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NUTRITIVNA TERAPIJA COVID-19 OBOLJENJA U JEDINICAMA INTENZIVNOG LEČENJA

Sažetak: Od početka 2020. godine u žiži interesovanja naučnih krugova, a i šire, našao se *SARS – CoV 2 (Severe Acute Respiratory Syndrome – Corona Virus 2)*, posebno se prepoznao značaj pronalaska najefektnijeg terapijskog modaliteta u prevenciji i lečenju do tada nepoznatog oboljenja *COVID – 19 (Corona Virus Disease – 2019)*. SARS-CoV 2 različitim mehanizmima vodi bolesnika u malnutriciju, koja je detekтовna većom učestalošću na prijemu za bolničko lečenje, pogotovo na prijemu u Jedinicu intenzivnog lečenja (JIL). Malnutricija ima negativan uticaj na tok i ishod oboljenja. Sa pandemijom porastao je i broj bolesnika lečenih u JIL, zatim na različitim vidovima oksigenoterapije i mehaničke ventilacije, s tim u vezi pojavila se i veća potreba za znanjem i edukacijom osoblja za korišćenje različitih terapijsko-dijagnostičkih modaliteta, te i različitih pristupa ishrane kritično oboljelih bolesnika. Nutritivna terapija

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predstavlja osnovu za očuvanje telesne mase, područsku respiratorne funkcije, kao i pomoć pri sveobuhvatnom oporavku bolesnika. Potencijalno blagotvorno dejstvo protiv COVID-19 oboljenja pokazale su omega 3 masne kiseline, vitamin C i D.

Cilj ovog rada je da objedini dosadašnja saznanja i preporuke iz oblasti nutritivne terapije kod bolesnika sa *COVID – 19* lečenih u Jedinici intenzivnog lečenja.

Ključne reči: *COVID-19*; Jedinica intenzivnog lečenja; Malnutricija; Nutritivna terapija

Abstract: Since the beginning of 2020, SARS-CoV 2 (Severe Acute Respiratory Syndrome - Corona Virus 2) has been in the focus of scientific circles and beyond. Finding the most efficient therapeutic protocol in prevention and treatment of the new and unknown COVID – 19 (Corona Virus Disease - 2019) disease has been identified as especially important. SARS-CoV 2 uses various mechanisms to lead patients to malnutrition, which is detected by a higher frequency of admission to hospital treatment, especially on admission to the Intensive Care Unit (ICU). Malnutrition has a negative impact on the course and outcome of the disease. In the pandemic, the number of patients on various types of oxygen therapy and mechanical ventilation increased, and in correlation with that, there has been a greater need for knowledge and education of staff to use different diagnostic and therapeutic modalities and different approaches in feeding critically ill patients. Nutritional therapy is the basis for maintaining body weight, supporting respiratory function, as well as helping in the overall recovery of patients. Omega 3 fatty acids, vitamins C and D have shown potentially beneficial effects against COVID-19 diseases.

The aim of this paper is to consolidate the current knowledge and recommendations in the field of nutritional therapy in patients with COVID - 19 treated in the Intensive Care Unit.

Key words: *COVID-19*; Intensive care unit; Malnutrition; Nutritional therapy

Uvod

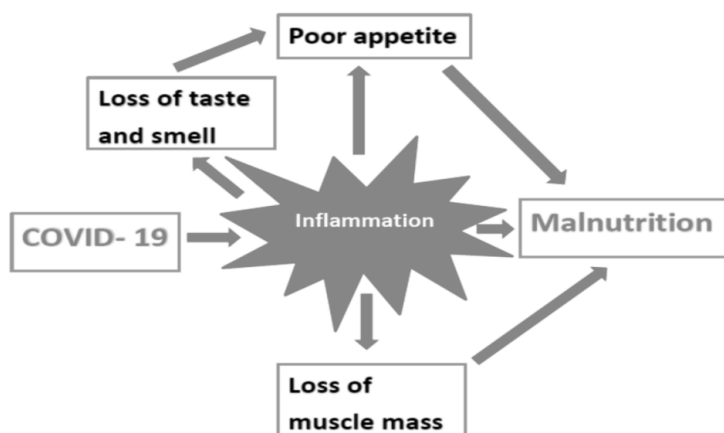
Od početka 2020. godine u žiži interesovanja naučnih krugova, a i šire, našao se *SARS – CoV 2 (Severe Acute Respiratory Syndrome – Corona Virus 2)*, posebno se prepoznao značaj pronalaska najefektnijeg terapijskog modaliteta u prevenciji i lečenju do tada nepoznatog oboljenja *COVID – 19 (Corona Virus Disease – 2019)*. Osnovni principi lečenja ogledaju se u primeni antivirusnih lekova, biološke terapi-

je, kortikosteroidne terapije, antikoagulantne terapije, neutrališućih monoklonskih antitela, plazme rekoalescenata, zatim oksigenoterapije i drugih metoda održavanja dobre oksigenacije krvi (neinvazivna i invazivna mehanička ventilacija), kao i simptomatske i vitaminske terapije [1]. Pored nabrojanih terapijskih modaliteta, potrebno je svakodnevno vršiti adekvatnu nutritivnu potporu bolesnika, fizikalni tretman, psihološku podršku, itd.

Cilj ovog rada je da objedini dosadašnja saznanja i preporuke iz oblasti nutritivne terapije kod bolesnika sa *COVID – 19* lečenih u Jedinici intenzivnog lečenja (JIL).

COVID-19 i malnutricija

Infekcije gornjih respiratornih puteva povezane su sa gubitkom čula mirisa prevažno usled mehaničke opstrukcije, inflamacije i neurodegeneracije olfaktornih ćelija. *SARS – CoV2* infekcija dovodi do izmenjenog, delimičnog ili potpunog gubitka čula mirisa i ukusa što utiče na apetit bolesnika, smanjujući ga. Smatra se da gubitak mirisa kod *COVID-19* oboljenja se razlikuje od drugih infekcija gornjeg respiratornog trakta, iz razloga što prevažno nije praćeno izraženom inflamacijom i nazalnom opstrukcijom. Pretpostavlja se da se u osnovi toga nalazi ekspresija *ACE2* i *TMPRSS2* receptora na neuroepitelijalnim olfaktornim ćelijama, što omogućava ulazak, akumulaciju i repikaciju virusa [2]. Sistemska inflamacija različitim mehanizmima dovodi do lošijeg apetita što zajedno sa gubitkom čula mirisa i ukusa dovodi do smanjenog unosa hrane. Dodatno, akutno infektivno oboljenje dovodi do inflamatornog sindroma i hipermetabolizma i gubitka mišićne mase. Dakle, možemo zaključiti da *SARS – CoV2* dovodi do jednog začarnog kruga koji različitim putevima vodi ka malnutriciji [3].



Slika 1. Malnutricija i COVID-19 [3].

Istraživanje sprovedeno u Italiji koje je obuhvatilo 213 hospitalizovanih bolesnika sa *COVID-19* oboljenjem, pokazalo je da je 54,7% bolesnika u riziku od malnutricije, dok je 6,6% sa malnutricijom prema *Mini Nutritional Assessment* skoru [4]. Allard i saradnici su u svojoj studiji koja je uključivala 108 bolesnika, dokazali da je njih 42 (38.9%) bilo sa dijagnostikovanom malnutricijom na prijemu u bolnicu za lečenje *COVID-19* oboljenja [5]. Zatim, istraživanje Bedock i saradnika koje je uključilo 112 bolesnika sa infekcijom *SARS-CoV2* virusom, pokazalo je da je po *GLIM* (Global Leadership Initiative on Malnutrition) kriterijumima 42% bolesnika bilo u malnutriciji, i to 24% sa umerenom i 18% sa teškom. Takođe, dokazali su da je prevalencija malnutricije signifikantno veća kod bolesnika lečenih u JIL [6]. Wierdsma i saradnici u svom istraživanju su dokazali da svaki peti bolesnik na prijemu za hospitalno lečenje *COVID-19* ima ozbiljni akutni gubitak telesne mase (>5 kg), gde 85% sa detektovanim akutnim gubitkom telesne mase biva primljeno u JIL, a da 73% bolesnika ima veći rizik od sarkopenije [7].

