Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments

Boban, Marko

Received: 29 April 2020 | Accepted: 22 November 2020

DOI: 10.1111/ijcp.13868

NON-SYSTEMATIC

GENERAL/SURGERY/INTERNAL

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments

Marko Boban[1,2,3,4]

[1]Sisters of Charity" University Hospital, Zagreb, Croatia

[2]Faculty of Dental Medicine and Health, Osijek, Croatia

[3]Medical Faculty, University of Rijeka, Rijeka, Croatia

[4]Medical Faculty, University of Osijek, Osijek, Croatia

Correspondence
Marko Boban, Department of Cardiology and Internal Medicine, "Sisters of charity" University Hospital, Vinogradska 29, Zagreb 10 000.
Email: marcoboban@yahoo.com

Abstract

During the December of 2019, a series of patients with pneumonia caused by novel coronavirus; the severe acute respiratory syndrome (SARS) corona (COV-2), that is, COVID-19. Since the first cluster of cases was reported in China on 31 December 2019 until the 28 April 2020, there were internationally reported 3'000'000 cases, in over 185 countries, and 207'265 deaths. To date, it is still not unanimously clear which effects parameters of virus and host are important for the development of severe disease course. According to the most updated internationally available online cases register, COVID-19 disease has mild symptoms in around 85% of cases, there are 3%-10% of critical cases, and mortality is around 5%-7%. Since currently there is no available vaccine and no well-established specific antiviral therapy, numerous agents are being tested in clinical scenarios. The most common regimens include remdesivir, convalescent plasma. Widely used chloroquine, hydroxychloroquine and azithromycin combinations, as well as lopinavir-ritonavir were shown to have less efficient treatment effects. More severe cases of pneumonia and dyspnoea, or uncontrollable fever are treated as inpatients, and nearly 10% in intensive care units. Oxygen supplementation is indicated to maintain peripheral blood oxygenation over 90%-96%. Advanced support systems include mechanical ventilation and extracorporeal membranous support; however, those without targeted antiviral therapy represent only temporary bridge for scarce potential restitution in patient themselves. The aim of review is to present current state of the art in epidemiology, pathogenesis, clinical course and treatment of COVID-19 patients.

1 | INTRODUCTION

During the December of 2019, a series of patients with pneumonia of unknown cause occurred in Wuhan, province Hubei, China.[1,2] Those were later confirmed to be caused by the novel coronavirus; the severe acute respiratory syndrome (SARS) corona (COV-2), that is, COVID-19.[2] Human coronaviruses mostly cause mild respiratory illnesses, with the exception of SARS and Middle East respiratory syndrome (MERS). The first case of SARS appeared in Guangdong province China in November 2002 and there were 305 cases on 11 February, and 792 cases and 31 deaths on 21 March, totalling 5327 and 349 deaths at the end of epidemic cycle in China.[3] The first cases reported in Hong Kong were noted in February 2003[3] and in about 29 other countries totalling globally to 8422 patients and 916 deaths.[3] MERS emerged in Saudi Arabia in 2012, and until the 2018

there were 2206 (1831 in Saudi Arabia) cases with mortality of 787 (35.7%).[4]

Since the first cluster of cases was reported in China on 31 December 2019, COVID-19 virus was isolated on 7 January 2020, there were 41 cases and one death on 11 January 2020.[2] The World Health Organization (WHO) issued Practical traveller advices for international transporters on 10 January 2020; Declared the outbreak to be a Public Health Emergency of International Concern on 30 January 2020 (11'950 cases of infection in 27 countries, 259 deaths), and categorised it as a pandemic on 11 March 2020 (126'214 cases of infection in 126 countries, 4'628 deaths).[5,6] As of 27 April 2020, there were 3'013'803 cases in over 185 countries, and 207'894 deaths.

