Marija Laban Lazović¹, Jelena Veličković^{2,4}, Marija Milenković^{3,4},
Dragana Marić^{1,4}, Bojana Aćimović⁵, Željko Garabinović⁶,
Violeta Mihailović-Vučinić^{1,4}

PREZENTACIJA I LEČENJE TEŠKIH COVID PNEUMONIJA

– aktuelna saznanja i iskustvo Jedinice intenzivne nege Klinike za pulmologiju KCS –

Sažetak: Teška COVID infekcija najčešće se prezentuje kao bilateralna pneumonija, a prema dosadašnjim saznanjima može se objasniti citokinskom olujom, izraženom hiperkoagulabilnošću i mikrovaskularnim trombozama. Bolesnici sa rizikom od lošeg ishoda su gojazni muškarci srednje životne dobi i osobe sa kardiovaskularnim i pulmološkim komorbiditetima i dijabetesom. Jedna od specifičnosti COVID 19 pneumonija jeste čest nesklad između kliničke prezentacije, radiografskog nalaza i saturacije kiseonikom. Redovan monitoring i primena skorova ranog upozorenja poboljšavaju preživljavanje i smanjuju broj hitnih prijema u jedinicu intenzivne nege. Kamen temeljac tretmana teških bolesnika čine kiseonična, antiinflamatorna i antikoagulantna terapija. Najbolji rezultati postižu se primenom visokog protoka kiseonika i neinvazivnom mehaničkom ventilacijom.

Ključne reči: COVID, pneumonija, ARDS, kortikosteroidi

Abstract: Severe COVID infection is most often presented as bilateral pneumonia and, according to current knowledge, can be explained by cytokine storm, hypercoagulability and microvascular thromboses. Patients at risk of poor outcome include obese middle-aged men and persons with cardiovascular and pulmonary comorbidities and diabetes. One of specific traits of COVID 19 pneumonias is frequent discrepancy

¹ Klinika za pulmologiju, Klinički centar Srbije, Beograd

² Klinika za digestivnu hirurgiju, Klinički centar Srbije, Beograd

³ Urgentni centar, Klinički centar Srbije, Beograd

⁴ Medicinski fakultet, Univerzitet u Beogradu

⁵ Gradski zavod za hitnu medicinsku pomoć, Beograd

⁶ Klinika za grudnu hirurgiju, Klinički centar Srbije, Beograd

between clinical presentation, radiographic findings and oxygen saturation. Regular monitoring and use of early warning scores improve survival and decrease rates of emergency admissions to intensive care units. Corner-stone of treatment of critically ill patients include oxygen, anti-inflammatory and anticoagulant therapy. Best results are obtained through administering high flow oxygen and non-invasive mechanical ventilation.

Key words: COVID, pneumonia, ARDS, corticosteroids

Uvod

Teška COVID infekcija najčešće se prezentuje kao bilateralna pneumonija, a prema dosadašnjim saznanjima može se objasniti stanjem citokinske oluje, izraženom hiperkoagulabilnošću i mikrovaskulanim trombozama. Bolesnici sa rizikom od lošeg ishoda su gojazni muškarci srednje životne dobi i osobe sa kardiovaskularnim i pulmološkim komorbiditetima i dijabetesom. Značajan broj teških bolesnika sa negativnim PCR testom ima tipičnu kliničku sliku i radiografski nalaz za COVID pneumoniju, te ih je neophodno tretirati i lečiti kao COVID. Serološki testovi (IgG I IgM) na SARS-CoV 2 se ne preporučuju za dijagnostiku i skrining (1). Kamen temeljac tretmana čine kiseonična, antiinflamatorna i antikoagulantna terapija. Kod određenog broja bolesnika mesecima zaostaju fizička slabost i jak zamor, posebno nakon produženog boravka na respiratoru.

Klinička prezentacija

Najčešća prezentacija teške COVID infekcije je bilateralna pneumonija sa respiracijskom insuficijencijom. Sistemska oblik infekcije, osim pneumonije, podrazumeva neurološke simptome, dijarealni sindrom i kardiovaskularne komplikacije. Najčešći simptom bolesti je povišena telesna temperatura. Oko 20% bolesnika ima tešku kliničku sliku, od čega oko 6% ima kritičnu bolest. Ne postoji jedan određeni parametar koji bi ukazao u kom pravcu će se bolest razvijati. Kliničko pogoršanje, pogoršanje radiografskog nalaza i produbljivanje hipoksije obično nastaje 7–12 dana od početka bolesti. Klinička slika COVID pneumonija koje se hospitalizuju u jedinicama intenzivne nege (JIN) može biti umereno teška, teška i vrlo teška – slika kritično obolelih. Bolesnici sa umereno teškom kliničkom slikom (oblik 3) mogu se hospitalizovati i u poluintenzivnim negama (PIN), uz stalni nadzor. Tešku kliničku sliku (oblik 4) imaju bolesnici sa izraženom dispnejom, visokom respiracijskom frekvencom i SaO₂ ispod 90%, dok se slika kritično obolelih karakteriše razvojem ARDS-a, multiorganske disfunkcije ili septičkog šoka.