Prethodnih meseci brojna istraživanja su dovela do sledećih zaključaka: utvrđena je visoka incidenca malnutricije kod bolesnika sa *COVID-19* na prijemu za bolničko lečenje, zatim dokazan je negativan uticaj malnutricije na prognozu *COVID-19*, kao i negativan uticaj *COVID-19* na telesnu masu i kod hospitalizovanih i nehospitalizovanih bolesnika [8].

Trebalo bi napomenuti da i gojaznost predstavlja jednu od formi malnutricije. Masno tkivo predstavlja veliki izvor makrofaga koji luče inflamatorne medijatore. Leptin, hormon koji povećava apetiti i ubrzava metabolizam, se povećano oslobađa iz masnog tkiva, stukturmo je sličan IL-6 i IL-12. Takođe, kod gojaznih osoba povećana je produkcija Th1 ćelija i B limfocita. Sve ovo dovodi do stanja konstantne inflamacije niskog stepena, što može biti nepogodno kod infekcija i precipitirati nesvrshodan imunski odgovor, odnosno hiperprodukciju IL-6, te citokinsku oluju, oštećenje plućnog tkiva, itd. Smatra se da, upravo usled postojanja niskog stepena konstantne inflamacije, gojaznost predstavlja faktor rizika za težu formu bolesti i smrtni ishod bolesnika sa *COVID-19* bolešću [9].

Nutritivna terapija bolesnika sa COVID-19

Po prijemu bolesnika na hospitalno lečenje pogotovo kod starijih bolesnika, onih sa komorbiditetima i gojaznih osoba, potrebno je izvršiti skrining i eventualnu dijagnozu malnutricije. Dijagnoza malnutricije prema kriterijumima *Global Leadership Initiative on Malnutrition* postavlja se kroz dva koraka. U prvom koraku potrebno je izvršiti skrining na malnutriciju kroz *MUST* (*Malnutrition Universal Screening Tool*) ili *NRS-2002* (*Nutrition Risk Screening*) kriterijume, a u drugom koraku se potvrđuje malnutricija postojanjem minimum jednog fenotipskog i minimum jednog etiološkog kriterijuma [10].

Tabela 1. Fenotipski i etiološki kriterijumi za dijagnozu malnutricije prema *Global Leadership Initiative on Malnutrition*

Fenotipski kriterijumi	Etiološki kriterijumi
Gubitak telesne mase (%) >5% unutar 6 meseci > 10% preko 6 meseci	Smanjen unos grane 50% od energetske potrebe > 1 nedelja, ili bilo kakvo smanjenje > 2 nedelje, ili bilo koji hronični gastrointestinalni poremećaj koji nepovoljno utiče na iskorišćavanje hrane ili apsorpciju
Nizak ITM (kg/m²) <20 (< 70 god) < 22 (>70 god)	Inflamacija Aktuno oboljenje/ povreda / hronična oboljenja
Smanjene mišićne mase Smanjene verifikovano validiranim tehnikama merenja sastava tela	

ITM- indeks telesne mase

Kao što je prethodno navedeno, velika je učestalost malnutricije kod bolesnika sa *COVID-19* i pretpostavlja se da sama malnutricija negativno utiče na tok i ishod oboljenja, te je potrebno, kako bi samanjili komplikacije oboljenja i pretendirali ka dobrom ishodu lečenja, uvesti adekvatnu ishranu bolesnicima.

Svako uvođenje ishrane polazi od određivanja energetske potrebe individue. Najbolji, ali ujedno i najkompleksniji metod određivanja potreba za energijom jeste indirektna kalorimetrija, koja predstavlja metod izračunavanja potrebe osobe za energijom indirektno računajući potrošnju energije u miru. Tačnije, stepen potrošnje energije izračunava se putem merenja potrošnje O₂ i količine CO₂ u izdahnutom vazduhu [11]. Danas se sve više teži ka indirektnoj kalorimetriji s obzirom da drugi vidovi izračunavanja energetske potreba mogu dovesti do prekomernog ili premalog unosa nutrijenata u odnosu na potrebe. Preveliki unos kod kritično obolelih povezan je sa hiperglikemijama, steatozom jetre, kao i povećanim mortalitetom, dok je nedovoljan unos nutrijenata povezan sa povećanim mortalitetom, dužim vremenom hospitalizacije i periodom na mehaničkoj ventilaciji, većim rizikom od infekcija, zatim organskim zatajivanjem idr. Međutim kako indirektna kalorimetrija predstavlja izuzetno skupu i često ne pristupačnu tehniku, energetske potrebe mogu biti izračunate i putem merenja količine izdahnutog CO₂ (*EEVCO₂ - energy expenditure based on CO₂ measurements*). Nakon očitavanja vrednosti količina CO₂ (VCO₂), energetske potrebe organizma se izračunavaju sledećom formulom $EEVCO_2 \text{ (kcal/dan)} = VCO_2 \text{ (ml/min)} \times 8,19$. Ova metoda jeste inferiornija od indirektna kalorimetrije, ali je superiornija u odnosu na izračunavanje preko formula koje koriste telesnu masu [12].

Alternativni češće korišćen metod izračunavanja energetske potrebe jeste izračunavanje preko telesne mase. Evropsko udruženje za kliničku ishranu i metabolizam dalo je preporuku da energetski unos kod kritično obolelih iznosi 25 kcal/kg/dan, sa postepenim uvođenjem pune ishrane u prvih 3 dana. Zatim, preporučuje se da unos proteina bude 1,3 g/kg/dan kao i da odnos zastupljenosti masti i ugljinih hidrata u ishrani bude 30:70 kod bolesnika bez respiratorne insuficijencije i 50:50 kod bolesnika koji su na nekom vidu mehaničke ventilacije. Treba napomenuti da se kod gojaznih osoba potrebe za energijom i proteinima izračunavaju preko idealne telesne mase [10].

Bolesnici kod kojih se *per os* ishranom ne mogu obezbediti energetske, mikro- i makronutivne potrebe, pogotovo kod starijih i polimorbiditetnih osoba, potrebno je uvesti oralne nutritivne suplemente. Oralni nutritivni suplementi kod bolesnika sa rizikom ili evidentiranom malnutricijom treba da obezbede najmanje 400 kcal/dan i najmanje 30 g proteina [13]. U slučaju nemogućnosti oralne ishrane, enteralna ishrana predstavlja drugi izbor nutritivne potpore, dok parenteralna ishrana predstavlja poslednji izbor nutritivne potpore kada prethodna dva vida nisu izvodljiva [10].

Nutritivna terapija u Jedinici intenzivnog lečenja

Godine *COVID-19* pandemije donele su izuzetno povećanje broja bolesnika koji su zahtevali lečenje u JIL. Sa pandemijom porastao je i broj bolesnika na različitim vidovima oksigenoterapije i mehaničke ventilacije, s tim u vezi pojavila se i veća potreba za znanjem i edukacijom osoblja za korišćenje različitih terapijsko-dijagnostičkih modaliteta, te i različitih pristupa ishrane kritično obolelih bolesnika.

Kao što je prethodno navedeno, velika je učestalost bolesnika sa malnutricijom, pogotovo u JIL. Međutim, smatra se da je samo polovina bolesnika u malnutriciji detektovana u kliničkoj praksi, dok je sarkopenija uglavnom ne prepoznata [14,15].

Nutritivna terapija bolesnika na HFNC – high flow nasal cannula

Nazalna kanila visokog protoka kiseonika efikasno se pokazala u lečenju akutne hipoksemijske respiratorne insuficijencije, akutnog srčanog popuštanja i plućnog edema, posthirurške respiratorne insuficijencije, kao dobar vid oksigenacije u preintubacionom i postekstubacionom periodu, itd [16]. Takođe, svoju efikasnost pokazala je i kod bolesnika sa *COVID-19*. Ishrana bolesnika na HFNC se ne razlikuje od ishrane bolesnika sa drugačijim vidom oksigenoterapije (nazalnom kanilom niskog protoka, O₂ maskom,...) ili bolesnika bez date terapije. Mali broj istraživanja postoji koja govore o ishrani bolesnika na HFNC.

