskom tržištu, vreme će pokazati (15-17).

Antivirusni lekovi u lečenju Kovid-19

Osim neuspelih antivirusnih lekova, bilo je pokušaja sa kamostat mesilatom i umifenovirom, ruskim antivirusnim lekom, koji su u početku dosta obećavali. Rezultat je i ovde bio polovičan. Ovi lekovi deluju tako što se zakače za „spike“ proteine virusa i spreče njihov kontakt sa ACE2

receptorima i ulaz u ćeliju (9). Danas se intezivno klinički ispituju 2 antivirusna leka, koja su već i registrovana u nekim zemljama. Oba su bila inovirana u prethodnim SARS, MERS i ebola infekcijama, ali njihova klinička istraživanja nisu bila privedena kraju. Favipiravir je u mnogim zemljama u III fazi kliničkih ispitivanja, a FDA je već dala zeleno svetlo za ubrzanu registraciju remdesivira, za kojeg se očekuje da će biti specifični antivirusni lek kod odraslih. Favipiravir je registrovan u Rusiji, Kini i Indiji, ali se koristi i ima ga u skoro svim nacionalnim protokolima. Može se davati oralno, od rane faze i već kod blagih oblika bolesti (tablete 1.600 mg na 12 h, prvi dan, od 2 - 5. dana (tj. još 4 dana) 600 mg na 12 h, ukupno 5 dana) (18).

Drugi antivirusni lek, remdesivir, je odobren u Sjedinjenim Američkim Državama (SAD), za lečenje teških oblika bolesti, kod kojih je potreban kiseonik, kod odraslih i dece starije od 12 godina. Vlada SAD i predsednik Tramp, su međutim otkupili godišnju proizvodnju ovog leka od proizvođača i time je ostatak sveta ostao uskraćen. Kliničke studije su pokazale efikasnost, manju učestalost teških kliničkih slučajeva, brže ozdravljenje i ublažavanje simptoma (200 mg prvi dan i.v., pa 100 mg i.v. sledećih 9 dana, po nalogu infektologa) (19).

Antiinflamatorni lekovi u lečenju Kovid-19

Od primene interferona (alfa-2b i beta-1b) bilo je pokušaja da se ova bolest leči imunološkim preparatima. Najviše dobrih rezultata je bilo sa tocilizumabom (8 mg/kg i.v. u dve doze, a maksimalno 800 mg po dozi), monoklonskim antitelima protiv IL-6 receptora, kao i sarilumabom ili siltuksimabom koji se koriste u reumatološkim inflamatornim oboljenjima. Završene su studije koje dovode u sumnju efikasnost tocilizumaba. Ovi lekovi ostaju terapijska opcija, naročito u teškim oblicima bolesti (20). Intravenski imunoglobulini u dozi 10 do 20 mg/kg u toku 3 do 5 dana su takođe terapijska opcija (21).

Plazma pacijenata koji su preležali bolest je terapija koja dosta obećava, pitanje je, međutim, u kojoj meri je ona bogata specifičnim antitelima koja mogu pomoći obolelima od Kovid-19. Nedavno je u SAD data dozvola da se plazma rekonvalescenata uvrsti u regularnu terapiju pacijenata sa Kovid-19 (22). Na osnovu

did not have a desired therapeutic success and therefore, it was left, except in pregnant patients, who could not be given other antiviral medicines (10).

Chloroquine in the treatment of Covid-19

The first medicine, which gave us hope, was actually an old antimalarial chloroquine and its synthetic derivative hydroxychloroquine. These medicines have been used for a long time, but as anti-inflammatory medications in patients with systemic lupus or rheumatoid arthritis as well as in malaria therapy. Since the first therapeutic protocols in Wuhan, to the incautious statement of the American president Trump that it was a miraculous drug, and the study of virologists from Marseille that it was 100% successful in combination with azithromycin, as well as to the sobering effect connected with its side effects and the proposal of the French Minister of Health not to give this medicine anymore. Well-planned randomized clinical studies, which would show its effectiveness and security, are still missing. This old medicine has numerous mechanisms of action; it prevents the virus from displacing iron from the hemoglobin, it prevents the entry of the virus into the cells of the host, its replication and exit from the cells, it diminishes the synthesis of pro-inflammatory cytokines, which are important in the cytokine storm, first of all, all interleukins IL-6 and TNF-alpha and it has a pro-immune effect (11,12). According to earlier versions of the national protocol, it was suggested that hydroxychloroquine should be given in the following way: pills 2 x 400 mg p.o. during the first day (2 x 600 mg if the patient has a nasogastric tube), then 400 mg p.o. seven days more, depending on the clinical picture. Pediatric doses are: the starting dose 2 x 6.5 mg/kg (max 400 mg) on the first day, then 2 x 3.5 mg/kg daily (max 200 mg) for four days. In addition to that, there is a great possibility that this medicine causes cardiac arrhythmia, especially in predisposed patients with comorbidities, and therefore, the starting euphoria turned into great sobriety which meant that this medicine could be given only with great measures of precaution and with special attention (13). According to numerous studies, which showed the inefficiency of chloroquine