Patofiziologija

Patofiziologija teškog COVID-a najpre se pripisuje hiperimunom odgovoru domaćina usled direktnog oštećenja ćelija i oslobađanja proinflamatornih supstanci i aktiviranja urođenog odgovora aktivacijom alveolarnih makrofaga i kaskade komplementa. Jaka proinflamatorna reakcija izaziva oštećenje alveolarnih epitelnih ćelija i vaskularnog endotela, kao i mikrovaskularne mikrotromboze, što vodi razvoju ARDS-a. Zbog toga je jedna od hipoteza razvoja ARDS-a na terenu teške COVID infekcije – tzv. MicroCLOTS – *microvascular COVID 19 lung vessels obstructive thromboinflammatory syndrome* (2). Pomenuti progresivni endotelni tromboinflamatorni sindrom može biti uključen i u promene u mikrovaskularnom koritu mozga, bubrega, creva, vodeći multiorganskoj disfunkciji i smrti (2). U odnosu na ovakvu patogenezu logičan je i pozitivan efekat antiinflamatorne i antikoagulantne terapije. Citokinska oluja (Cytokine storm syndrome, CSS) je jedan od oblika sistemskog inflamatornog odgovora domaćina na virusnu infekciju, veoma karakteristična za COVID (3). Ovakva sistemska inflamacija, kao rezultat limfocitne i monocitne infiltracije pluća i srca, može da dovede do ARDS- a i srčane insuficijencije. Zbog toga svi COVID bolesnici sa težom kliničkom slikom treba da prođu osnovni skrining u smislu citokinske oluje ili hiperinflamacije (analiza CRP, LDH, IL 6, D dimera i feritina), ukoliko za to ima uslova. Interleukin 6 (IL 6) je važan parametar za procenu težine bolesti, a jedan je i od prediktora fatalnog ishoda (4).

Imidžing

Najčešći radiografski nalaz bolesnika hospitalizovanih u jedinicama intenzivne nege je kombinacija retikularnih promena, *ground glass* opacifikacija i konsolidacija, dominantno periferno i u donjim i srednjim reznjevima pluća. Radiografsko pogoršanje obično se razvija između 6–12 dana od početka simptoma, u vidu progresije retikularnih promena i perifernih konsolidacija, do nalaza nalik ARDS-u. Radiografski nalaz često ne prati kliničko poboljšanje jer se promene sporo povlače, ostavljajući mnoge terapijske dileme, kao i dileme vezane za proces ekstubacije, odvajanje od mehaničke ventilacije ili otpust. Prema preporukama Katedre za radiologiju Medicinskog fakulteta u Beogradu, nisu indikovane svakodnevne radiografije kod stabilnih intubiranih pacijenata sa COVID-om (5). CT grudnog koša kod COVID bolesnika hospitalizovanih u JIN bio je indikovao kod kliničkog i radiografskog pogoršanja, najčešće kod sumnje na plućnu tromboemboliju, edem pluća, bakterijsku superinfekciju ili pneumotoraks, ali i za praćenje promena kod pacijenata sa sporom i nezadovoljavajućom radiografskom regresijom. Većina pacijenata hospitalizovanih u JIN imala je tipičan CT nalaz sa perifernim *ground glass* promenama i/ili konsolidacijama u donjim i srednjim reznjevima pluća.