Leder i saradnici, ispitali su uticaj oralne ishrane kod novorođančadi i odraslih osoba i doneli su zaključke da je 78% odraslih i 34% novorođenčeta koji su bili na

terapiji *HFNC*-om, bilo je sposobno da se hrani oralno. *Per os* ishrana bila je uspešna kod svih kod kojih je i započeta, te nije bilo potrebe za uvođenjem enteralne ishrane. Samo korišćenje *HFNC* per se ne bi trebalo da odlaže započinjanje *per os* ishrane [17]. Evropsko udruženje za intenzivnu medicinu (*ESCIM*) navodi u svojim preporukama da bi započinjanje ishrane trebalo biti u periodu 24-48h od prijema i da *HFNC* oksigenacija nije kontraindikacija za zadovoljavanje energetskog i proteinskog unosa [18].

Nutritivna terapija bolesnika na neinvazivnoj mehaničkoj ventilaciji

Neinvazivna mehanička ventilacija (NIV) pored korišćenja u respiratornoj insuficijenciji, hroničnoj opstruktivnoj bolesti pluća, kardiogenom plućnom edemu i drugim stanjima, efikasno se pokazala i u lečenju *SARS-CoV 2* indukovanom oštećenju pluća. Zvanične *ESPEN*-ove preporuke za ishranu bolesnika sa *COVID – 19* vode se time da ishrana bolesnika na NIV treba da bude per osi ako je ona neizvodljiva treba uvoditi enteralnu, pa tek na kraju pareneteralnu ishranu.

Osobe koje su na NIV-u, retko se mogu hraniti oralnim putem. Studija koja je rađena u Japanu pokazala je da 107 osoba od 150, koje su primljene u JIL zbog akutnog respiratornog distresa, nisu bile u mogućnosti da per os unose hranu, što predstavlja više od 70% hospitalizovanih bolesnika u JIL. Takođe, bolesnici koji su u toku lečenja bili na NIV i hranjeni enteralnim putem, imali su značajno učestalije komplikacije kao što su povraćanje i aspiraciona pneumonija, dok intrahospitalni mortalitet nije se razlikovao između bolesnika koji su hranjeni enteralnim putem i kontrolne grupe [19]. Međutim, drugo istraživanje koje je uključivalo 1075 bolesnika u primljenih u JIL, pokazalo je da je učestalost kasnije potrebe za invazivnom mehaničkom ventilacijom i smrtnog ishoda dva puta veća kod bolesnika koji su hranjeni enteralnim putem [20].

Dakle, enteralni pristup hranjenja bolesnika na NIV sa sobom nosi određene nuspojave, te je potrebno primeniti postulate savremene medicine i individualizovati terapiju u najvećoj mogućoj meri, kao i sprečiti, na vreme prepoznati i lečiti neželjene efekte.

Nutritivna terapija bolesnika na invazivnoj mehaničkoj ventilaciji

Ishrana bolesnika na mehaničkoj ventilaciji sa *COVID-19* oboljenjem, se ne razlikuje u mnogome od ishrane bolesnika sa drugim stanjima koje zahtevaju invazivnu mehaničku ventilaciju. Prema *ESPEN*-ovim preporukama svim bolesnicima koji će u JIL ostati duže od 48h treba započeti ishranu [21].

Enetralni pristup predstavlja prvi izbor ishrane. Tek po iskorišćenju svih mogućnosti enetaralne ishrane, ili usled kontraindikacija za primenu enteralne ishrane (insuficijencija creva, teška crevna upala, intestinalna opstrukcija, nemogućnost pla-

siranja sonde za ishranu, itd.), treba započeti parenteralnu ishranu. Enteralna ishrana se započinje nazogastričnim putem. Usled postojanje gastrične intolerancije (veliki gastrični rezidualni volumen) koja je rezistentna na primenu prokinetika (eritromicina, metoklopramida) kod bolesnika koji se hrane nazogastričnim putem potrebno je preći na postpiloričnu ishranu. Kod kritično obolelih pacijenata u JIL započinje se hipokalorijska ishrana sa sukcesivnim povećanje energetske unosa u prvih 3 dana, da bi se od 4. dana unosila puna ishrana, tj. 25 kcal/kg/dan i 1,3 g proteina/kg/dan. Enteralnu ishranu ne treba započinjati kod hemodinamski nestabilnih pacijenata kao ni kod pacijenata sa životno ugrožavajućom hipoksijom, hiperkapnijom i acidozom [10,21,22].

Parenteralna ishrana pokazala je prednost u odnosu na enteralnu ishranu kod bolesnika koji su bili na mehaničkoj ventilaciji i vazopresornoj terapiji (usled regulacije šoknog stanja). Mortalitet unutar 28 i 90 dana, zatim dužina hospitalizacije, vreme provedeno na mehaničkoj ventilaciji, vazopresornoj terapiji i potreba za dijalizom nije se razlikovala između ispitanika koju si bili hranjeni enteralnim i parenteralnim putem. Osobe hranjene enteralnim putem imale su značajno veće komplikacije na nivou gastrointestinalnog trakta, kao što su dijareja, ishemija creva, akutna pseudoopstrukcija kolona [23].

Prone položaj kao adjuvantna terapija pronašla je mesto u *COVID-19* pandemiji. Prebacivanje bolesnika u *prone* položaj ukoliko se adekvatno i na vreme sprovede može biti efikasno u smanjenju mortaliteta bolesnika sa *ARDS-om* (*Acute Respiratory Distress Syndrome*) [24].

Postavlja se pitanje da li prebacivanje bolesnika u *prone* položaj može nepovoljno uticati na enteralnu ishranu povećavajući gastrični rezidualni volumen, povraćanje, aspiraciju, pa i incidencu aspiracionih pneumonija? Smatra se da enteralna ishrana bolesnika koji se premeštaju u *prone* položaj nije povezana sa većim intolerancijama i komplikacijama iste [25].

Imunonutricija

Unazad niz godina vode se istraživanja u pravcu ispitivanja nutrijenata, tačnije njihovog dejstva na imunski odgovor bolesnika. Ispitivane su aminokiseline arginin, glutamin, zatim nukleotidi, omega-3 masne kiseline (DHA - dokozaheksaenska kiselina, EPA - eikozapentaenska kiselina) itd. Veći unos DHA i EPA, kao i njihova veća koncentracija u krvi povezana je sa manjim brojem inflamatornih citokina. Takođe, omega-3 masne kiseline povećavaju aktivnost ćelija urođenog i stečenog imunog sistema [26,27].

Smatra se da omega-3 masne kiseline mogu različitim mehanizmima uticati na tok i ishod *COVID - 19* oboljenja. Omega-3 masne kiseline smanjuju lučenje proinflamatornih citokina IL-1 β , IL-6, TNF- α i samim tim smanjuju rizik od nastanka

citokinske oluje. Sa druge strane, EPA i DHA pokazuju antivirusni efekat prevashodno pojačavajući aktivnosti fagocitne aktivnosti ćelija urođenog imunskog sistema - neutrofila i makrofaga. Dodatno, omega 3 masne kiseline potencijalno povećavaju IFN koji deluje inhibitorno na virusnu replikaciju [28]. Omega 3 masne kiseline mogu dovesti i do inhibicije enzima COX (ciklooksigenaze) i sinteze prostaglandina koji su takođe proinflamatorne prirode [29].

Formule za parenteralnu ishranu obogaćene omega 3 masnim kiselinama pokazale su značajnu prednost u odnosu na formule koje nisu obogaćene DHA i EPA. Značajno manji rizik od infekcije za 40% i sepse za 56% u toku hospitalizacije zabeležen je kod bolesnika koji su dobijali parenteralne preparate obogaćene omega-3 masnim kiselinama. Takođe, osobe su bile u proseku za 2 dana manje hospitalizovane, kao i otprilike 2 dana kraće boravile u JIL [30].

