Review Article

Evidence based practice a viable tool to manage the COVID-19 pandemic

Syeda Mehwish[1], Sheharyar Khan[2], Erum Choudry[3], Syed Uzair Mahmood[3]*, Aisha Yaqub Mulla[1], Salma Zahir Imam[4]

[1]Department of Dentistry, Karachi Medical and Dental College Karachi, Pakistan
[2]Department of Medicine, Baqai Medical University, Karachi, Pakistan
[3]Indus Hospital Research Centre, Karachi, Pakistan
[4]Department of Medicine, Liaquat National Hospital, Karachi, Pakistan

*Correspondence:
Dr. Syed Uzair Mahmood,
E-mail: uzair.hbb@gmail.com

ABSTRACT

Evidence based practice is the steps taken for precaution, treatment and intervention of a disease that is dictated by the previous studies. The data collected by the predecessors who observed the initiation, progression and the termination or cure of a disease would be the guidance to future treatment. Years of trials and tests are done to determine the timeline of a disease and its termination, along with the effects that it leaves behind in long term. These facts and figures are important evidence to the future treatments. The idea of evidence based practice was coined in the late 1970s. It dictates that the care of patients done based on the evidence provided by the previous studies results in better recovery of the patients and less load on the healthcare system. This system is supposed to be efficient and provide the basic guidelines for the healthcare workers with a concrete basis for their work. The patients treated under evidence based practice ideally have a higher chance of survival than those who are treated without it. COVID-19 being a new disease has lack of previously accumulated evidence to support any treatment regimen that can ease the symptoms. Most of the treatments are based on recent trials and tests which are helping but in a limited scope.

Keywords: COVID-19, Corona virus, Evidence-based practice, SARS-Cov2

INTRODUCTION

The term evidence based practice is directed towards treatment procedures, interventions and precautions taken in the wake of a disease that is based on prior studies and practices. This kind of medical practice undertakes the research and data collected by the previous studies, tests and trials and helps indicate towards the right path that should be taken in the current situation. The amount of risks and the resulting advantages are carefully calculated and perfected beforehand.[1] Evidence based practice requires years upon years of data that has a number of possible outcomes, clearing up a definite path and a

reliable guideline towards a possible cure.[2] Plan derived from evidence based practice is favorable as the physicians are accustomed to handling the particular treatment course and the results that the treatment produces are calculated and precise based on previous use. The use of evidence based practice has led to a decrease in number of fatalities.[3]

Evidence on a particular illness identifies its incidence, prevalence and possible mutative abilities of the pathology that is behind it. The data is collected that was once used by specialists over time based on the practice of the people who first came in contact with the disease

and the practices they found to be useful towards developing a possible cure.[4] The trials and tests that they took and the method of therapies they studied and found helpful, all are documented and observed in evidence based practice. Not only their triumphs, but also the routes that led to failures and the trials that worsened the illness are written down and studied by the later generations. In this way, evidence based practice can become a stepping stone in curing any illness.

One of the biggest challenges that epidemiologists face in the initial stages of an epidemic is how to control the spread of the disease as well as provide care to the diseased individuals all while obtaining a cure. For this reason, in cases involving pathogens that are recurrent like the influenza virus, treatment planning is done based on the previous literature.[5] These viruses became a seasonal illness and every year a number of people lose their lives to them. Evidence based practice for these diseases provides better groundwork that leads to improved results in the infected population and lowers mortality rate.[4]

EVIDENCE BASED PRACTICE IN THE ERA OF COVID-19

Such practices mentioned above needs to be applied to COVID-19 which is a viral infection, primarily targets the respiratory organs. The infectious agent that is responsible for this disease is a novel coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), such a variant of coronavirus has never been reported in human history before. The virulence and spread of the disease is very high, a single person infected with COVID-19 can infect 3 people on average and this number can go higher. The fatality rate for this infection is below 4% but varies based on various countries, like in the US, the fatality rate is about 5.6% while in Italy, it is 13.3%.[6] Though the general fatality rate might not be higher than 4% (3.5%) on average, this virus being highly virulent and spreading at an exponential speed makes it difficult for the healthcare systems to handle the surge of infected patients.[7] COVID-19 is a disease affecting respiratory airways of the infected individual which can develop into viral pneumonia that can worsen into severe acute respiratory distress syndrome.[8]