Iskustvo

Jedna od specifičnosti COVID pneumonija jeste čest nesklad između kliničke prezentacije, radiografskog nalaza i saturacije kiseonikom. Slučajevi rapidnog kliničkog pogoršanja sa brzim prijemima u jedinice intenzivne nege doveli su do razumevanja neophodnosti redovnog praćenja i pravilne procene težine stanja bolesnika. Jedan od osnovnih kriterijuma za prijem COVID bolesnika u JIN bio je respiratorni distress (gde se pod oksigenoterapijom sa protokom 4l/ min ne može održati SaO₂ 92%, tj. PaO₂ 8,66 Kpa), zatim izražena dispnea, hemodinamska nestabilnost i značajan komorbiditet. Zbog toga se posebno insistiralo na skorovima ranog upozorenja za pacijente sa COVID 19 infekcijom. U Klinici za pulmologiju KCS korišćen je MEWS – modifikovani indeks ranog upozorenja. Nakon objektivne procene donošena je odluka o daljim postupcima - korekciji terapije, učestalijem monitoringu ili prijemu/ prevodu bolesnika u JIN ili PIN. Krucijalna stvar tokom COVID epidemije bila je dobro organizovanje jedinice intenzivne nege i formiranje uigranih timova. U Jedinici intenzivne nege Klinike za pulmologiju KCS u svakom trenutku u timu su bili istovremeno pulmolog i anesteziolog, organizovani u sedam ekipa koje su se smenjivale na 4h. Zajednički rad i ujedinjeno znanje i iskustvo imali su za rezultat veliki broj uspešno izlečenih i bolesnika odvojenih od mehaničke ventilacije. Druga važna stvar bilo je formiranje poluintenzivne nege, koju su takođe nadzirali pulmolozi i anesteziolozi, a gde su hospitalizovani teški COVID bolesnici koji nisu bili na mehaničkoj ventilaciji, ali su zahtevali neki od vidova kontinuirane oksigenoterapije i neprekidni monitoring. Formiranje PIN i u drugim COVID centrima u Srbiji kao efekat je imalo poboljšanje preživljavanja bolesnika. Specifičnost JIN i PIN Klinike za pulmologiju bio je i svakodnevni angažman fizijatara i fizioterapeuta u procesu rane rehabilitacije najtežih bolesnika. Lečenje bolesnika u JIN trajalo je u proseku tri do četiri nedelje.

Lečenje

Za bolest COVID 19 u ovom trenutku ne postoji lek i nijedna od terapijskih opcija nema potvrdu efikasnosti u randomizovanim kliničkim studijama. U odsustvu vakcine, tretman teške COVID pneumonije danas podrazumeva kombinacije postojećih antivirusnih, imunosupresivnih i imunomodulatornih lekova, simptomatsko-suportivnu i oksigenoterapiju. U Srbiji je od jula 2020. aktuelna 8. verzija terapijskog protokola za COVID-19 (6). Najznačajnija novina ove verzije je slobodnija upotreba kortikosteroida i upotreba novih antivirotika (favipiravir). Loš ishod bolesti uslovljen je jačinom upalnog odgovora, neadekvatnom procenom težine stanja bolesnika, predugom hipoksijom, zakasnelom primenom mehaničke ventilacije, gojaznošću i nezadovoljavajuće regulisanim komorbiditetima. Visok mortalitet, karakterističan za jedinice intenzivne nege i bolesnike na mehaničkoj ventilaciji koji dostiže čak 88%