Vitamin C i D vs. COVID-19

Sa početkom pandemije i svakodnevnim rastom obolelih značajno je i porasla upotreba suplemenata, prevashodno sa ciljem da se spreče ili umanje simptomi *COVID-19* bolesti. Odmah je postavljeno pitanje da li oni zaista to i mogu? Upotreba vitamina C i Zn unazad 3 meseca, 3 puta nedeljno nije povezana sa nižim rizikom od infekcije, međutim, upotreba vitamina D dovodi do smanjenja rizika od infekcije *SARS-CoV 2* virusom za 9% [31]. U prilog tome, niže vrednosti vitamina D u krvi povezane su sa većim rizikom od nastanka i teže forme *COVID-19* bolesti [32]. Smatra se da povoljni efekat vitamina D u *COVID-19* leži u povećanoj ekspresiji ACE2 i regulaciji imunskog sistema različitim mehanizmima. Osim što je receptor za ulazak virusa *SARS-CoV2* u ćeliju, ACE2 ima bitnu ulogu u sprečavanju nastanka komplikacija respiratornih infekcija. Takođe, vitamin D potencijalno može dovesti do smanjenja replikacije virusa [33].

Polazivši od prethodnih saznanja o vitaminu C, tj. da igra važnu ulogu u urođenoj i stečenoj imunosti, da je antioksidans, da održava epitelni integritet, poboljšava diferencijaciju i proliferaciju B i T ćelija kao i da smanjuje jačinu i trajanje prehlade, njegova upotreba našla je i u lečenju *COVID-19*. U nacionalnom protokolu za lečenje bolesnika sa *COVID-19* bolešću pored korišćenja vitamina D, preporučuje se i upotreba vitamina C. Blagotvorni efekat, vitamin C pokazao je kod bolesnika u ranim fazama sepse i *ARDS-a* smanjujući 28-dnevni mortalitet [34]. U prilog tome govori i studija koja je ispitivala efekte upotrebe vitamina C kod *COVID-19* bolesnika lečenih u JIL. Značajno niži mortalitet zabeležen je kod bolesnika koji su primali vitamin C [35].

Bez obzira na pozitivne efekte prethodnih studija, koliko upotreba vitamina D i C potencijalno može biti blagotvorna, treba voditi računa i pri njihovoj upotrebi. Prekomerni unos vitamina C može dovesti do mučnine, dijareje, abdominalnih grčeva, oksalatne nefropatije, dok primena vitamina D u visokim dozama može prouzrokovati

povraćanje, bolove u abdomenu, gubitak apetita, srčane aritmije, oštećenje bubrega od nastanka kalkulusa do pojave bubrežne insuficijencije [36,37].

Refeeding Sy

Refeeding sindrom je izuzeno značajan, ali često i zapostavljen u svakodnevnoj kliničkoj praksi. Nastaje usled započinjanja ishrane kod bolesnika sa malnutricijom ili bolesnika koji su izgladnjivani. Prevažodno se karakteriše potencijalno fatalnim disbalansom telesnih tečnosti i elektrolita (hipofosfateomija, hipokalijemija, hipomagnezijemija) [38].

Populacija u riziku od nastanka *refeeding* sindroma jesu pre svega kritično oboleli, osobe sa psihijatrijskim oboljenjima, osobe sa malignitetom, malapsorpcijom, zatim kao faktori rizika navode se i korišćenje alkohola i psihoaktivnih supstanci, itd. Nekarakteristični simptomi nam ne dozvoljavaju da se lako posumnja na *refeeding* sindrom, te se osnovni dijagnostički principi ogledaju u proveru elektrolitnog statusa bolesnika. Najčešći simptomi i znaci *refeeding* sindroma su poremećaji srčanog ritma (taahikardija), ubrzano disanje i edemi, takođe, mogu se javiti i poremećaj krvnog pritiska, srčani zastoj, plućni edem, respiratorni arest, poremećaj mentalnog statusa, trombocitna disfunkcija, abdominalni bolovi, dijareja, konstipacija, itd. Tretman *refeeding* sindroma ogleda su u nadoknadi elektrolita i mikronutrijenata, kao i u smanjenju kalorijskog unosa kod postojanja kliničkih manifestacija [39,40].

Zaključak

U svakodnevnoj kliničkoj praksi lekari moraju imati da umu da je adekvatna nutritivna potpora bolesnika sa *COVID – 19*, pogotovo u jedinicama intenzivnog lečenja, ključna za očuvanje telesne mase i podršku respiratorne funkcije, ali iznačajan doprinos sveobuhvatnom oporavku bolesnika.

Literatura

1. Pelemis M, Stevanovic G, Turkulov V, Matijasevic V, Milosević B, Milosevic I, et al. Nacionalni protocol za lečenje pacijenata sa COVID19 infekcijom (verzija 12). 2021 Sep.
2. Mullol J, Alobid I, Mariño-Sánchez F, Izquierdo-Domínguez A, Marin C, Klimek L, Wang DY, Liu Z. The Loss of Smell and Taste in the COVID-19 Outbreak: a Tale of Many Countries. *Curr Allergy Asthma Rep.* 2020 Aug 3;20(10):61
3. Rothenberg E. Coronavirus Disease 19 from the Perspective of Ageing with Focus on Nutritional Status and Nutrition Management—A Narrative Review. *Nutrients.* 2021; 13(4):1294.

4. Di Filippo L, De Lorenzo R, D'Amico M, Sofia V, Roveri L, Mele R, Saibene A, Rovere-Querini P, Conte C. COVID-19 is associated with clinically significant weight loss and risk of malnutrition, independent of hospitalisation: A post-hoc analysis of a prospective cohort study. *Clin Nutr*. 2021 Apr;40(4):2420-2426.
5. Allard L, Ouedraogo E, Molleville J, Bihan H, Giroux-Leprieur B, Sutton A, et al. Malnutrition: Percentage and Association with Prognosis in Patients Hospitalized for Coronavirus Disease 2019. *Nutrients*. 2020 Nov 28;12(12):3679.
6. Bedock D, Bel Lassen P, Mathian A, Moreau P, Couffignal J, Ciangura C, Poitou-Bernert C, Jeannin AC, Mosbah H, Fadlallah J, Amoura Z, Oppert JM, Faucher P. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. *Clin Nutr ESPEN*. 2020 Dec;40:214-219.
7. Wierdsma NJ, Kruizenga HM, Konings LA, Krebbers D, Jorissen JR, Joosten MI, et al. Poor nutritional status, risk of sarcopenia and nutrition related complaints are prevalent in COVID-19 patients during and after hospital admission. *Clin Nutr ESPEN*. 2021 Jun;43:369-376.
8. Barazzoni R, Bischoff SC, Busetto L, Cederholm T, Chourdakis M, Cuerda C, et al; endorsed by the ESPEN Council. Nutritional management of individuals with obesity and COVID-19: ESPEN expert statements and practical guidance. *Clin Nutr*. 2021 May 11:S0261-5614(21)00248-X.
9. Fedele D, De Francesco A, Riso S, Collo A. Obesity, malnutrition, and trace element deficiency in the coronavirus disease (COVID-19) pandemic: An overview. *Nutrition*. 2021 Jan;81:111016.
10. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al; endorsed by the ESPEN Council. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr*. 2020 Jun;39(6):1631-1638.
11. Haugen HA, Chan LN, Li F. Indirect calorimetry: a practical guide for clinicians. *Nutr Clin Pract*. 2007 Aug;22(4):377-88.
12. Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. *J Intensive Care*. 2021 Jan 12;9(1):8.
13. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr*. 2019 Feb;38(1):10-47.
14. Kruizenga HM, de Jonge P, Seidell JC, Neelemaat F, van Bodegraven AA, Wierdsma NJ, et al. Are malnourished patients complex patients? Health status and care complexity of malnourished patients detected by the Short Nutritional Assessment Questionnaire (SNAQ). *Eur J Intern Med*. 2006 May;17(3):189-94.
15. Sheean PM, Peterson SJ, Gomez Perez S, Troy KL, Patel A, Sclamberg JS, et al. The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment. *JPEN J Parenter Enteral Nutr*. 2014 Sep;38(7):873-9.
16. Sharma S, Danckers M, Sanghavi D, Chakraborty RK. High Flow Nasal Cannula. 2021 Jul 25. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing;.