Coronaviridae family is a large group of animal and human viruses made up from single-stranded RNA. COVID-19 is member of sarbecovirus sub-genus, beta-coronavirus, phylogenetically closely related (88%) with two bat-derived SARS-like coronaviruses from Zhoushan, China in 2018; a bit less concordant with SARS-CoV (79%) and MERS-CoV (50%).[7] Similar to other coronaviruses, COVID-19 has four structural proteins spike(S); membrane (M); envelope (E) and nucleocapsid (N). S protein has close resemblance with angiotensin-converting enzyme 2 (ACE-2) receptor on human cells and was confirmed as a receptor for SARS-CoV-2, that is, COVID-19.[8] ACE-2 receptor is abundantly found on respiratory epithelial cells,[9] arterial smooth muscle cells, arterial and venous endothelial cells, as well as in myocardial pericytes, capillary endothelial cells and intramyocardial microvascular network.[10-12] Due to these particular cell localisations, concordance with COVID-19 predilection organ systems impairments of the endothelial function meaningfully intermediates clinical course. In addition, this is supported with clinical observation of generally worsened course in patients with preexisting comorbidities, particularly cardiovascular, respiratory, metabolic and cancerous diseases.[13] The aim of this review is to present contemporary state of the art around epidemiology, pathogenicity clinical course and treatments of COVID-19 patients worldwide.

2 | METHODS

Methodological issues around narrative review in regard to novel coronavirus disease are currently exceedingly challenging and those will be cautiously presented in order to point out potential blind spots. Due to the fact that the ongoing pandemic of COVID-19 is of total existence for only a few months, there are numerous limitations in currently available studies and practices. From first characterisation of novel virus in January 2020, until the WHO recognised global epidemic in March 2020, and including the time to the present day, there has been less than 5 months of any data considering the novel disease. Reports on spread of the virus, rate of transmission, incubation periods and prevalence of various clinical entities of COVID-19 disease were changed several times, as the pace of epidemic was outspread in Wuhan, China, to ongoing global pandemics in other countries, particularly Italy, Spain and UK, and to date, the most serious geographical outburst of cases in the United States and Russian federation. Baseline health response was grounded on a set of practices which was as close as possible to earlier known disease entities. For this reason, some initial treatment strategies and salvage therapies were only rather recently shown to be less effective. To the best of authors knowledge, to date, even a single study of prospective randomised controlled settings is not available. The most relevant limitation is concealed in the homogeneity of reporting, study settings and primer outcomes. One must take into notion, that the latter is due to highly variable organisational settings of healthcare systems (including the reporting of the single hospital, sets of hospitals within some local network, through local, regional or national health authorities), local threshold for hospitalisation, variable proportion of critically ill patients, availability of intensive care unit beds, different extent of epidemiologic lockdown in different countries with a high diversity of clinical presentations and reporting of the of cases.

Nevertheless, substantial effort was made around collecting and selecting the most relevant data to date. This narrative review focused mostly on the data from the national library of medicine (PUBMED) under the search terms of COVID-19, last search 27 April 2020 (and all available synonyms, mentioned previously) combined with various entities discussed in the text. Secondary resources included one study from pre-print servers (https://www.medrxiv.org/), last search 27 April 2020, with notion of non-peer review status; and continuously updated international "Worldmeters" database on reported cases and status of COVID-19 pandemic globally (https://www.worldometers.info/coronavirus/#countries), last search 27 April 2020. Ranking of studies was made using evidence-based principles and available evidence of highest rank was selected.[14] Epidemiologic data on disease life cycle and clinical presentations were obtained from mostly retrospective case series. Reports of the various disease entities in terms of hospitalisations were also presented from larger case studies and multicentric case series, as initial reports from China, Italy and United states. The treatment part included the most utilised antiviral drug regimens, with the largest available study of satisfactory settings, or the most relevant information (1 study from pre-print server about two commonly used drug regimens, where cases-based studies were of non-unanimous findings), treatment on currently the most efficient drug was dominantly made on basis on one multicentric non-randomised study on subgroup of critical cases, with add on several case-based reports, using this drug in other settings. Some treatments, that were shown to be highly promising, like convalescent plasma treatment, were only presented as reports on various cases series, due to the fact that there is no available study of higher rank of evidence. Statements on utilisation of supportive measures and non-direct antiviral therapeutics, were presented from experiences in reported case series, or endorsement by relevant supranational organisations and societies (as American heart association, European society for cardiology or International society for hypertension).