i u razvijenim zemljama, nije bio odlika JIN Klinike za pulmologiju, upravo zbog neprekidnog monitoringa i pravovremenog delovanja timova (7). Pored oksigenoterapije, od početka epidemije u JIN naglasak je bio na imunosupresivnoj, pre svega kortikosteroidnoj terapiji. Primenjivane su doze 0,5–2 mg/kg TM, 5–14 dana. Postojao je stav da je rana primena kortikosteroida u početnom stadijumu ARDS-a nezamenljiva u cilju zaustavljanja citokinske oluje i daljeg napredovanja bolesti prema mehaničkoj ventilaciji. Prema najnovijim smernicama, savetuje se uvođenje kortikosteroida kod pacijenata koji imaju ARDS srednje i teške kategorije i kod pacijenata koji imaju ARDS i šok u cilju zaustavljanja kliničke i radiografske progresije umereno teške kliničke slike i izbegavanja mehaničke ventilacije. Preporučena doza metilprednizolona je 1–2 mg/kg TT, 3-5 dana (6). U slučaju septičkog šoka i insuficijencije pojedinih organa, indikovana je, takođe, njihova parenteralna primena. Porast CRP u COVID infekciji najčešće predstavlja znak izražene aktivnosti bolesti i hiperimunog odgovora, a rede bakterijske superinfekcije, te je tada indikovano u terapiju uvesti kortikosteroide, pre nego antibiotike. Pored metilprednizolona, druga terapijska opcija je deksametazon u dozi 6 mg/dan iv tokom 10 dana, prema različitim vodičima- za bolesnike sa umereno teškom ili teškom kliničkom slikom (6, 8). Kortikosteroidi (deksametazon) su jedini lekovi koji smanjuju smrtnost kod teških COVID pneumonija (9). Tocilizumab, rekombinantno monoklonsko antitelo – antagonist IL 6 receptora primenjuje se u teškoj COVID pneumoniji (oblici 3, 4, 5) u slučaju kliničke i radiografske progresije i porasta parametara zapaljenja (IL 6, D dimer, feritin) (6). Prema pojedinačnim studijama tocilizumab može redukovati rizik od invazivne MV i smrti kod bolesnika sa teškom COVID -19 pneumonijom (10). Tocilizumab je primenjivan kod COVID bolesnika u JIN, ali se klinički benefit ne može pravilno proceniti jer je primenjivan istovremeno sa kortikosteroidima. Rezultati poslednjih studija ne pokazuju jasnu korist, niti uticaj tocilizumaba na tok i ishod COVID infekcije (11,12). Od ostalih lekova i terapijskih postupaka, neki su po prvi put korišćeni u ovoj indikaciji (lopinavir-ritonavir, favipiravir, hlorokin), pa su praćene interakcije lekova i njihova neželjena dejstva. Kod bolesnika lečenih u JIN najčešća neželjena dejstva ispoljio je hlorokin. Neželjena dejstva hlorokina bila su posebno izražena kod kardioloških bolesnika i prezentovala su se poremećajima ritma (bradiaritmije) ili pogoršanjem srčane slabosti, te su i hlorokin, a kasnije i hidroksihlorokin, primenjivani veoma selektivno i kratko – bez jasnog benefita. Najozbiljnije interakcije primećene su usled istovremene primene hlorokina/hidroksihlorokina sa azitromicinom i levofloxacinom. Od juna 2020. godine hlorokin i hidroksihlorokin nemaju odobrenje za hitnu upotrebu kod teških COVID infekcija, niti dovode do kliničkog poboljšanja bolesnika sa COVID-om (13, 14). Zbog teških bilateralnih pneumonija (oblici 3, 4, 5) svi bolesnici u JIN Klinike za pulmologiju KCS lečeni su i antibiotskom terapijom, najpre prema lokalnom vodiču za vanbolničke pneumonije, a potom prema uzorcima kultura i parametrima zapaljenja. Favipiravir, jedini antivirotik u 8. verziji, preporučen je kod bolesnika sa inicijalno

teškim pneumonijama (oblik 3, 4, 5), dok je prema azijskim vodičima i najnovijim saznanjima preporučeno za blage oblike bolesti. Ima efekta ukoliko se primeni u prvih 5–7 dana od početka simptoma, što je veoma sužavalo prostor njegove primene u JIN (6, 9). Kada je reč o antikoagulantnoj terapiji, s obzirom na težinu bolesti, kod svih bolesnika u JIN primenjivane su terapijske doze niskomolekularnog heparina, uz kontrolu antiXa. Terapijske doze niskomolekularnog heparina korigovane su u odnosu na bubrežnu funkciju ili BMI (15). Pod ovakvom terapijom, nije bilo MSCT angiografijom potvrđenih plućnih tromboembolija. Zbog moguće koinfekcije sa H1N1 virusom gripa, na početku COVID epidemije primenjivan je i oseltamivir, koji nije pokazao terapijsku efikasnost kada je u pitanju COVID 19 (16).

Jedna od ključnih stvari u tretmanu teških COVID bolesnika jeste pravilna procena trenutka započinjanja neinvazivne ili invazivne mehaničke ventilacije, kao i odvajanje iste. Ukoliko je intubacija neophodna, primenjuje se protektivna plućna ventilacija, sa izbegavanjem asinhronije. Veoma važan deo lečenja je i stavljanje bolesnika u položaj potruške (*prone position*), kojim se smanjuju neželjena dejstva ventilatora, a omogućava bolji efekat i ventiliranje svih delova pluća (prema preporukama SZO kod ARDS-a položaj potruške treba primenjivati 12–16 h/dan) (17). Najkorisnijim modom NIV-a pokazao se CPAP (kontinuirani pozitivni pritisak u disajnim putevima), koji je i u JIN Klinike za pulmologiju najviše primenjivan. High Flow oksigenoterapija (HFO) sveobuhvatno je dala najbolje rezultate jer je šire korišćena od NIV, s obzirom na to da je bila pogodna i za klinička odeljenja. Oksigenacija visokim protocima kiseonika (HFO) popravljala gasnu razmenu u akutnoj respiracijskoj insuficijenciji, smanjuje disajni rad i respiracijsku frekvencu, olakšava dispneju i komforna je za pacijenta. Nakon neuspešne primene HF oksigenacije, prema iskustvima nekih centara, indikovano je odmah intubirati bolesnike. Iskustvo Klinike za pulmologiju pokazalo je povoljan efekat prelaska sa HFO na NIV, čime se, uz promene položaja bolesnika sa dominantnim položajem potruške, izbegao veći broj intubacija. Kod svih bolesnika u JIN, osim visokofebrilnih, primenjivan je restriktivni unos tečnosti (30 ml/h) uz diuretike, da bi se izbegla hipervolemija. Ishrana je podrazumevala ciljni kalorijski unos od 20 kCal/kg uz obaveznu primenu suplemenata (vitamin C i D, cink, probiotik). Među vazopresorima prvi izbor je bio noradrenalin, potom dobutamin, adrenalin i dopamin retko su primenjivani. Od anestetika najčešće su korišćeni midazolam, propofol, rokuronijum bromid, fentanil, remifentanil i dexmedetomidin.