Affected individuals can spread the disease during the incubation period, while they remain asymptomatic. About 80% of the individuals receive mild symptoms only and only 13.8% develop severe symptoms, like pneumonia. About 18% find the need to get hospitalized and of those only 4.7% develop a critical illness, like acute respiratory distress syndrome (ARDS) and need mechanical ventilation.[9] The percentage might not seem high but the number that this percentage denotes are tens of thousands of people. For example the number of case fatalities in the US with the rate of fatality being 5.6% is 53,418 as of 26th April 2020, while the infected individuals in total are 954,000.[10]

The healthcare systems are overwhelmed with such a high number of patients coming in and increasing exponentially everyday resulting in the facilities not being able to keep up. This surge in numbers not only means an inadequate patient to healthcare provider ratio but also means putting a stress on hospital resources, the lack of Personal Protective Equipment (PPE), overworked staff and depleted supplies all add up to a downward spiral of the healthcare system, predicting to a possible collapse of the systems when it is needed the most.

EVIDENCE FOR THE CLINICAL FEATURES OF COVID-19

Various symptoms have been identified along the timeline of the disease. The most common symptoms are fever, cough, sore throat, fatigue, breathlessness and headache. Some patients who are COVID-19 positive are found to be complaining about new found loss of sense of smell (anosmia) and taste (aguesia). Along with these, some patients have come up with gastrointestinal symptoms like diarrhea and some with hematological symptoms like blood clots in a number of recent studies. A study conducted that consisted of 7736 patients in various hospitals of Wuhan, China, concluded that out of total, 88.7% patients developed a fever during the course of disease, 67.8% develop dry cough, 5.0% had diarrhea as a symptom.[11]

The more severe symptoms include a viral pneumonia with broken glass opacity in the CT scans. Around 86.2% of the CT scans were not normal upon admission and around 56.4% develop bilateral patchy showing of ground glass opacity. These were the cases that had developed a severe disease. Pneumonia develops after about 4 days of hospital admission in patients who show signs of deterioration of condition. If the condition progresses towards a critical one, these patients develop severe acute respiratory distress syndrome (ARDS) after 8-10 days of hospital admission.[12]

Recent reports have shown a surge in strokes among young and middle aged patients having positive COVID-19 their hematological studies show presence of blood clots due to the viral infection.[13] Although it is majorly a respiratory infection, however, due to the viral nature of infecting through ACE2 receptors, which are also present in endothelial lining. As these viral particles damage the endothelial lining which in turn causes inflammation, Von Willebrand's factor is released into the blood stream. Von Willebrand's factor is suspected to be the cause of increased coagulation of the blood and blood clots.[14]

Some patients have found to be having neurological symptoms who are COVID-19 positive at the hospitals. Though these symptoms are less common, a study found that out of 214 patients admitted to the hospital, the ones who had severe symptoms of the disease (about 45.5%) were more likely to have neurological symptoms, such as acute cerebrovascular disease in 5% of the patients,

impaired consciousness in 14%, and skeletal muscle injury in 17% of them.[15]

EVIDENCE FOR THE SPREAD AND TRANSMISSION OF COVID-19

Initially, it is speculated that the virus entered a human via bat, presumably by the consumption of an infected bat.[8] SARS-CoV-2 belongs to the family of viruses called Coronaviridae, the other two viruses that caused infections of large proportions, belonging to the same family SARS-CoV-1 which caused widespread infections in 2002 and Middle Eastern Respiratory Stress Coronavirus MERS-CoV which caused infection in Middle East during 2012, also originated from bats and camels respectively and infected humans.[16] It was first reported in the wildlife animals' market used to trade while animals in the Chinese city of Wuhan in December of 2019 while China alerted the World Health Organization (WHO) regarding the detection of this pathogen by January 1st 2020. That was the time of Chinese New Year and a considerable number of people migrated to their homeland from various parts of the world. Unknowingly coming in contact with the deadly virus, some of them escaped the screenings and spread the virus to other parts of the world as well. The city of Wuhan was put under a lockdown on 11 January 2020 but the virus had escaped the borders already.[17]