17. Leder SB, Siner JM, Bizzarro MJ, McGinley BM, Lefton-Greif MA. Oral Alimentation in Neonatal and Adult Populations Requiring High-Flow Oxygen via Nasal Cannula. *Dysphagia*. 2016 Apr;31(2):154-9.
18. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM et al., Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med*. 2017; 43:380–98.
19. Kogo M, et al. Enteral nutrition is a risk factor for airway complications in subjects undergoing noninvasive ventilation for acute respiratory failure. *Respir Care*. 2017;62(4):459–67.
20. Terzi N, et al. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study. *Critical care (London, England)*. 2017;21(1):293–293.
21. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019 Feb;38(1):48-79.
22. Pat Howard. Basics in clinical nutrition: Enteral nutrition. *E Spen Eur E J Clin Nutr Metab*. 2009 4:(5) e223–e225.
23. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, et al; NUTRIREA-2 Trial Investigators; Clinical Research in Intensive Care and Sepsis (CRICS) group. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet*. 2018 Jan 13;391(10116):133-143.
24. Mora-Arteaga JA, Bernal-Ramírez OJ, Rodríguez SJ. The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis. *Med Intensiva*. 2015 Aug-Sep;39(6):359-72.
25. Behrens S, Kozeniecki M, Knapp N, Martindale RG. Nutrition Support During Prone Positioning: An Old Technique Reawakened by COVID-19. *Nutr Clin Pract*. 2021 Feb;36(1):105-109.
26. Gutiérrez S, Svahn SL, Johansson ME. Effects of Omega-3 Fatty Acids on Immune Cells. *Int J Mol Sci*. 2019 Oct 11;20(20):5028.
27. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochim Biophys Acta*. 2015 Apr;1851(4):469-84.
28. Omega 3 Fatty Acids and COVID-19: A Comprehensive Review. *Infect Chemother*. 2020;52(4):478-495.
29. Fernández-Quintela A, Milton-Laskibar I, Trepiana J, Gómez-Zorita S, Kajarabille N, Léniz A, et al. Key Aspects in Nutritional Management of COVID-19 Patients. *J Clin Med*. 2020 Aug 10;9(8):2589.
30. Pradelli L, Mayer K, Klek S, Omar Alsaleh AJ, Clark RAC, Rosenthal MD, et al. ω -3 Fatty-Acid Enriched Parenteral Nutrition in Hospitalized Patients: Systematic Review With Meta-Analysis and Trial Sequential Analysis. *JPEN J Parenter Enteral Nutr*. 2020 Jan;44(1):44-57.
31. Louca P, Murray B, Klaser K, Graham MS, Mazidi M, Leeming ER, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. *BMJ Nutr Prev Health*. 2021 Apr 19;4(1):149-157

32. Kazemi A, Mohammadi V, Aghababae SK, Golzarand M, Clark CCT, Babajafari S. Association of Vitamin D Status with SARS-CoV-2 Infection or COVID-19 Severity: A Systematic Review and Meta-analysis. *Adv Nutr.* 2021 Oct 1;12(5):1636-1658.
33. Hadizadeh F. Supplementation with vitamin D in the COVID-19 pandemic? *Nutr Rev.* 2021 Jan 9;79(2):200-208.
34. Fowler AA, 3rd, Truwit JD, Hite RD. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. *JAMA.* 2019;322:1261–1270.
35. Krishnan S, Patel K, Desai R, Sule A, Paik P, Miller A, et al. Clinical comorbidities, characteristics, and outcomes of mechanically ventilated patients in the State of Michigan with SARS-CoV-2 pneumonia. *J Clin Anesth.* 2020 Dec;67:110005.
36. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiwicz J, Płudowski P, Jones G. Vitamin D Toxicity-A Clinical Perspective. *Front Endocrinol (Lausanne).* 2018 Sep 20;9:550.
37. Pacier C, and Martirosyan D. Vitamin C: optimal dosages, supplementation and use in disease prevention. *Funct Foods Health Dis.* 2015; 5(3):89-107.
38. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. *BMJ.* 2008 Jun 28;336(7659):1495-8.
39. Friedli N, Odermatt J, Reber E, Schuetz P, Stanga Z. Refeeding syndrome: update and clinical advice for prevention, diagnosis and treatment. *Curr Opin Gastroenterol.* 2020 Mar;36(2):136-140.
40. da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al; Parenteral Nutrition Safety and Clinical Practice Committees, American Society for Parenteral and Enteral Nutrition. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutr Clin Pract.* 2020 Apr;35(2):178-195.

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NUTRITIONAL THERAPY OF COVID-19 DISEASE IN INTENSIVE CARE UNITS

Abstract: Since the beginning of 2020, SARS-CoV 2 (Severe Acute Respiratory Syndrome - Corona Virus 2) has been in the focus of scientific circles and beyond. Finding the most efficient therapeutic protocol in prevention and treatment of the new and unknown COVID – 19 (Corona Virus Disease - 2019) disease has been indentified as especially important. SARS-CoV 2 uses various mechanisms to lead patients to malnutrition, which is detected by a higher frequency of admission to hospital treatment, especially on admission to the Intensive Care Unit (ICU). Malnutrition has a negative impact on the course and outcome of the disease. In the pandemic, the number of patients on various types of oxygen therapy and mechanical ventilation increased, and in correlation with that, there has been a greater need for knowledge and education of staff to use different diagnostic and therapeutic modalities and different

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approaches in feeding critically ill patients. Nutritional therapy is the basis for maintaining body weight, supporting respiratory function, as well as helping in the overall recovery of patients. Omega 3 fatty acids, vitamins C and D have shown potentially beneficial effects against COVID-19 diseases.

The aim of this paper is to consolidate the current knowledge and recommendations in the field of nutritional therapy in patients with COVID - 19 treated in the Intensive Care Unit.

Key words: *COVID-19*; Intensive care unit; Malnutrition; Nutritional therapy

Introduction

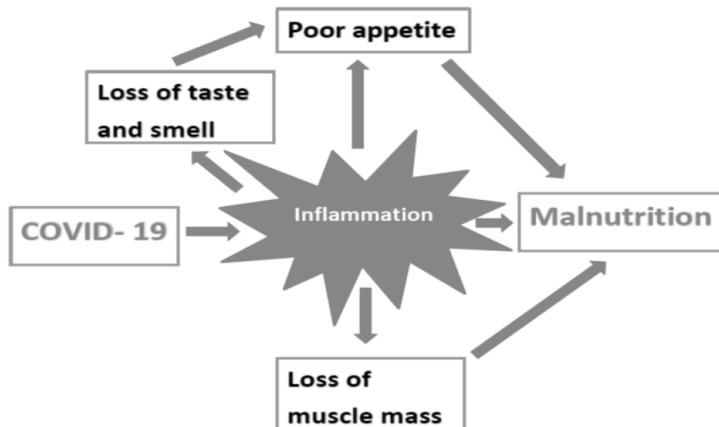
Since the beginning of 2020, SARS – CoV – 2 (Severe Acute Respiratory Syndrome - Corona Virus 2) has been the main focus of interest in scientific circles and beyond. Finding the most efficient therapeutic protocol in prevention and treatment of the new and unknown COVID – 19 (Corona Virus Disease - 2019) disease has been indentified as especially important. The basic principles of treatment are the use of antiviral drugs, biological therapy, corticosteroid therapy, anticoagulant therapy, neutralizing monoclonal antibodies, convalescent plasma, oxygen therapy and other methods of maintaining good blood oxygenation (non-invasive and invasive mechanical ventilation), as well as symptomatic and vitamin therapy [1]. In addition to the listed therapeutic modalities, it is necessary to perform adequate nutritional support of patients, physical treatment, psychological support, etc. on a daily basis.

The aim of this paper is to consolidate the current knowledge and recommendations in the field of nutritional therapy in patients with COVID - 19 treated in the Intensive Care Unit (ICU).

COVID-19 and malnutrition

Upper respiratory tract infections are associated with loss of sense of smell primarily due to mechanical obstruction, inflammation, and neurodegeneration of olfactory cells. SARS - CoV 2 infection leads to altered, partial or complete loss of sense of smell and taste, which affects the patient's appetite, reducing it. This loss of smell in COVID-19 disease is thought to be different from other upper respiratory tract infections, primarily due to a lack of severe inflammation and nasal obstruction. It is thought to be based on the expression of ACE2 and TMPRSS2 receptors on neuroepithelial olfactory cells, allowing virus to enter, accumulate and replicate [2]. Systemic inflammation caused by various mechanisms leads to poorer appetite which

together with loss of sense of smell and taste leads to reduced food intake. In addition, acute infectious disease leads to inflammatory syndrome and hypermetabolism and loss of muscle mass. Thus, we can conclude that SARS - CoV 2 leads to a vicious circle that leads to malnutrition in different ways [3].