Bakterijske superinfekcije nisu bile česte, a sepsa i dekubitalne rane značajno ređe nego kod bolesnika sa H1N1 infekcijom. Učinjeno je nekoliko terapijskih bronhoskopija, endoskopski nalaz odgovarao je kod svih bolesnika samo hiperemičnoj vulnerabilnoj sluznici, bez veće količine sekreta i gnoja.

Povišen troponin u bilateralnim teškim pneumonijama bio je najčešće marker akutnog mioperikarditisa, dok porast BNP (NT pro BNP) takođe nije tretiran kao

apsolutno specifičan za srčano popuštanje, već markerom zapaljenja i delom citokinske oluje. Znaci oštećenja kardiovaskularnog sistema u COVID infekciji prezentovali su se uglavnom kao ishemija koronarnih krvnih sudova, mioperikarditis ili poremećaj ritma. Posledice oštećenja ovog sistema ostaju najduže prisutne, i nakon otpusta bolesnika značajno ograničavaju njegovu funkcionalnost, više nego plućna oštećenja i komplikacije. Najpreciznije metode koje omogućavaju procenu težine COVID-a nakon završenog lečenja su MSCT grudnog koša, difuzijski kapacitet pluća za CO, UZ i MR srca.

Zaključak

Za COVID infekciju u ovom trenutku ne postoji efikasan lek. U odsustvu vakcine, čini se da su oksigenoterapija, kortikosteroidi i antikoagulansi najvažniji lekovi koji dovode do povoljnog ishoda. Dovoljan broj dobro edukovanog medicinskog kadra, pravilna procena započinjanja adekvatne terapije, fizikalna rehabilitacija, nega i psihološka podrška omogućavaju zadovoljavajući oporavak velikog broja teških COVID bolesnika.

Nekoliko dana pre upućivanja rada u časopis objavljena je 9. verzija Protokola za lečenje COVID infekcije u Srbiji. Najznačajnije promene u odnosu na 8. verziju odnose se na antikoagulantnu terapiju i izostanak preporuka za hlorokin.

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Marija Laban Lazović¹, Jelena Veličković^{2,4}, Marija Milenković^{3,4},
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Violeta Mihailović-Vučinić^{1,4}

PRESENTATION AND TREATMENT OF SEVERE COVID PNEUMONIA

– Current Knowledge and Experiences of Intensive Care Unit of the Clinic of Pulmonology, Clinical Center of Serbia –

Abstract: Severe COVID infection is most often presented as bilateral pneumonia and, according to current knowledge, can be explained by cytokine storm, hypercoagulability and microvascular thromboses. Patients at risk of poor outcome include obese middle-aged men and persons with cardiovascular and pulmonary comorbidities and diabetes. One of specific traits of COVID 19 pneumonias is frequent discrepancy between clinical presentation, radiographic findings and oxygen saturation. Regular monitoring and use of early warning scores improve survival and decrease rates of emergency admissions to intensive care units. Corner-stone of treatment of critically ill patients include oxygen, anti-inflammatory and anticoagulant therapy. Best results are obtained through administering high flow oxygen and non-invasive mechanical ventilation.

Key words: COVID, pneumonia, ARDS, corticosteroids

Introduction: Severe COVID infection is most frequently presented as bilateral pneumonia and, according to current knowledge, can be explained by cytokine storm, hypercoagulability and microvascular thromboses. Patients at risk of poor outcome include obese middle-aged men and persons with cardiovascular and pulmonary comorbidities and

¹ Clinic for Pulmonology, Clinical Center of Serbia, Belgrade

² Clinic for Digestive Surgery, Clinical Center of Serbia, Belgrade

³ Emergency Care Center, Clinical Center of Serbia, Belgrade

⁴ University of Belgrade Medical School, Belgrade

⁵ City Institute for Emergency Medical Aid, Belgrade

⁶ Clinic for Thoracic Surgery, Clinical Center of Serbia, Belgrade

diabetes. A significant number of critical patients with negative PCR test have typical clinical picture and radiographic findings of COVID pneumonia, and therefore require to be treated as COVID patients. Serologic testing (IgG and IgM) for presence of SARS-CoV-2 antibodies is not recommended for diagnostics and screening (1). Corner-stone of treatment of critically ill patients include oxygen, anti-inflammatory and anticoagulant therapy. Certain number of patients suffers from physical weakness and severe fatigue for months, particularly after prolonged ventilation.