(14), the World Health Organization suggested that clinical studies with this medicine should not be approved, and the Food and Drug Administration supported this, while a lot of countries have removed it from their protocols, including Serbia, as well. On the other hand, some groups of researchers still believe and try to find proofs that hydroxychloroquine alone or in combination with azithromycin, especially if it is administered on time, still presents one of the key drugs for the treatment of Covid-19 infection. The time will show whether hydroxychloroquine is really worthless or it is the victim of intrigues and games of big players in the pharmaceutical world market (15, 16,17).

Antiviral drugs in the treatment of Covid-19 infection

In addition to the unsuccessful antiviral drugs, there were attempts to use camostat mesylate and umifenovir, a Russian antiviral drug, and they were promising in the beginning. The result was partial in this case, as well. These drugs bind to the "spike" proteins of the virus and thus prevent their contact with ACE2 receptors and the entry into the cell (9). Today, two antiviral drugs are being examined intensively, and they have already been registered in some countries. Both drugs were innovated in the previous SARS, MERS and Ebola infections, but their clinical research was not brought to an end. Favipriavir is in many countries in phase III of clinical research, while the FDA has already given a green light for the faster registration of remdesivir, which is expected to be a specific antiviral drug for adults. Favipiravir has been registered in Russia, China and India, but it is used and it is present in almost all national protocols. It can be administered orally, from the early phase and in mild forms of disease (tablets 1600 mg per 12 hours, during the first day, and from the 2nd to the 5th day (that is, four days more) 600 mg per 12 hours, in total for five days) (18).

The other antiviral drug, remdesivir got a green light in the United States of America for the treatment of severe forms of disease in adults and children older than 12. The Government of the United States of America and the president Trump purchased the production

verzije 9 našeg terapijskog protokola, plazma rekonvalescenata se može uvesti u terapiju unutar 2 nedelje od početka tegoba i nakon konsultacije sa infektologom i transfuziologom.

Antiinflamatorna terapija je nedvosmisleno potrebna. U početku pandemije WHO i druge organizacije imale su stav da je lek izbora paracetamol (do 1.500 mg na dan) jer nesteroidni antiinflamatorni lekovi (NSAIL) navodno potenciraju teže oblike bolesti. Ubrzo su naučne studije i stavovi mnogih državnih i stručnih organizacija razbile ovaj mit, pa se danas NSAIL upotrebljavaju paralelno sa paracetamolom (ibuprofen do 1.200 mg na dan). Neki eksperti skloni su preporuci za upotrebu malih doza acetilsalicilne kiseline zbog antiagregacionog dejstva (23). Ne zna se da li ovo može prevenirati mikrotromboze.

Primena sistemskih kortikosteroida se inače smatra racionalnom samo kod najtežih slučajeva i samo pod određenim uslovima. Oni se inače smatraju imunosupresorima i agensima koji povećavaju replikaciju virusa. Neki autori su skloni da preporuče metilprednizolon (1-2 mg/kg, 3 do 5 dana uz nadzor intenziviste), neki prednizon (0,5 mg/kg u 2 dnevne doze, pri čemu večernja doza iznosi maksimalno 10 mg, trajanje terapije je 4 nedelje, a doze prednizona se smanjuju po šemi), a neki hidrokortizon. Kliničke studije sa malim dozama deksametazona (6 mg/dan, deset dana) kod pacijenata na mehaničkoj ventilaciji ili kiseoničnoj potpori su pokazale dobre rezultate, smanjenje letaliteta i poboljšanje kliničke slike, te se tako deksametazon nameće kao vodeći kortikosteroid u terapiji Kovid-19 oboljenja (24). Prema našem protokolu (verzija 9) predlaže se primena metilprednizolona 1-2 mg/kg, 3-5 dana (uz procenu rizika i saglasnost intenziviste/infektologa/pulmologa).

Ukoliko su pacijenti sa imunološki posredovanim inflamatornim bolestima na kortikosteroidima i obole od Kovid-19 preporučuje se njihovo ukidanje, ako je moguće održati remisiju bez njih, ili prebacivanje na budesonid za koji se smatra da ima najmanji imunosupresivni potencijal. Biološku terapiju kod ovih pacijenata ne treba prekidati, jer ona ne potencira sklonost ka težim oblicima bolesti. Naprotiv, inhibitori TNF-alfa čak mogu poboljšati simptome bolesti, jer se smatra da je on pokretač citokinskog

odgovora, te se neki od njih i ispituju kao mogući antikovid agensi (25).