Picture 1. Malnutrition and COVID-19 [3].

A study conducted in Italy, which included 213 hospitalized patients with COVID-19 disease, showed that 54.7% of patients are at risk of malnutrition, while 6.6% had malnutrition according to the Mini Nutritional Assessment score [4]. Allard et al., in their study of 108 patients, proved that 42 (38.9%) of them were diagnosed with malnutrition on admission to the hospital for the treatment of COVID-19 disease [5]. Later on, a study by Bedock et al., which included 112 patients with SARS-CoV2 virus infection, showed that according to GLIM (Global Leadership Initiative on Malnutrition) criteria, 42% of patients were malnourished, 24% moderately and 18% severely. They also proved that the prevalence of malnutrition is significantly higher in patients treated in ICU [6]. Wierdsma et al., proved in their study that every fifth patient admitted for hospital treatment of COVID-19 has severe acute weight loss (> 5 kg), where 85% of patients with detected acute weight loss are admitted to the ICU, and 73% of patients have a higher risk of sarcopenia [7].

In recent months, numerous studies have led to the following conclusions: there is a high incidence of malnutrition in patients with COVID-19 at hospital admission, a negative impact of malnutrition on the prognosis of COVID-19 was proven, as well as a negative impact of COVID-19 on body weight in both hospitalized and non-hospitalized patients [8].

It should be noted that obesity is also a form of malnutrition. Adipose tissue is a major source of macrophages that secrete inflammatory mediators. Leptin, a hormone

that increases appetite and speeds up metabolism, is released from adipose tissue, and is structurally similar to IL-6 and IL-12. Also, in obese people, the production of Th1 cells and B lymphocytes is increased. All of this leads to a state of constant low-grade inflammation, which can be unfavorable for infections, and precipitate an ineffective immune response, i.e. hyperproduction of IL-6 and cytokine storm, damage to lung tissue, etc. It is believed that due to the existence of this constant low-grade inflammation, obesity is a risk factor for a more severe form of the disease as well as death in patients with COVID-19 disease [9].

Nutritional therapy of COVID-19 patients

After admission of patients for hospital treatment, especially in elderly patients, those with comorbidities and obese people, it is necessary to perform screening and potential diagnosis of malnutrition. The diagnosis of malnutrition, according to the criteria of the Global Leadership Initiative on Malnutrition, is made through two steps. In the first step, it is necessary to screen for malnutrition through MUST (Malnutrition Universal Screening Tool) or NRS-2002 (Nutrition Risk Screening) criteria, and in the second step, malnutrition is confirmed by the existence of at least one phenotypic and at least one etiologic criterion [10].

Table 1. *Phenotypic and etiologic criteria for diagnosing malnutrition accord to Global Leadership Initiative on Malnutrition*

Phenotypic criteria	Etiologic criteria
<p>Body weight loss (%) >5% within 6 months > 10% beyond 6 months</p> <p>Low BMI (kg/m²) <20 (< 70 years) < 22 (>70 years)</p> <p>Reduced muscle mass Reduction verified by validated body composition measuring techniques</p>	<p>Reduced food intake 50% of energy need > 1 week, or any reduction for > 2 weeks, or any chronic gastrointestinal disorder that adversely impacts food assimilation or absorption</p> <p>Inflammation Acute disease/injury/chronic diseases</p>

BMI- body mass index

As mentioned above, the incidence of malnutrition is high in patients with COVID-19 and it is assumed that malnutrition itself negatively affects the course and

outcome of the disease, and therefore it is necessary to introduce adequate nutrition to patients in order to reduce disease complications and strive for a good treatment outcome.

Every introduction of nutrition starts by determining the individual's energy needs. The best, but also the most complex method of determining energy needs is indirect calorimetry, which is a method of calculating a person's need for energy indirectly by calculating energy consumption at rest. Specifically, the degree of energy consumption is calculated by measuring the consumption of O₂ and the amount of CO₂ in exhaled air [11]. Today, there is an increased tendency towards indirect calorimetry, considering that other types of calculating energy needs can lead to excessive or insufficient intake of nutrients in relation to needs. Excessive nutrient intake in critically ill patients is associated with hyperglycemia, liver steatosis, as well as increased mortality, longer hospital stays and duration of mechanical ventilation, higher risk of infections, organ failure, etc. However, as indirect calorimetry is an extremely expensive and often inaccessible technique, energy needs can also be calculated by measuring the amount of exhaled CO₂ (EEVCO₂ - energy expenditure based on CO₂ measurements). After reading the amount of CO₂ (VCO₂), the energy needs of the organism are calculated by the following formula $EEVCO_2 \text{ (kcal / day)} = VCO_2 \text{ (ml / min)} \times 8.19$. This method is inferior to indirect calorimetry, but is superior to using formulas that based on body weight [12].

An alternative, more commonly used method of calculating energy needs are calculations with body weight. The European Association for Clinical Nutrition and Metabolism has recommended that the energy intake of critically ill patients should be 25 kcal/kg/day, with the gradual introduction of a full diet within the first 3 days. Also, the protein intake is recommended to be 1.3g/kg/day and the ratio of fats and carbohydrates in the diet is recommended to be 30:70 in patients without respiratory insufficiency and 50:50 in patients who are on some kind of mechanical ventilation. It should be noted that in obese people, energy and protein needs are calculated through ideal body weight [10].

Patients in whom per os diet cannot provide energy and micro- and macronutrient needs, especially in the elderly and polymorbid individuals, it is necessary to introduce oral nutritional supplements. Oral nutritional supplements in patients at risk or recorded malnutrition should provide at least 400 kcal/day and at least 30g of protein [13]. In case that oral nutrition is impossible, enteral nutrition is the second choice of nutritional support, while parenteral nutrition is the last choice of nutritional support when the previous two types are not feasible [10].

Nutritional therapy in Intensive Care Unit

The years of COVID-19 pandemic brought an extraordinary increase in the number of patients who required treatment in the ICU. In the pandemic, the number of patients on various types of oxygen therapy and mechanical ventilation increased, and in correlation with that, there has been a greater need for knowledge and education of staff to use different diagnostic and therapeutic modalities and different approaches in feeding critically ill patients.

As mentioned beforehand, there is a high incidence of patients with malnutrition, especially in ICUs. However, it is estimated that only half of malnourished patients are detected in clinical practice, while sarcopenia is mostly unrecognized [14,15].

Nutritional therapy of patients on HFNC – high flow nasal cannula

High oxygen flow nasal cannula has been shown as effective in the treatment of acute hypoxemic respiratory failure, acute heart failure and pulmonary edema, post-surgical respiratory failure, as a good form of oxygenation in the preintubation and postintubation period, etc. [16]. It has also shown its effectiveness in patients with COVID-19. The diet of patients on HFNC does not differ from the diet of patients with a different type of oxygen therapy modality (low-flow nasal cannula, O₂ mask, ...) or patients without it. There are few studies concerning the diet of patients on HFNC.

Leder et al., examined the impact of oral nutrition in infants and adults and concluded that 78% of adults and 34% of infants treated with HFNC were able to eat. The per os diet was successful in all those who started it, so there was no need to introduce enteral nutrition. The use of HFNC alone should not delay per os diet initiation [17]. The European Society of Intensive Medicine (ESCIM) states in its recommendations that the start of the diet should be within 24-48 hours of admission and that HFNC oxygenation is not a contraindication for adequate energy and protein intake [18].

Nutritional therapy of patients on non-invasive mechanical ventilation

Non-invasive mechanical ventilation (NIV), in addition to its use in respiratory failure, chronic obstructive pulmonary disease, cardiogenic pulmonary edema and other conditions, has been shown as effective in the treatment of SARS-CoV 2-induced lung damage. The official ESPEN recommendations for the nutrition of patients with COVID-19 are based on the fact that the nutrition of patients on NIV should be per os, if it is not possible then enteral nutrition should be introduced, and parenteral nutrition should be used as a last resort.