Clinical presentation

Severe COVID infection is most often presented with bilateral pneumonia with respiratory insufficiency. Systemic form of the infection, apart from pneumonia, includes neurological symptoms, diarrheal syndrome and cardiovascular complications. Most common symptom is high body temperature. Approximately 20% of patients develop severe clinical picture, and 6% of them get critically ill. There is no single parameter that would predict the course of the disease. Clinical deterioration, worsening of radiographic findings and aggravated hypoxia usually occur within 7-12 days from the onset of the disease. Clinical picture of patients with COVID pneumonias hospitalized in intensive-care units (ICU) can be moderately severe, severe and very severe – in case of critically ill. Patients with moderately severe clinical picture (form 3) can also be admitted to semi-intensive-care units (SICU), with permanent monitoring. Severe clinical picture (form 4) include serious dyspnea, high respiratory frequency and SaO₂ below 90%, while the picture of critically ill is characterized by onset of ARDS, multiple organ dysfunction or septic shock.

Pathophysiology

Severe COVID pathophysiology is primarily attributed to the hyperimmune response of the host due to direct cell damage, release of proinflammatory substances and activation of innate response of activating alveolar macrophages and complement cascades. Strong proinflammatory response causes damage to alveolar epithelial cells and vascular endothelium, as well as microvascular micro-thromboses, which lead to the development of ARDS. Therefore, one of the hypotheses explaining development of ARDS in severe COVID infections points to so-called MicroCLOTS – *microvascular COVID 19 lung vessels obstructive thrombo-inflammatory syndrome* (2). Progressive endothelial thrombo-inflammatory syndrome may also be involved in changes of microvascular bed of the brain, kidneys, and intestines, leading to multiorgan dysfunction and death (2). With such pathogenesis, it is logical that anti-inflammatory and anti-

coagulant therapies are beneficial. Cytokine storm (Cytokine storm syndrome, CSS) is one of the forms of systemic inflammatory response of the host to viral infection, very typical of COVID (3). Such systemic inflammation, resulting from infiltration of lymphocytes and monocytes into lungs and heart, can lead to ARDS and cardiac insufficiency. Therefore all COVID patients with severe clinical picture should, if possible, undergo basic screening related to cytokine storm or hyperinflammation (CRP analysis, LDH, IL 6, D-dimer and ferritin). Interleukin 6 (IL 6) is significant parameter for assessing severity of the disease, and is also one of the predictors of lethal outcome (4).

Imaging

Most common radiographic findings in patients admitted to intensive-care units are combination of reticular changes, *ground glass* opacifications and consolidations, predominantly peripheral and in lower and middle lung lobes. Radiographic deterioration usually develops 6 to 12 days from the onset of symptoms, ranging from progression of reticular changes and peripheral consolidations to ARDS-like findings. Radiographic finding often lag behind clinical improvements, since changes recede slowly, leaving many therapy related dilemmas, as well as those related to the process of extubation, weaning of mechanical ventilation or discharge from the hospital. According to the recommendations of the Radiology Department of the Belgrade Faculty of Medicine, there are no indications for daily radiography of stable intubated COVID patients (5). Thoracic CT in COVID patients hospitalized in ICU was indicated in case of clinical and radiographic deterioration, mostly in cases of suspected pulmonary thromboembolism, pulmonary edema, bacterial superinfections or pneumothorax; also for the purpose of monitoring changes in patients with slow and unsatisfactory radiographic regression. Most patients in ICU had typical CT findings of peripheral *ground glass* changes and/ or consolidations in lower and middle lung lobes.