The disease then spread to exponential numbers and in just 5 months the numbers have exceeded well beyond 3 million mark with just over a million who have died. The disease has been identified to spread via respiratory droplets of an infected individual whether the patient is symptomatic or asymptomatic. The virus is evidently present in the airways of the infected individual as well as their blood. Coming in contact with the exhaled air from such an individual leads to the spread on infection to healthy ones.[18]

It is also mentioned in studies that the viral particle stays stable for about 4 hours in after being ejected in air. The virus can be found viable on the surfaces such as plastic, glass, steel and wood ranging from 2 to 4 days depending on the material. Therefore, not maintaining hand hygiene is also one of the major reasons of the spread of this disease. Mistakenly touching the face, nose or eyes after touching a contaminated surface will cause the individual to get infected.[19]

EVIDENCE FOR THE PECULIAR NATURE OF THE PATHOGEN

The viral pathogen itself does not differ much from its sister viruses, SARS-CoV-1 and MERS-CoV in structure and nature as well as origin. All these viruses are introduced to human populations from animal species like bats for both SARS viruses and camels for MERS-CoV. While SARS-CoV-2 is thought to have mutated from bat to human virus however, one thing that is astonishingly

different is the case fatality rate of all these.[8] For SARS-CoV-1, which was responsible for an outbreak in 2002 that lasted till June 2003, it was 9.6%, while for MERS-CoV that had an outbreak in 2012 in Saudi Arabia, it was 34.4%. SARS-CoV 2 has a fatality rate of about 3.5% on average which is much lower than its predecessor.[10]

SARS-CoV-2 is different in terms of spread of infection from SARS-CoV-1 or MERS-CoV. For both of those viruses, the carrier state is not infective and the spread can be limited by separating the infected individuals from the rest. However, for SARS-CoV-2, even during asymptomatic periods of infection, the infected individual spreads the virus to the healthy ones.[20]

EVIDENCE SUPPORTED SAFETY MEASURES AGAINST COVID-19

By looking at its mode of transmission and the data supporting that claim, the WHO has advised the act of "social distancing" to be of utmost importance in controlling the spread.[21] The countries that are most heavily affected by this virus have gone into an indefinite lockdown which refrains most businesses to be open as long as the number of people being affected diminishes. The practice of self-quarantine and social distancing has been advised in order to lower the number of people in general leaving their homes. Such actions by the authorities in prohibiting social calls and interactions of many within closed quarters are thought to lower the spread of infection by decreasing physical contact. Social distancing and self-quarantine helped in the control of the disease spread in the city of Wuhan, China, after over two months long hiatus in social activities as per government's commands. Therefore, it is thought to be one of the solutions in effectively minimizing the spread of the infection.[22]

As for the doctors and medical staff as well as the security forces that are deployed to assess and control the said situation, it is advised to always wear N-95 respirators.[23] Regular surgical masks lack a sieve small enough to filter out the viral particles that are reported to be 8 to 12 nm small.[24] For the medical staff directly in contact with the patients of COVID-19, it is advised to wear personal protective gear with a face shield, gloves and a gown that covers the body from head to toe. The patients are advised to be put into isolation whether it be in a negative pressure room or otherwise.[25]

It is suggested for the general public to maintain a strict hand hygiene. Washing hands for at least 20 seconds with soap and water is recommended to protect from a possible infection by hand. The instructions also dictate that it is essential to keep the hands away from eyes, nose, and oral areas as these are the possible routes of the spread of infection. It is recommended as well to don a facial mask for the general public, be it a cloth mask or a piece of scarf. This will limit the spread of the virus from asymptomatic individuals as well who remain undetected

UNICEF has given proper guidelines as to how one can maintain better hygiene at personally and keeping a clean environment at home as well.