2.1 | COVID-19 spectrum of clinical presentation

Human to human transmission was confirmed rather early from COVID-19 discovery.[15] Modes of spread are similar to other respiratory viruses and typically include close contacts, via respiratory droplets, produced by sneezing, coughing or even breathing and talking, with initial basic reproductive number of transmissions estimated to be 2.2-3.9.[16,17] Incubation period was found to be for most of the cases on average between 3 and 5 days, with interval range from 2 days to 2 weeks.[18] Symptomatic patients typically emerge with fever, malaise, nasal congestion, dyspnoea and cough from 4-7 day.[18] Other types of clinical presentation include anosmia, sore throat, fever, muscle weakness, tiredness, headache and diarrhoea.[19] Viral pneumonia develops from day 5 to second or third week, with radiologic signs of ground glass appearance, bilateral patchy consolidation, alveolar exudates and interlobular involvement, with hypoxaemia depending on the clinical severity. In case of worsening patient can develop severe acute respiratory syndrome, multiorgan failure and if does not manage to cope with viral disease eventually dies. Particularly underprivileged clinical course with high mortality happens in the case of cytokine storm, in which unscaled and disproportionally high immune response uncontrollably emerges to level of burst, as a consequence of response to external factor as COVID-19.[20] Laboratory tests, besides the confirming gene or antibody testing are changed in unspecific manner, presenting with lymphocytopenia, leukopenia, thrombocytopenia, increased levels of c-reactive protein, d-dimers, liver enzymes or signs of myocardial lesion.[21]

2.2 | Hospitalised and critically ill patients

To date, it is still not unanimously clear which parameters of the virus and host are important for the development of severe disease course. Viral load of initial infection, genetic background of host, acquired conditions, however, the most prominent are perplexed relations of age with/or comorbidities, also considering the connection existing between the two.[22,23] The most common clinical course of more severe disease is the worsening of dyspnoea and the development of hypoxia in relation with pneumonia. Guan et al reported on 1099 hospitalised patients (age range 35-58) in January 2020, from 550 hospitals in China with 5% of cases being admitted to intensive care units(ICU), 2.3% need mechanical ventilation and 1.4% of patients died, with cumulative prevalence of primary endpoint in 6.1% (32109013). Interestingly, 41.3% of patients received oxygen therapy, 6.1% were on mechanical ventilation and 0.5% had extracorporeal membrane oxygenation (ECMO).[24] Patients with severe disease course were generally older (52 vs. 45 years), one-third of them had one or more chronic comorbidities like hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease and cancer.[24] From baseline cluster of 41 patients (age 25-64, median 49) with pneumonia from Wuhan, China, 32% of patients had to be treated in ICU, ARDS developed in 29%, myocardial injury in 12%, secondary infections emerged in 10%, and six patients, that is, 15% had died.[2] Grasselli et al reported on 1591 consecutive COVID-19 patients hospitalised in intensive care units within a network of 72 hospitals from Lombardy, Italy, for a period between 20 February 2020 and 18 March 2020.[6] Reported patients from Italy were older than in previous reports from China, 63 (56-70) years, 1304 (82%) were male, 709/1043 (68%) had at least one comorbidity and 509 (49%) had hypertension.[6] Most of the patients needed respiratory support 1287/1300 (99%), of which 137 (11%) had non-invasive support and 1150 (88%) had mechanical respiratory support. During follow-up, which was close to 1 month, only 256 (16%) were discharged, while 920 patients (58%) stayed in the ICU, and 405 (26%) had died (36% mortality rate for patients older than 64).[6] So far, the largest case series of COVID-19 hospitalised patients was in study by Richardson et al from 12 New York hospitals in period between 1 March and 4 April 2020, which included data on 5700 patients, median age was 63 years; 39.7% female.[25] The most common comorbidities were hypertension (3026; 56.6%), obesity (1737; 41.7%) and diabetes (1808; 33.8%).[25] The number of patients treated in ICU was 373 (14.2%); mechanical invasive ventilation was performed in 320 (12.2%) and total death toll in studied period 553 (9.7%).[25] The effects of mechanical ventilation, due to the narrow timeline of study could hardly be estimated, with 831 (72.2%) persisted in hospital; 38 (3.3%) were discharged alive and 282 (24.5%) died.[25]

2.3 | COVID-19 treatments and supportive measures

Due to the fact that currently there is no available vaccine and no well-established specific antiviral therapy, numerous agents are being tested in clinical scenarios. Milder clinical presentations are treated as quarantined outpatients similar to common flu, with antipyretics, non-steroidal anti-inflammatory drugs, resting and rehydration. In case of more severe course, uncontrollable fever, profound dyspnoea or other high-risk associated factors more optimal treatment actions could be rehearsed only in hospitals. Pronounced dyspnoea and/or hypoxia, mostly due to complications of pneumonia is being treated with oxygen supplementation via nasal catheters/masks and other modalities discussed in more detail after the common drug regimens.