Mnogobrojne organizacije koje se bave alergijskim bolestima, astmom ili hroničnom opstruktivnom bolešću pluća (EUFOREA, ARIA, GINA, GOLD, EACI i dr.) su zauzele stav da intranazalne i inhalatorne kortikosteroide ne treba prekidati ukoliko ovi pacijenti dobiju Kovid-19. Naprotiv, postoji stav da lokalni kortikosteroidi smanjuju ekspresiju ACE2 receptora i replikaciju virusa, a da je njihova sistemska resorpcija mala, te mogu da imaju i olakšavajuću funkciju ili čak i preventivnu (26).

Američki lekar Ričard Bartled je čak predložio terapijski koktel: inhalatorni budesonid, cink, klaritromicin i acetilsalicilna kiselina, kao bazični set lekova za lečenje Kovid-19 oboljenja već u ranoj fazi bolesti. Moguća primena inhalatornog budesonida u prevenciji prelaska u teže oblike bolesti i u bržem ozdravljenju delimično je potvrđena i rezultatima STOIC studije. Uprkos tome neke druge grupe istraživača osporavaju ovakav koncept (27).

Postoji još jedna procedura, koja predstavlja hemodijalizu kojom se iz tela odstranjuju citokini u toku citokinske oluje. Metoda se zove Citosorb, ali je, nažalost, skupa i nije pogodna za masovnu upotrebu (28).

Antibiotska terapija

Primena antibiotika smatra se neophodnom kod ARDS-a ili prema antibiogramu ili kod lečenja već nastale sekundarne bakterijske infekcije.

Moguće perspektive u lečenju Kovid-19

Nikada u svetu farmakoloških istraživanja nije bilo ovakve dinamike u naučnim i stručnim pokušajima i ovoliko mnogo istraživanja. Informacija stiže informaciju i trenutno se u svetu istražuje najmanje 70 starih ili novih lekova sa mogućnošću primene kod Kovid-19 infekcije. Najmanje je 400 kliničkih studija u toku. I dalje smo terapijski u potpunom mraku, sa malim, ali nedovoljnim pomacima, međutim, očekujemo da se ubrzo pojave vakcine i da imamo specifičnu antivirusnu terapiju.

Prevenција Kovid-19

Suplementacija i moguća preventiva kod ove bolesti su predmet stalnog interesovanja.

of this drug from the manufacturer for year and thus deprived the rest of the world of it. Clinical studies showed efficacy, lower incidence of severe clinical cases, faster recovery and relief of symptoms (200 mg during the first day iv, and then 100 mg iv during the following 9 days, by the order of infectologist) (19).

Anti-inflammatory drugs in the treatment of Covid-19

Since the administration of interferon (alfa-2b and beta-1b), there have been attempts to treat this disease with immunological preparations. Good results were achieved mostly by tocilizumab (8 mg/kg i.v. in two doses, and maximally 800 mg per dose), monoclonal antibodies against IL-6 receptors, as well as by sarilumab or siltuximab, which are used for rheumatologic inflammatory diseases. These drugs have remained the therapeutic option, especially in severe forms of disease (20). Intravenous immunoglobulins in doses 10 to 20 mg/kg during 3 to 5 days are also a therapeutic option (21).

The plasma of patients, who have overcome this disease, is still promising. The question remains to what extent it is abundant in specific antibodies, which could help in curing people with Covid-19. An approval has recently been made in the United States of America to include the plasma of convalescents in the regular therapy of patients with Covid-19 (22).

The anti-inflammatory therapy is unambiguously necessary. At the beginning of pandemic, the position of the WHO and other organizations was that paracetamol was the drug of choice (to 1.500 mg a day) because the non-steroidal anti-inflammatory drugs (NSAIL) allegedly induce more severe forms of disease. Soon the scientific studies and positions of many state and professional organizations dispersed this myth, and today NSAIL are used in parallel with paracetamol (ibuprofen to 1.200 mg daily). Some experts tend to accept the recommendation to use small doses of acetylsalicylic acid due to the anti-aggregation effect (23). It is not known whether this can prevent micro-thrombosis.

The administration of systemic corticosteroids is deemed to be rational only in most severe cases and under certain circumstances. They are deemed to be immunosuppressive

drugs and agents that increase the virus replication. Some authors tend to recommend methylprednisolone (1-2 mg/kg, 3 to 5 days under the supervision of intensivist), some recommend prednisone (0.5 mg/kg I 2 daily doses, while the evening dose amounts to max. 10 mg, and duration of therapy is 4 weeks, and doses of prednisone are reduced according to the plan), while some recommend hydrocortisone. Clinical studies with small doses of dexamethasone (6 mg/a day, 10 days) in patients on mechanical ventilation or oxygen support have showed good results, reduced mortality and improved the clinical picture, and therefore, dexamethasone is imposed as a leading corticosteroid in the treatment of Covid-19 infection (24).