INTERVENTIONS TESTED AND TRIED TO CURE COVID-19

This novel coronavirus has never before found or tested in the documented human history. Some of its features resemble the family of viruses that it belongs to but most harmful of its characteristics are markedly different from any virus that has ever infected a large number of people or has caused a pandemic. This is why the interventions taken to cure COVID-19 are mostly trial based and there is little data present that supports any outcome. There have been a number of drugs and drug cocktails tested in the past 4 months since the outbreak; however no drug has been put to randomized double blind trials. There is no FDA approved drug available to cure this disease as of yet.[26]

The tuberculosis vaccine, called as BCG vaccine is being considered as a possible prophylactic treatment. It will not provide specific immunity against the virus of COVID-19, however, it is thought to spike up the innate immunity which will in turn help fend off the initial onset of the infection. The healthcare professionals and the caretakers at home who are in direct contact with the patients of COVID-19 are thought to be the candidates for this prophylactic measure.[27]

Passive immunity is one of the suggested treatments for either prophylactic use or to treat the illness of COVID-19. The procedure of using a healthy patient's plasma with the required antibodies, in the case of COVID-19, the antibodies against SARS-CoV-2, is termed as passive immunity. The patients who have recovered from the disease will be needed to donate their blood plasma for the treatment to work. For the treatment of COVID-19, Palivizumab antibody titre is given.[28]

A number of drugs have been tested that have shown some promising results on a smaller scale. One of those drugs is chloroquine, an antimalarial drug that has been in use for decades. This drug was tested as a Zinc Ionophore in the body that facilitated zinc absorption into the cells. Zinc has been known to disrupt the activity of viral RNA being assimilated and expressed by a human cell at the stage of transcription, hence, even if the virus enters the body, it will not be able to replicate and harm the patient.[29] Various studies have been conducted to compare the test results and to see if the drug can be used to treat the disease. A recent study however, found out that in older patients, chloroquinolone increased the number of people deceased after the administration of this drug to treat COVID-19. Canada has recently sounded an alert against the use of this drug outside of physician's prescription as one of the serious adverse effects include cardiac arrhythmias.[30]

The drug tocilizumab, an immunosuppressant which is included in the treatment course of rheumatoid arthritis has also shown promise. An Italian doctor affected with the viral infections showed some improvements after taking the medicine and his oxygen saturation was reported to improve after administration of this drug.[31] It works by the blockade of pro-inflammatory IL-6 at binding sites and helps in the reduction of uncontrolled inflammation. FDA has approved the Phase 3 clinical trials of this drug as well.[32]

Ivermectin is another anti parasitic drug that showed promise in the fight against COVID-19. The tests were done on the patients on ventilators in the US. The mortality rate of the ones treated with Ivermectin reduced to 7.3% while the ones who were not given this drug, the mortality rate stayed at 21.3%. The overall mortality rate also improved after the administration of ivermectin by reaching 1.3% as opposed to the rate of 8.7% for the ones not treated with the drugs.[33] Evidence suggests that this drug is capable of eliminating the virus in mere 48 hours from the system. However, the safety of this treatment is still under question.[40] WHO has claimed that this drug is not used enough in order to yield a definitive result, however much beneficial it has proven to be in the current situation.

Another celebrated drug that has shown some positive results is remdesevir. This drug is an antiviral drug that inserts itself into the viral RNA and terminates its progression inside the human body 34. This drug has shown promise in recent trials. A randomized trial which was double blind and placebo controlled was conducted in 10 hospitals of China showed that the patients showed better recovery rates after 12 days of being hospitalized.[36]

Recent trials of dexamethasone in patients needing supplemental oxygen have shown remarkable results against Covid-19. According to WHO, the drug is included in life saving medicine against Covid-19 and it can decrease the mortality to a third of total. The patients treated with Dexamethasone, an anti-inflammatory agent, show improved oxygen saturation and an overall decrease in the inflammatory symptoms.[37]

IMPORTANCE OF EVIDENCE BASED PRACTICE IN THE ERA OF COVID-19

There is no concrete evidence that can lead the practitioners towards a single direction with success as a goal. However, every day new researches emerge and the death tally keeps on rising. The number of recovered individuals is also high, well over a million individuals have recovered till June 18, 2020 and the rate of infection is not slowing down. The studies conducted for prevention and cure of COVID-19 produce different data every day.[5] There is little prior accumulated evidence on which any mode of treatment can be based. There is very limited data on studies that can help in assessing the situation or make any predictions that can be supported

by the evidence. The medicine and the route of prevention are evaluated regularly and tested to find if they really are helpful in providing the cure.[38] Hence, there is a severe lack of evidence that can back up any treatment modality in the case of COVID-19. Even after strict lockdowns and social distancing, the people who don't mind those rules are becoming a vector for the spread of the disease. This in itself is becoming a huge issue as the healthcare systems throughout the world are working at their 100% and more burden can cause them to collapse. Right now, the major aim of most institutions is to lower the number of infections so that the people coming into the hospitals with symptoms or severe illness can be dealt with efficiently, otherwise called as "flattening the curve" of the number of cases reported each day.[39]