Remdesivir is a nucleotide analogue prodrug that is metabolised to analogue of adenosine triphosphate and inhibits viral RNA polymerases. Remdesivir was being developed for epidemiologically high-risk viral illnesses like Ebola, Marburg and Nipah; however, it was also found to have effects on other RNA viruses, especially Coronaviridae family including SARS-CoV, MERS-CoV and COVID-19.[15,26] The most voluminous current study was by Grein et.al. reported on th ecompassionate use of Remdesivir in 61 patients, of which 53 had full follow-up.[27] Patients had severe COVID-19 infection and blood oxygen saturation ≤94% on ambiental air or respiratory support, with 34 patients on invasive ventilation modalities vs 19 on non-invasive respiratory support.[27] Improvement of oxygen

support was documented in 36 of 53 patients (68%), including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated; 25 patients (47%) were discharged.[27] During the study course, seven patients (13%) died; mortality was higher in patients with invasive ventilation vs. controls; 18% (6 of 34) vs. 5% (1 of 19), respectively.[27] Other studies reported on clinical improvement of cases, as in three of five users in ECMO patients.[28] Eventhough currently there is a general lack in prospective randomised studies, Remdesivir still shows very promising results. One must not disregard the fact that it was only being used in patients with advanced, clinically more severe disease, in which the potential for full recovery might also be limited. Further studies, on larger sample sizes, different COVID-19 stages and patients profile, with additional scenarios would be necessary to finalise its position in treatment of COVID-19, particularly around length of stay, viral titre dynamics, radiological restitution, need for ICU, mortality, potential for outpatient management in daily care.

Convalescent plasma treatment using antibodies of COVID-19 survivors was applied in several studies, dominantly in case-based settings. Shen et al reported on convalescent plasma utilisation in five critically ill patients with ARDS on mechanical ventilation (age range, 36-65 years; 2 women).[29] Fever normalised in 3 days in four of five patients, the SOFA score decreased, and Pao2/Fio2 increased within 12 days, Viral titre turned negative in 12 days, ARDS resolved in four patients at 12 days, and three patients were taken off mechanical ventilation within 2 weeks of treatment. Three patients were discharged from the hospital (length of stay: 53, 51 and 55 days), and two were in a stable condition at 37 days after transfusion.[29] Duan et al included 10 clinically severe COVID-19 patients (age range 34-78 years, six male, four with comorbidities) who received single dose of 200 mL convalescent plasma derived from donors with the neutralising antibody titres above 1:640 as an addition to maximal supportive care and antiviral agent.[30] There were no severe adverse reactions to application of convalescent plasma, radiologic examinations showed various degree of resolution of the lesions within 7 days, symptoms meaningfully improved in 3 days, and viral load was negativised to undetectable in seven patients. Zhang et al reported on major clinical improvement of all four critically ill patients, with important comorbidities (age 69, 55, 72 and 31) treated with convalescent plasma.[31] Ye et al reported on six COVID-19 patients from Wuhan, China, where all but one patient increased concentration of antibodies, while the remaining patients showed improvements in terms of resolution of ground glass opacities and consolidation in five of six patients, and viral clearance for two patients.[32]

Chloroquine, *hydroxychloroquine and azithromycin* combinations. These permutations of drugs have yielded some popularity and potential for promising treatment; however, there are some controversies and divergences among studies and conclusions. Several in vitro-based studies reported on suppressive effects of hydroxychloroquine, chloroquine (in combination with Remdesivir) on COVID-19.[15,33] Gautret et al reported uncontrolled non-comparative observational study in a cohort of 80 relatively mildly infected COVID-19 in patients treated with a combination of hydroxychloroquine and azithromycin over a period of at least 3 days.[34] Authors reported on a rapid fall of nasopharyngeal viral burden, with 83% negative at Day 7, and 93% at Day8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day 5.[34] Similar results were also published by group of Gautret et al on 36 patients who were asymptomatic, and signs of upper or lower respiratory infection, with similar primer objectives, study settings and results.[35] Both studies are importantly limited with several issues as settings, primer outcomes, statistical analyses and interpretation. A study by Magagnoli et al reported on retrospective analysis of data from patients hospitalised with confirmed COVID-19 infection in all United States Veterans Health Administration medical centres. In this preliminary report, without peer review 368 patients were evaluated (HC, n = 97; HC + AZ, n = 113; no HC, n = 158). Rates of death in the HC, HC + AZ, and no HC groups were 27.8%, 22.1%, 11.4% respectively. Rates of ventilation in the HC, HC + AZ, and no HC groups were 13.3%, 6.9%, 14.1% respectively. Compared to the no HC group, the risk of death from any cause was higher in the HC group (adjusted hazard ratio, 2.61; 95% CI, 1.10 to 6.17; $P = .03$) but not in the HC + AZ group (adjusted hazard ratio, 1.14; 95% CI, 0.56 to 2.32; $P = .72$). The risk of ventilation was similar in the HC group (adjusted hazard ratio, 1.43; 95% CI, 0.53 to 3.79; $P = .48$) and in the HC + AZ group (adjusted hazard ratio, 0.43; 95% CI, 0.16 to 1.12; $P = .09$), compared to the no HC group. Authors concluded on no existing evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalised with COVID-19. An association of increased overall mortality was identified in patients treated with hydroxychloroquine alone.