If patients with immunologically mediated inflammatory diseases on corticosteroids get infected with Covid-19, their usage is recommended to be cancelled if remission is possible to be maintained without them, as well as transition to budesonide which has the least immunosuppressive potential. Biological therapy in these patients should not be stopped, because it does not induce the inclination to more severe forms of disease. On the contrary, inhibitors TNF-alpha can even improve the symptoms of disease, because it is deemed to be the initiator of cytokine response, and therefore, some of them are examined as possible anti-Covid agents (25).

Numerous organizations, which deal with allergic diseases, asthma or chronic obstructive lung disease (EUFOREA, ARIA, GINA, GOLD, EACI etc.), have taken the position that patients who get Covid-19 should not stop to use intranasal and inhaled corticosteroids. On the contrary, there is opinion that local corticosteroids reduce the expression of ACE2 receptors and the virus replication, and that their systemic reabsorption is small, and therefore, they can have a relieving function or even a preventive one (26).

An American doctor, Richard Bartlett even suggested a therapy cocktail: inhaled budesonide, zinc, clarithromycin and acetylsalicylic acid, as a basic set of drugs for treating Covid-19 infection in the early phase of disease. The possible administration of inhaled budesonide in the prevention of transition to more severe forms of disease and in faster recovery has partially been

Nesporna je preventivna uloga visokih doza vitamina D (10.000 IJ na dan u toku nekoliko nedelja, posle čega se može preći na 5.000 IJ na dan) (29). Vitamin D ima svoje receptore i na ćelijama urođenog i na ćelijama stečenog imuniteta, pospešuje stvaranje antimikrobnih protina, ublažava citokinsku oluju i sintezu proinflammatoryh citokina, ublažava sva stanja koja kao komorbiditeti pogoršavaju Kovid-19 i ima mnogobrojne druge terapijske efekte.

Zbog smanjenja proinflammatoryh uticaja i subepitelne lokalne metaboličke inflamacije u crevima koja je preduslov za sistemsku inflamaciju, probiotici se smatraju racionalnom preventivom i terapijom (30).

Cink (najmanje 15 mg dnevno) očigledno sprečava replikaciju virusa, polinezasićene masne kiseline smanjuju sintezu proinflammatoryh supstanci, vitamin C (500 mg) deluje antioksidanto i imunomodulatorno, alfaliponska kiselina (300 do 600 mg) deluje neuroprotektivno i popravlja i prevenira anosmiju.

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confirmed by the results of STOIC study. In spite of that, some other groups of researchers have denied such a concept (27).

There is one more procedure that presents hemodialysis, with the help of which cytokines are removed from the body during the cytokine storm. The method is called Citosorb, but unfortunately, it is expensive and it is not suitable for mass usage (28).

Antibiotic therapy

The use of antibiotics is considered necessary in ARDS or according to the antibiogram or in the treatment of already developed secondary bacterial infection.

Possible perspectives in the treatment of Covid-19

There has never been such dynamism in the scientific and professional attempts and so much research in the pharmacological world. The information comes one after another and currently at least 70 old or new drugs are being examined around the world with the possibility of administration in Covid-19 infection. At least 400 clinical studies are in progress now. In the sense of therapy, we are still in the complete dark, with little, but insufficient advances, expecting the appearance of vaccine and specific antiviral therapy.

The Prevention of Covid-19

Supplementation and possible prevention of this disease is the subject of constant interest. The preventive role of high doses of vitamin D is indisputable (10.000 IU a day during a few weeks, and after that 5.000 IU can be administered daily). Vitamin D has its receptors on the cells of inborn immunity and acquired immunity as well. It induces the creation of antimicrobial proteins, alleviates the cytokine storm and the synthesis of pro-inflammatory cytokines, it alleviates the conditions, which as comorbidities worsen Covid-19 and it has numerous other therapeutic effects (29).

Due to the reduction of pro-inflammatory influence and subepithelial local metabolic inflammation in the bowels, which is a precondition of systemic inflammation, probiotics are deemed to be rational prevention and therapy, as well (30).

Zinc (at least 15 mg a day) evidently prevents the virus replication, polyunsaturated fatty acids reduce the synthesis of pro-inflammatory substances, vitamin C (500 mg) has the antioxidant and immunomodulatory effect, alpha lipoic acid (300 to 600 mg a day) has a neuroprotective effect, improves and prevents anosmia etc.

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