Experience

One of specific traits of COVID 19 pneumonias is frequent discrepancy between clinical presentation, radiographic findings and oxygen saturation. Cases of rapid clinical deterioration with emergency admissions to intensive-care units led to the understanding of the need for regular monitoring and proper assessment of the severity of condition. Some of the main criteria for admission of COVID patients into ICU was respiratory distress (when oxygen flow of 4 l/min cannot sustain SaO₂ at 92%, i.e. PaO₂ 8,66 Kpa), severe dyspnea, hemodynamic instability and significant comorbidity. Therefore a special emphasis was on early warning scores in patients

with COVID 19. In the Clinic for Pulmonology of Clinical Center of Serbia we used MEWS – Modified Early Warning Score. After objective assessment, a decision was made on further treatment – correction of therapy, more frequent monitoring or admitting/moving patients to ICU or SICU. Crucial thing during COVID epidemic was to the good organization of ICU and forming well-coordinated teams. In the Intensive Care Unit of the Clinic of Pulmonology of CCS at all times we had both pulmonologist and anesthesiologist on the team, organized in seven teams working 4-hour shifts. Joint work, knowledge and experience have resulted in a number of successfully cured and patients separated from mechanical ventilation. Another important thing was to form semi-intensive care unit, also under the supervision of pulmonologists and anesthesiologists, where we accommodated severe COVID patients without mechanical ventilation, but still requiring some form of continual oxygen therapy and permanent monitoring. Forming SICU in other COVID centers in Serbia also resulted in improved survival of patients. Another characteristic of ICU and SICU of Clinic of Pulmonology was daily engagement of physiatrists and physiotherapists in the process of early rehabilitation of patients with the most severe forms of the disease. Treatment of patients in ICU averagely lasted from three to four weeks.

Treatment

At the moment there is no cure for COVID 19 whatsoever, and none of the therapeutic options has been confirmed as efficient in randomized clinical studies. Since there is no vaccine, severe COVID pneumonia is currently treated with combination of existing antiviral, immunosuppressant and immunomodulatory medication, symptomatic-supportive and oxygen therapy. As of July 2020 in Serbia has been used the current 8th version of the treatment protocol for COVID-19 (6). The most significant novelty of this version is more liberal use of corticosteroids and use of new antiviral medication (favipiravir). Poor outcome is due to the severity of inflammatory response, inadequate assessment of the severity of patient's condition, prolonged hypoxia, delayed initiation of mechanical ventilation, obesity and inadequately treated comorbidities. High mortality rate, typical for intensive-care units and mechanically ventilated patients, reaching up to 88% even in developed countries, was not the case in the Intensive Care Unit of the Clinic of Pulmonology, and the reasons were permanent monitoring and timely team work (7). Apart from oxygen therapy, the emphasis in our ICU from the very beginning of epidemics has been on immunosuppressive, above all corticosteroid therapy. Doses were 0,5–2 mg/kg of body weight, for 5 to 14 days. Early administration of corticosteroids, in the initial stage of ARDS, has been considered irreplaceable for stopping cytokine storm and further progression of the disease toward mechanical ventilation. According to the latest guidelines, it is recommended to administer corticosteroids to patients having moderate and severe ARDS and patients with ARDS

and shock, in order to stop clinical and radiographic progression of the moderately severe clinical picture and to avoid mechanical ventilation. Recommended dose of methylprednisolone is 1-2 mg/kg of body weight, for 3 to 5 days (6). Its parenteral use is also indicated in case of septic shock and some organ insufficiency. Elevated CRP in COVID infection most often indicates highly active disease and hyper-immune response, and seldom is an indicator of bacterial superinfection. Therefore it indicates introducing corticosteroids, rather than antibiotics. Another option, beside methylprednisolone, is dexamethasone, 6 mg/kg of body weight intravenous for 10 days, in patients with moderately severe or severe clinical picture, depending on different guidelines (6, 8). Corticosteroids (dexamethasone) are the only medications that do decrease mortality in severe COVID pneumonias (9). Tocilizumab, a recombinant monoclonal antibody, IL-6 receptor antagonist, is used in severe COVID pneumonias (forms 3, 4, 5) in case of clinical and radiographic progression and elevation of parameters of inflammation (IL 6, D-dimer, ferritin) (6). According to some studies, tocilizumab can reduce the risk of invasive mechanical ventilation and death in patients with severe COVID – 19 pneumonia (10). Tocilizumab was administered to COVID patients in ICU, but clinical benefit cannot be adequately assessed, since it was used together with corticosteroids. Yet, most recent studies show neither clear benefits, nor influence of tocilizumab on the course and outcome of COVID infection (11, 12). Out of other medications and treatment procedures, some were used for the first time for this indication (lopinavir – ritonavir, favipavir, chloroquine) and drug interactions and their side effects were followed. Among patients treated in ICU most frequent side effects were observed in case of use of chloroquine. Side effects of chloroquine were particularly pronounced in patients with cardiac diseases, and were presented as arrhythmias (bradyarrhythmias) or worsened heart insufficiency, so chloroquine, and later hydroxychloroquine too, were used very selectively, shortly and with no clear benefits. Most serious interactions were observed due to simultaneous use of chloroquine / hydroxychloroquine and azithromycin and levofloxacin. Since June 2020 chloroquine and hydroxychloroquine have not been approved for use against severe COVID infections, because they brought no clinical improvements for COVID patients (13, 14). All patients in ICU of the Clinic of Pulmonology of CCS with severe bilateral pneumonias (forms 3, 4, 5) also received antibiotics, first according to the local guidelines for community-acquired pneumonias, and then in accordance with culture samples and inflammation parameters. Favipavir, the only antiviral drug in 8th version, is recommended for use in patients with initially severe pneumonias (form 3, 4, 5), while Asian guidelines and the most recent findings recommend it for mild forms of the disease. It is effective if used within the first 5–7 days from the onset of symptoms, which substantially narrows the scope of its use in ICU (6,9). When it comes to anticoagulant therapy, due to severity of the disease in all patients in ICU, therapeutic doses of low molecular weight heparin were used, with monitoring of