Combination of *lopinavir-ritonavir* drug regimen seemed only theoretically promising; however, several studies are shown to not be of satisfactory efficiency and associated with side effects. In a study by Cao et al which was prospective randomised controlled, open-label trial involving hospitalised adult critically ill patients with confirmed COVID-19 infection, and an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg in 50:50 arms of lopinavir-ritonavir (400 and 100 mg, respectively) vs standard of care.[36] Regimen lopinavir-ritonavir was similar to standard of care in the time to clinical improvement; mortality at 28 days (19.2% vs 25.0%); viral concentrations at different control points were also similar. Furthermore, lopinavir-ritonavir was found not to be efficient in terms of short duration of SARS-CoV-2 shedding in patients with mild pneumonia.[37] Summary of previous studies in a review report by Ford et al found no well-established benefits of lopinavir-ritonavir combination in serious human coronavirus infections.[38]

Il-6 monoclonal antibodies were introduced to treatment of COVID-19-associated cytokine release syndrome and so far, were only used in several case series around the world, generally with a somewhat positive experiences.[23,39] Luo et al reported on use of 15 COVID-19 patients, where treatment decreased inflammatory

proteins CRP and Il-6; however, four patients were resistant to this treatment and three eventually died.[40]

Use of *renin angiotensin aldosterone antagonists* like ACE inhibitors and sartans is generally recommended to be continued, which was in terms of safety endorsed by all cardiac societies, among which are American Heart association, European society for cardiology, International Society of Hypertension and others. Commonly known side effects and compelling indications are still determined on a case-to-case bas-s, as with development of renal failure, hyperkalaemia, dehydration and others. *Statins* are also considered safe, and those exhibit important preventive effects on the prevalence of atherosclerosis, stabilisation of atherosclerotic plaques and recovery of endothelial dysfunction.[41] Thrombogenicity is frequent in patients with COVID-19, due to immobility, vascular stasis, endothelial lesions, cytokine actions and systemic inflammatory response in ARDS or sepsis, so thromboprophylaxis is generally recommended among hospitalised, particularly ICU treated patients.[42,43] To date, it is not clear whether novel direct anticoagulant drugs have safe profile in the circumstances of COVID-19. Testa et. al. reported on significant increase in DOAC concentrations, possibly as a consequence of antiviral treatments, with no reported clinical bleeding outcomes; however, there is precautionary recommendation of this group about stopping the drugs and switching to low molecular weight heparin, at least during the hospitalisation.[44]

2.4 | Oxygen, mechanical and circulatory support

If dyspnoea persists and haemoglobin saturation falls below 94%, it is generally recommended to initiate oxygen supplementation, to maintain peripheral saturation levels over 90%-96%. Low flow (up 6o 6L/min) nasal catheters or face-masks are sufficient for dyspnoeic patients. High-flow oxygen via nasal mask is indicated with acute respiratory failure in patients with COVID-19.[45] For the latter, there are active arguments on modality of high-flow oxygen, in terms of non-invasive (using tight fitting face mask) or high-flow via nasal cannula, due to the fact that there is greater potential to outspread viral aerosol of patients.[46,47] Furthermore, it is also reasonable to think about early intubation and mechanical ventilation in order to bypass the high-flow modes, since it is expected that patients generally will need it and the risk of repeated manipulations and potential of viral outspread in high-flow modes.[48] The most common initial form of ventilation is the low tidal volume in volume-limited assisted mode and positive end expiratory pressure, and further adjustments are being made in order to maintain sufficient oxygenation and decrease potential for barotrauma or oxygen toxicity.[49] One must be cautious in care around patients with ARDS and prolonged intubation due to development of complications in terms of cachexia, secondary infections, hemorheological complications etc Utilisation of nutritional support was even found to be harmful, so further investigations would be warranted.[50] Generally, nebulizers as therapeutic modalities should be avoided in patients with COVID-19.