The data, however, that has been collected over the past few months has proven to be a basis for the treatments that are undergoing right now. The evidence that has been collected in this very short while has proven to be of much use in alerting the masses of the gravity of this situation and so, it has helped in preventing the spread by the general alerts of social distancing. The number of people potentially coming in contact with the pathogen has decreased and therefore, less number of people are getting sick. This has been the most effective mode of controlling the spread of the disease thus far.

Limitation due to lack of evidence

Due to a general lack of evidence, the procedures that should have moved faster have been slowed down. The modes of treatment have been limited and the drug trials are taking long. In the past 4 months only, a huge amount of data has been accumulated that has helped in the treatment and control of the disease, however, the overall result is still not good enough.

The procedures that could have taken a shorter period of time have gone on longer which is costing us lives every day. The fact that this virus spreads even during incubation period or even if the patient is symptomless, came out later than it should have.[40] This fact caused the spread of the virus from the borders outside of china and the people who stayed asymptomatic never realized that they are becoming a vector for the spread of a deadly pandemic. This was due to the lack of evidence regarding the way COVID-19 spread and caused infection. Another example would be the stability of viral particles outside of the human body for extended periods of time. The fact that it survives on surfaces like plastic, paper, glass, and that it stays suspended in air for about 3 to 4 hours, all these evidences came in after the infection had already spread to multiple countries throughout the world. This became a huge handicap in containing the spread and caused a lag in the primary mode of prevention of this disease.

CONCLUSION

To say that the lack of evidence has hindered effective management against COVID-19 would be an understatement. However, the scientific community is doing every possible endeavour to make sure that they collect enough data in time so that more people can be saved. There is a lack of evidence and data which can direct us in the right path towards salvation, but this gap is continuously being filled each day and the trials are giving more and more results as time passes by. However, it can be safely stated that by employing the methods of evidence based practices we can improve our future management of such situations.

REFERENCES

1. Harris C, Carson G, Nair H. An evidence-based framework for priority clinical research questions for COVID-19. J Glob Health. 2020;10(1):011001.
2. Nicole W. Coronavirus cancellations show evidence-based decisions are rare during epidemics. Available at: https:// www. theverge. com/ 2020/2/14/21136819/coronavirus-mwc-meetings-canceling -face-masks-evidence-risk. Accessed on 12 February 2020.
3. Trisha G. Evidence based medicine: a moment in crisis. BMJ. 2014;348:3725.
4. Peeri NC, Shrestha N, Rahman MS, Zaki R. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol. 2020;22:33.
5. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007;7(10):658-66.
6. Worldometer. Available at: Worldometer. com.Https://www.worldometers.info/coronavirus/co untry/italy/. Accessed on 26 March 2020.
7. Epidemiology working group for NCIP epidemic response, Chinese center for disease control and prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-51.
8. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;4(87):71-9.
9. Majority of coronavirus cases are mild. Available at: https://www.statista.com/chart/20856/coronavirus-case-severity-in-china/. Accessed on 12 April 2020.
10. Centers for disease control. Available at: https:// www.cdc.gov/coronavirus/2019-ncov/COVID-data/ covidview/index.html. Accessed on 26 April 2020.