anti-xa. Therapeutic doses of low molecular weight heparin were adjusted to renal function or BMI (15). MSCT angiography confirmed no lung thromboembolisms with this kind of treatment. Due to possible co-infections with flu virus H1N1, oseltamivir was also used at the beginning of COVID epidemics, but demonstrated no therapeutic efficiency when it comes to COVID 19 (16).

One of crucial elements of the treatment of severely ill COVID patients is proper assessment of the moment of initiation of non-invasive or invasive mechanical ventilation, as well as of separation from it. If the intubation is necessary, lung-protective ventilation was used, avoiding asynchrony. Very important part of the treatment was prone positioning of patients, which reduces adverse effects of ventilation and enables better efficiency and ventilation of all parts of lungs (WHO recommends prone positioning of patients with ARDS for 12-16 hours a day) (17). CPAP (continuous positive airway pressure) was proven to be the most useful method of non-invasive ventilation, and it was used the most in the ICU of Clinic of Pulmonology. High flow oxygen therapy (HFO) in total provided the best results, since it was more extensively used than NIV, because it could be used at other wards too. High flow oxygenation improves gas exchange in acute respiratory insufficiency, decreases work of breathing and respiratory rate, relieves dyspnea and is comfortable for patients. According to experiences of some centers, if high flow oxygen therapy fails, it is indicated to intubate patient right away. Experience of the Clinic of Pulmonology showed positive effect of switching from HFO to NIV, which, together with changing position of patients, with prevailing prone position, helped to avoid higher rate of intubations. In all patients in ICU, except in highly febrile patients, fluid intake was restricted (30 ml/h), along with administration of diuretics, in order to avoid hypervolemia. Their diet consisted of target caloric intake of 20 kCal/kg, including mandatory use of supplements (vitamin C and D, Zinc, probiotics). First choice vasopressor was noradrenaline, then dobutamine, while adrenalin and dopamine were rarely used. Most frequently used anesthetics were midazolam, propofol, rocuronium bromide, fentanyl, remifentanyl and dexmedetomidine.

Bacterial superinfections were infrequent, and sepsis and decubital wounds significantly less frequent than in patients with H1N1. Several therapeutic bronchoscopies were performed and endoscopic findings in all patients showed only mucosal hyperemia and vulnerability, without significant quantities of secretions and pus.

Elevated troponin in severe bilateral pneumonias was most usually a marker of acute myopericarditis, while elevation of BNP (NT pro BNP) wasn't treated as absolutely specific marker of heart failure, but as marker of inflammation and cytokine storm. Signs of damage to the cardiovascular system in COVID infection presented mostly as coronary ischemia, myopericarditis or arrhythmias. Most long-lasting are these consequences of damage to the cardiovascular system, persisting even after patients get discharged, more than pulmonary damage and complications. Most accurate methods for assessing severity of COVID infection after the completion of

treatment are thoracic MSCT, diffusion capacity of the lungs for CO, and ultrasound and magnetic resonance of the heart.

Conclusion

There is no effective cure for COVID infection at the moment. Since there is no vaccine, it seems that oxygen therapy, corticosteroids and anticoagulants are the most important therapies leading to favorable outcome. Sufficient number of well-educated medical personnel, proper assessment of timely initiation of adequate therapy, physical rehabilitation, care and psychological support make satisfactory recovery of a large number of severe COVID patients possible.

A few days before the article was sent to the journal, the 9th version of the Protocol for the treatment of COVID infection in Serbia was published. The most significant changes compared to version 8 relate to anticoagulant therapy and the lack of recommendations for chloroquine.

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