Extracorporeal membrane oxygenation (ECMO) can be used in form of venovenous or venoarterial modalities, depending on the substitution of oxygenation and/or circulation. Jacobs et al reported on 32 consecutive cases of ECMO in COVID-19 critically ill patients with a 24-day timeline.[28] During the study course, a bit over half 17/32 patients persisted on ECMO, 10 died prior to or shortly after decannulation.[28] Medical therapy in the surviving ECMO patients was as follows: four of five survivors received intravenous steroids, three of five survivors received antiviral medications (Remdesivir), two of five survivors were treated with anti-interleukin-6-receptor monoclonal antibodies and one of five survivors received hydroxychloroquine.[28] Sultan et al reported on use of venovenous ECMO in 10 COVID-19 patients (31-69 years, 70% male), where two patients were discharged and only one patient died from multiorgan failure during the study course.[51] Useful therapeutic possibility of ECMO procedure is availability of cytokine absorption, that is, immunomodulators, which were previously shown to have positive effects in another group of critically ill patients with ARDS and sepsis.[52,53] One must underscore the fact that oxygen supplementation via mechanical ventilation and/or circulatory support are advanced methodologies of ICU treatment; however, those are still enhancers of acutely diminished body functions. In this way, machines are prolonging life, as a bridge to scarce potential that the patient self-recovers or by adding effective antiviral or other treatments that intervene in dominant pathogen life cycle.

In conclusion, novel coronavirus disease is the most serious pandemic of this millennium. Through several months of human to human air borne transmission, it affected over 3 million population in over 185 states/territories and there are over 220 000 of dead. Patients with pronounced fever, dyspnoea or pneumonia are generally hospitalised, around 10% of those are critical cases and mortality in currently known cases is estimated to be 4%-7%. The most promising results came from the application of remdesivir and convalescent plasma of survivors; however, further studies are needed in order to define optimal therapeutic management for various types of COVID-19 infection. Supportive measures in intensive care units include mechanical ventilation and extracorporeal membranous oxygenation. Numerous groups are focused on the development of vaccine, which could become available in the months to come.

DISCLOSURES

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the National library of medicine and its service PubMed at [available at url: https://pubmed.ncbi.nlm.nih.gov/], as reference number and over openly available database, for example, figshare over DOIs and references. Information on epidemiology were obtained from the "Worldmeters" database, on international number of COVID-19

reported cases (available at url: https://www.worldometers.info/coronavirus/#countries).