People who are on NIV can rarely be fed orally. A study conducted in Japan showed that 107 out of 150 people admitted to the ICU due to acute respiratory distress

were unable to ingest food per os, which represents more than 70% of hospitalized patients in the ICU. Also, patients who were on NIV and enterally fed had significantly more frequent complications such as vomiting and aspiration pneumonia, while intrahospital mortality did not differ between enterally fed patients and control groups [19]. However, another study involving 1,075 patients admitted to the ICU showed that the incidence of later need for invasive mechanical ventilation and death was twice as high in patients who were fed enterally [20].

Therefore, the approach of enteral feeding patients with NIV has certain side effects, so it is necessary to apply the postulates of modern medicine and individualize the therapy as much as possible, as well as prevent, recognize and treat side effects in time.

Nutritional therapy of patients on invasive mechanical ventilation

The diet of patients on mechanical ventilation with COVID-19 disease does not differ much from the diet of patients with other conditions that require invasive mechanical ventilation. According to ESPEN recommendations, all patients who are likely to stay in the ICU for more than 48 hours should start the diet [21].

Enteral feeding is the first choice of diet. Parenteral nutrition should be started only after using all the possibilities of enteral nutrition, or due to contraindications for the use of enteral nutrition (intestinal insufficiency, severe intestinal inflammation, intestinal obstruction, inability to place a feeding tube, etc.). Enteral nutrition should be started by the nasogastric route. Due to the existence of gastric intolerance (large gastric residual volume) resistant to the use of prokinetics (erythromycin, metoclopramide) in patients who feed by the nasogastric route, it is necessary to switch to a postpyloric diet. In critically ill patients in the ICU, a hypocaloric diet is started with a successive increase in energy intake in the first 3 days, and from the 4th day a full diet is introduced, ie. 25 kcal/kg/day and 1.3 g protein/kg/day. Enteral nutrition should not be initiated in hemodynamically unstable patients as well as in patients with life-threatening hypoxia, hypercapnia, and acidosis [10,21,22].

Parenteral nutrition showed an advantage over enteral nutrition in patients who were on mechanical ventilation and vasopressor therapy (due to the regulation of shock). Mortality within 28 and 90 days, length of hospitalization, time spent on mechanical ventilation, vasopressor therapy, and need for dialysis did not differ between subjects who were fed enterally and parenterally. People fed enterally had significantly greater complications connected with the gastrointestinal tract, such as diarrhea, intestinal ischemia, acute pseudoobstruction of the colon [23].

Prone position as an adjuvant therapy has found a place in the COVID-19 pandemic. Switching patients to a prone position may be effective in reducing mortality in

patients with ARDS [Acute Respiratory Distress Syndrome] if performed adequately and in a timely manner [24].

The question is whether the transfer of patients to the prone position can adversely affect enteral nutrition by increasing the gastric residual volume, vomiting, aspiration, and even the incidence of aspiration pneumonia. It is considered that the enteral nutrition of patients who move to the prone position is not associated with higher intolerances and complications [25].

Immunonutrition

Over the years, research has been conducted in the direction of examining nutrients, more precisely their effect on the patient's immune response. The amino acids arginine, glutamine, nucleotides, omega-3 fatty acids (DHA - docosahexaenoic acid, EPA - eicosapentaenoic acid), etc. were tested. Higher intake of DHA and EPA, as well as their higher concentration in the blood, is associated with a lower number of inflammatory cytokines. Also, omega-3 fatty acids increase the activity of cells of the innate and acquired immune system [26,27].

It is believed that omega-3 fatty acids can affect the course and outcome of COVID-19 disease by various mechanisms. Omega-3 fatty acids reduce the secretion of proinflammatory cytokines IL-1 β , IL-6, TNF- α and thus reduce the risk of cytokine storm. On the other hand, EPA and DHA show an antiviral effect, primarily by enhancing the phagocytic activity of cells of the innate immune system - neutrophils and macrophages. In addition, omega 3 fatty acids potentially increase IFN, which has an inhibitory effect on viral replication [28]. Omega 3 fatty acids can also lead to inhibition of the COX enzyme (cyclooxygenase) and prostaglandin synthesis, which are also proinflammatory in nature [29].

Formulas for parenteral nutrition enriched with omega 3 fatty acids have shown a significant advantage over formulas that are not enriched with DHA and EPA. A significantly lower risk of infection by 40% and sepsis by 56% during hospitalization was observed in patients receiving parenteral preparations enriched with omega-3 fatty acids. Also, these people were hospitalized on average 2 days less, and had approximately 2 days shorter stay in the ICU [30].

Vitamins C and D vs. COVID-19

With the onset of the pandemic and the daily growth in number of patients, the use of supplements has significantly increased, primarily with the aim of preventing or reducing the symptoms of COVID-19 disease. The question that was immediately asked was whether they can really do that. The use of vitamins C and Zn for 3

months, 3 times a week is not associated with a lower risk of infection, however, the use of vitamin D reduces the risk of infection with SARS-CoV 2 virus by 9% [31]. In addition, lower levels of vitamin D in the blood are associated with a higher risk of developing more severe forms of COVID-19 disease [32]. The beneficial effect of vitamin D in COVID-19 is thought to lie in increased ACE2 expression and regulation of the immune system by various mechanisms. In addition to being a receptor for the entry of SARS-CoV2 virus into the cell, ACE2 plays an important role in preventing the occurrence of complications of respiratory infections. Also, vitamin D could potentially lead to reduced virus replication [33].

Starting with previous knowledge about vitamin C, its important role in innate and acquired immunity, its role as an antioxidant, in maintaining epithelial integrity, improving the differentiation and proliferation of B and T cells as well as in reducing the severity and duration of common colds, it has also found its role in the treatment of COVID-19. In the national protocol for the treatment of patients with COVID-19 disease, in addition to the use of vitamin D, the use of vitamin C is also recommended. Vitamin C has been shown to have a beneficial effect in the early stages of sepsis and ARDS by reducing 28-day mortality [34]. This is supported by a study that examined the effects of vitamin C use in COVID-19 patients treated in ICU. Significantly lower mortality was observed in patients receiving vitamin C [35].

Regardless of the positive effects of previous studies, the extent to which the use of vitamins D and C can potentially be beneficial, one should be careful when using them. Excessive intake of vitamin C can lead to nausea, diarrhea, abdominal cramps, oxalate nephropathy, while the use of vitamin D in high doses can cause vomiting, abdominal pain, loss of appetite, cardiac arrhythmias, kidney damage anywhere from calculus formation to renal failure [36, 37].

Refeeding syndrome

Refeeding syndrome is extremely significant, but often neglected in everyday clinical practice. It occurs due to the initiation of diet in patients with malnutrition or patients who are in starvation. It is primarily characterized by a potentially fatal disbalance of body fluids and electrolytes (hypophosphatemia, hypokalemia, hypomagnesaemia) [38].

The population at risk of developing refeeding syndrome are firstly critically ill patients, then people with psychiatric illnesses, people with malignancy, malabsorption, alcohol and psychoactive substances abuse etc. Uncharacteristic symptoms do not allow us to easily suspect of refeeding syndrome, so the basic diagnostic principles are reflected in checking the electrolyte status of the patient. The most common symptoms and signs of refeeding syndrome are heart rhythm disorders (tachycardia), rapid breathing and edema, but blood pressure disorders, cardiac arrest, pulmonary edema,

respiratory arrest, mental status disorders, platelet dysfunction, abdominal pain, diarrhea, constipation, etc. can be found as well. The treatment of refeeding syndrome is replacement of electrolytes and micronutrients, as well as in the reduction of caloric intake in the presence of clinical manifestations [39,40].

Conclusion

In everyday clinical practice, physicians must keep in mind that adequate nutritional support for patients with COVID-19, especially those in intensive care units, is key to maintaining body weight and supporting respiratory function, but also has a significant contribution to the overall recovery of patients.