11. Guan WJ, Ni ZY, Hu Y, Liang W, Ou C. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382:1708-20.
12. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;7:281-6.
13. Young and middle-aged people, barely sick with COVID-19, are dying of strokes. Available at: https:// www.washington post.com/health/2020/04/ 24/strokes-coronavirus-young-patients/. Accessed on 5 April 2020.
14. Lovren F, Py O. Angiotensin converting enzyme-2 confers endothelial protection and attenuates atherosclerosis. Am J Physiol Heart Circ Physiol. 2008;45(6):82-9.
15. Mao L, Chao MW. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. The Lancet. 2020;65:102-9.
16. Mohd HA, Tawfiq JA, Memish ZA. Middle east respiratory syndrome coronavirus (MERS-CoV) origin and animal reservoir. Virol. 2016;76:92-9.
17. Rothe C, Schunk M, Sothmann P, Bretzel G. Transmission of 2019-ncov infection from an asymptomatic contact in Germany. N Engl J Med. 2020;382:970-1.
18. Epidemiology working group for NCIP epidemic response, Chinese center for disease control and prevention. (2020). The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) China, 2020. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-51.
19. Wu, Chi Y, Sung C, Jiun Y. The outbreak of COVID-19: an overview. J Chinese Med. 2020;83(3):217-20.
20. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmunity. 2020;53:44-9.
21. Anderson RM, Heesterbeek H, Klinkenberg D. How will country-based mitigation measures influence the course of the COVID-19 epidemic? The Lancet. 2020;43:39-42.
22. Prem K, Liu Y, Russell TW. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. Lancet. 2020;5(5):261-70.
23. Wong J, Goh QY, Tan Z, Lie SA, Tay YC, Ng SY. Preparing for a COVID-19 pandemic: a review of operating room outbreak response measures in a large tertiary hospital in Singapore. Canadian J Anesthesia. 2020;8:75-9.
24. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;65:97-105.
25. Holland M, Zaloga DJ, Friderici CS. COVID-19 personal protective equipment (PPE) for the emergency physician. Visual J Emerg Med. 2020;7:76-83.
26. Coronavirus disease 2019 (COVID-19). Available at https://www.fda.gov/emergency-preparedness-and- response/ counterterrorism- and- emerging-threats/ coronavirus-disease-2019-COVID-19. Accessed on 27 April 2020.
27. Vrieze JD. Can a century-old TB vaccine steel the immune system against the new coronavirus? Available at: https:// www. sciencemag. org/news/ 2020/03/can-century-old-tb-vaccine-steel-immune-system-against-new-coronavirus. Accessed on 3 May 2020.
28. Luke TC. Passive immunotherapy for influenza and other serious infections. Crit Care Med. 2010;7:65-9.
29. Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ. Chloroquine is a zinc ionophore. Plos One. 2014;65:765.
30. Canada warns against chloroquine use as coronavirus treatment. Available at: https://www. Thenews .com. pk /print/650407-canada-warns - against-chloroquine-use-as-coronavirus-treatment. Accessed on 27 April 2020.
31. Tocilizumab (Actemra) for COVID-19 coronavirus treatment. Available at https://www medicinenet.com/script/main/art.asp?Articlekey=23 0014. Accessed on 27 April 2020.
32. Cennimo R, David J. What is the role of the IL-6 inhibitor tocilizumab (Actemra) in the treatment of coronavirus disease 2019 (COVID-19)? Mediscape. 2020.
33. FDA approves phase III clinical trial of tocilizumab for COVID-19 pneumonia. Slater, Hannah. 2020, MH life sciences. Available at: https:// www.cancernetwork.com/view/fda-approves-phase-iii-clinical-trial-tocilizumab-covid-19-pneumonia. Accessed on 27 April 2020.
34. Antiparasitic drug ivermectin reduces coronavirus fatality rate. Available at: https:/ /mainichi.jp/english/articles/20200425/p2a/00m/0na /007000c. Accessed on 27 April 2020.
35. Mass treatment with ivermectin: an underutilized public health strategy. WHO bulletin.
36. Caoa YC, Denga Q. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing. Travel Medi Infect Dis. 2020;34:43-9.
37. Rastogi A, Akintorin SM, Bez ML, Morales P, Pildes RS. A controlled trial of dexamethasone to prevent bronchopulmonary dysplasia in surfactant-treated infants. Pediatrics. 1996;98(2):204-10.
38. WangY. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020;5:87-94.
39. NIH guidelines emphasise lack of evidence for COVID-19 treatments. Available at: https:// mapmedtech. com/ 2020/ 04/nih -guidelines-emphasise-lack-of -evidence- for- covid- 19-treatments/. Accessed on 27 April 2020.
40. Sun P, Lu X, Xu C. Understanding of COVID-19 based on current evidence. J Med Virol. 2020;92:548-51.