ORCID

Marko Boban https://orcid.org/0000-0002-6129-575X

REFERENCES

1. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270-273.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China. Lancet*. 2020;395:497-506.
3. Chan-Yeung M, Xu RH. SARS: epidemiology. *Respirology*. 2003;8(Suppl):S9-14.
4. Nassar MS, Bakhrebah MA, Meo SA, et al. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics. *Eur Rev Med Pharmacol Sci*. 2018;22:4956-4961.
5. Lai C-C, Shih T-P, Ko W-C, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55:105924.
6. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 Admitted to ICUs of the Lombardy region, Italy. *JAMA*. 2020;323(16):1574.
7. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565-574.
8. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature Microbiol*. 2020;5:562-569.
9. Jia HP, Look DC, Shi L, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J Virol*. 2005;79:14614-14621.
10. Chen L, Li X, Chen M, et al. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;116:1097-1100.
11. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426:450-454.
12. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacol Ther*. 2010;128:119-128.
13. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Archives of academic emergency medicine*. 2020;8:e35.
14. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ*. 2001;323:334-336.
15. Wang R, Zhang X, Irwin DM, Shen Y. Emergence of SARS-like coronavirus poses new challenge in China. *J Infect*. 2020;80:350-371.
16. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet*. 2020;395:689-697.
17. He D, Zhao S, Lin Q, et al. The relative transmissibility of asymptomatic cases among close contacts. *Int J Infect Dis*. 2020;94:145-147.
18. Velavan TP, Meyer CG. The COVID-19 epidemic. *Trop Med & Int Health*. 2020;25:278-280.
19. Li H, Liu Z, Ge J. Scientific research progress of COVID-19/ SARS-CoV-2 in the first five months. *J Cell Mol Med*. 2020;24(12):6558–6570.
20. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect*. 2020;80(6):607–613.
21. Zhou Y, Zhang Z, Tian J, Xiong S. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. *Annal Palliative Med*. 2020;9:428-436.
22. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis*. 2020;20(6):656-657.
23. Piva S, Filippini M, Turla F, et al. Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy. *J Critic Care*. 2020;58:29-33.
24. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
25. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized With COVID-19 in the New York City area. *JAMA*. 2020;382(18):1708-1720.
26. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med*. 2017;9:eaal3653.
27. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020:382(24):2327-2336.
28. Jacobs JP, Stammers AH, St Louis J, et al. Extracorporeal membrane oxygenation in the treatment of severe pulmonary and cardiac compromise in COVID-19: experience with 32 patients. *ASAIO J*. 2020:66(7):722-730.
29. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA*. 2020;323(16):1582-1589.
30. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA*. 2020;117(17):9490-9496.
31. Zhang B, Liu S, Tan T, et al. Treatment with convalescent plasma for critically Ill patients with SARS-CoV-2 infection. *Chest*. 2020;158:e9-e13.
32. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020;92(10):1890-1901. http://dx.doi.org/10.1002/jmv.25882
33. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;71(15):732-739.
34. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis*. 2020;34:101663.
35. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56:105949.
36. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med*. 2020;382(19):1787-1799.
37. Cheng CY, Lee YL, Chen CP, et al. Lopinavir/ritonavir did not shorten the duration of SARS CoV-2 shedding in patients with mild pneumonia in Taiwan. *J Microbiol Immunol Infect*. 2020;53(3):488-–492.
38. Ford N, Vitoria M, Rangaraj A, et al. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. *J Int AIDS Soc*. 2020;23:e25489.

39. Di Giambenedetto S, Ciccullo A, Borghetti A, et al. Off-label use of tocilizumab in patients with SARS-CoV-2 infection. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.25897
40. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol*. 2020;92(7):814–818.
41. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. *Circ Res*. 2017;120:229-243.
42. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemost*. 2020;120(6):998-1000.
43. Kollias A, Kyriakoulis KG, Dimakakos E, et al. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *Br J Haematol*. 2020;189(5):846-847.
44. Testa S, Prandoni P, Paoletti O, et al. Direct oral anticoagulant plasma levels striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents. The Cremona experience. *J Thromb Haemost*. 2020;18(6):1320-1323.
45. Cinesi Gomez C, Penuelas Rodriguez O, Lujan Torne M, et al. Clinical consensus recommendations regarding non-invasive respiratory support in the adult patient with acute respiratory failure secondary to SARS-CoV-2 infection. *Medicina intensiva*. 2020;44(7):429-438.
46. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. *The European respiratory journal*. 2019;53(4):1802339.
47. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
48. Cheung JC, Ho LT, Cheng JV, et al. Staff safety during emergency airway management for COVID-19 in Hong Kong. *Lancet Respir Med*. 2020;8:e19.
49. Pan C, Chen L, Lu C, et al. Lung Recruitability in SARS-CoV-2 Associated Acute Respiratory Distress Syndrome: A Single-center. *Am J Respir Critic Care Med*. 2020;201(10):1294-1297.
50. Peterson SJ, Lateef OB, Freels S, et al. Early exposure to recommended calorie delivery in the intensive care unit is associated with increased mortality in patients with acute respiratory distress syndrome. *J Parenter Enteral Nutr*. 2018;42:739-747.
51. Sultan I, Habertheuer A, Usman AA, et al. The role of extracorporeal life support for patients with COVID-19: Preliminary results from a statewide experience. *J Card Surg*. 2020;35(7):1410–1413.
52. Akil A, Ziegeler S, Reichelt J, et al. Combined Use of CytoSorb and ECMO in Patients with Severe Pneumogenic Sepsis. *The Thoracic and Cardiovascular Surgeon*. 2020. https://doi.org/10.1055/s-0040-1708479
53. Calabrò MG, Febres D, Recca G, et al. Blood purification with CytoSorb in critically ill patients: single-center preliminary experience. *Artif Organs*. 2019;43:189-194.

How to cite this article: Boban M. Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. *Int J Clin Pract*. 2020;00:e13868. https://doi.org/10.1111/ijcp.13868