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References

1. Pelemis M, Stevanovic G, Turkulov V, Matijasevic V, Milosević B, Milosevic I, et al. Nacionalni protokol za lečenje pacijenata sa COVID-19 infekcijom (verzija 12). 2021 Sep.
2. Mullol J, Alobid I, Mariño-Sánchez F, Izquierdo-Domínguez A, Marin C, Klimek L, Wang DY, Liu Z. The Loss of Smell and Taste in the COVID-19 Outbreak: a Tale of Many Countries. *Curr Allergy Asthma Rep.* 2020 Aug 3;20(10):61
3. Rothenberg E. Coronavirus Disease 19 from the Perspective of Ageing with Focus on Nutritional Status and Nutrition Management – A Narrative Review. *Nutrients.* 2021; 13(4):1294.
4. Di Filippo L, De Lorenzo R, D’Amico M, Sofia V, Roveri L, Mele R, Saibene A, Rovere-Querini P, Conte C. COVID-19 is associated with clinically significant weight loss and risk of malnutrition, independent of hospitalisation: A post-hoc analysis of a prospective cohort study. *Clin Nutr.* 2021 Apr;40(4):2420-2426.
5. Allard L, Ouedraogo E, Molleville J, Bihan H, Giroux-Leprieur B, Sutton A, et al. Malnutrition: Percentage and Association with Prognosis in Patients Hospitalized for Coronavirus Disease 2019. *Nutrients.* 2020 Nov 28;12(12):3679.
6. Bedock D, Bel Lassen P, Mathian A, Moreau P, Couffignal J, Ciangura C, Poitou-Bernert C, Jeannin AC, Mosbah H, Fadlallah J, Amoura Z, Oppert JM, Faucher P. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. *Clin Nutr ESPEN.* 2020 Dec;40:214-219.
7. Wierdsma NJ, Kruiuzenga HM, Konings LA, Krebbers D, Jorissen JR, Joosten MI, et al. Poor nutritional status, risk of sarcopenia and nutrition related complaints are prevalent in COVID-19 patients during and after hospital admission. *Clin Nutr ESPEN.* 2021 Jun;43:369-376.

8. Barazzoni R, Bischoff SC, Busetto L, Cederholm T, Chourdakis M, Cuerda C, et al; endorsed by the ESPEN Council. Nutritional management of individuals with obesity and COVID-19: ESPEN expert statements and practical guidance. *Clin Nutr.* 2021 May 11;S0261-5614(21)00248-X.
9. Fedele D, De Francesco A, Riso S, Collo A. Obesity, malnutrition, and trace element deficiency in the coronavirus disease (COVID-19) pandemic: An overview. *Nutrition.* 2021 Jan;81:111016.
10. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al; endorsed by the ESPEN Council. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr.* 2020 Jun;39(6):1631-1638.
11. Haugen HA, Chan LN, Li F. Indirect calorimetry: a practical guide for clinicians. *Nutr Clin Pract.* 2007 Aug;22(4):377-88.
12. Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. *J Intensive Care.* 2021 Jan 12;9(1):8.
13. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr.* 2019 Feb;38(1):10-47.
14. Kruiuzenga HM, de Jonge P, Seidell JC, Neelemaat F, van Bodegraven AA, Wierdsma NJ, et al. Are malnourished patients complex patients? Health status and care complexity of malnourished patients detected by the Short Nutritional Assessment Questionnaire (SNAQ). *Eur J Intern Med.* 2006 May;17(3):189-94.
15. Sheean PM, Peterson SJ, Gomez Perez S, Troy KL, Patel A, Sclamberg JS, et al. The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment. *JPEN J Parenter Enteral Nutr.* 2014 Sep;38(7):873-9.
16. Sharma S, Danckers M, Sanghavi D, Chakraborty RK. High Flow Nasal Cannula. 2021 Jul 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;.
17. Leder SB, Siner JM, Bizzarro MJ, McGinley BM, Lefton-Greif MA. Oral Alimentation in Neonatal and Adult Populations Requiring High-Flow Oxygen via Nasal Cannula. *Dysphagia.* 2016 Apr;31(2):154-9.
18. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM et al., Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med.* 2017; 43:380–98.
19. Kogo M, et al. Enteral nutrition is a risk factor for airway complications in subjects undergoing noninvasive ventilation for acute respiratory failure. *Respir Care.* 2017;62(4):459–67.
20. Terzi N, et al. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study. *Critical care (London, England).* 2017;21(1):293–293.
21. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr.* 2019 Feb;38(1):48-79.
22. Pat Howard. Basics in clinical nutrition: Enteral nutrition. *E Spen Eur E J Clin Nutr Metab.* 2009 4:(5) e223–e225.

23. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, et al; NUTRIREA-2 Trial Investigators; Clinical Research in Intensive Care and Sepsis (CRICS) group. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet*. 2018 Jan 13;391(10116):133-143.
24. Mora-Arteaga JA, Bernal-Ramírez OJ, Rodríguez SJ. The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis. *Med Intensiva*. 2015 Aug-Sep;39(6):359-72.
25. Behrens S, Kozeniecki M, Knapp N, Martindale RG. Nutrition Support During Prone Positioning: An Old Technique Reawakened by COVID-19. *Nutr Clin Pract*. 2021 Feb;36(1):105-109.
26. Gutiérrez S, Svahn SL, Johansson ME. Effects of Omega-3 Fatty Acids on Immune Cells. *Int J Mol Sci*. 2019 Oct 11;20(20):5028.
27. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochim Biophys Acta*. 2015 Apr;1851(4):469-84.
28. Omega 3 Fatty Acids and COVID-19: A Comprehensive Review. *Infect Chemother*. 2020;52(4):478-495.
29. Fernández-Quintela A, Milton-Laskibar I, Trepiana J, Gómez-Zorita S, Kajarabille N, Léniz A, et al. Key Aspects in Nutritional Management of COVID-19 Patients. *J Clin Med*. 2020 Aug 10;9(8):2589.
30. Pradelli L, Mayer K, Klek S, Omar Alsaleh AJ, Clark RAC, Rosenthal MD, et al. ω -3 Fatty-Acid Enriched Parenteral Nutrition in Hospitalized Patients: Systematic Review With Meta-Analysis and Trial Sequential Analysis. *JPEN J Parenter Enteral Nutr*. 2020 Jan;44(1):44-57.
31. Louca P, Murray B, Klaser K, Graham MS, Mazidi M, Leeming ER, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. *BMJ Nutr Prev Health*. 2021 Apr 19;4(1):149-157
32. Kazemi A, Mohammadi V, Aghababae SK, Golzarand M, Clark CCT, Babajafari S. Association of Vitamin D Status with SARS-CoV-2 Infection or COVID-19 Severity: A Systematic Review and Meta-analysis. *Adv Nutr*. 2021 Oct 1;12(5):1636-1658.
33. Hadizadeh F. Supplementation with vitamin D in the COVID-19 pandemic? *Nutr Rev*. 2021 Jan 9;79(2):200-208.
34. Fowler AA, 3rd, Truwit JD, Hite RD. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. *JAMA*. 2019;322:1261–1270.
35. Krishnan S, Patel K, Desai R, Sule A, Paik P, Miller A, et al. Clinical comorbidities, characteristics, and outcomes of mechanically ventilated patients in the State of Michigan with SARS-CoV-2 pneumonia. *J Clin Anesth*. 2020 Dec;67:110005.
36. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiwicz J, Płudowski P, Jones G. Vitamin D Toxicity-A Clinical Perspective. *Front Endocrinol (Lausanne)*. 2018 Sep 20;9:550.
37. Pacier C, and Martirosyan D. Vitamin C: optimal dosages, supplementation and use in disease prevention. *Funct Foods Health Dis*. 2015; 5(3):89-107.

38. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. *BMJ*. 2008 Jun 28;336(7659):1495-8.
39. Friedli N, Odermatt J, Reber E, Schuetz P, Stanga Z. Refeeding syndrome: update and clinical advice for prevention, diagnosis and treatment. *Curr Opin Gastroenterol*. 2020 Mar;36(2):136-140.
40. da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al; Parenteral Nutrition Safety and Clinical Practice Committees, American Society for Parenteral and Enteral Nutrition. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutr Clin Pract*. 2020 Apr;35(2):178-195.