Vol 45 (2) June , 2021

Print: ISSN 0304 4904
Online: ISSN 2305-820X

PAKISTAN PEDIATRIC JOURNAL

A JOURNAL OF PAKISTAN PEDIATRIC ASSOCIATION

Indexed in EMBASE/Excerpta Medica, Index Medicus WHO
IMEMR & Global Health/CAB Abstracts and UDL-EDGE Products and Services

www.pakpedsjournal.org.pk

http://www.pakmedinet.com/PPJ

REVIEW ARTICLE

Novel Coronavirus 2019 (COVID-19) Diagnosis and Treatment: Recent Review Updates

HAYAT ULLAH, ASAD ULLAH, ANBAREEN GULL, Muhammad Waseem Khan

Pak Pediatr J 2021; **45(2):** 135-40

Correspondence to:

Hayat Ullah,
Department of Bio-informatics & Bio-technology, Faculty of Life Science, Government College University Faisalabad

E-mail: hayatullah22@gcuf.edu.pk

Received 12th July 2020;
Accepted for publication 13th April 2021

ABSTRACT

The pandemic caused by coronavirus disease 2019 (COVID-19) caused millions of deaths worldwide. To mitigate the pandemic, scientists are working on effective therapeutics to cure the patients however there is still no proper medication to treat the patients. From all over the world scientists are sharing their contributions related to disease prevention, epidemiology, diagnosis and treatment of COVID-19 disease. This literature review is another contribution, updating the diagnostic methods and medication effectiveness that could be most suitable therapeutic options for patients of COVID-19 disease.

Key Words: *SARS-CoV-2, Clinical diagnosis, Medication*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was discovered late December at Wuhan, China.[1] World Health Organization (WHO) declared COVID-19 pandemic on January 30, 2020. COVID-19 is a lethal disease which causes respiratory, hepatic, gastrointestinal and neurological infections. COVID-19 disease has asymptomatic transmission, long incubation period, no proper medication and vaccine.[2,3] Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) belongs to Coronavirus genus of Coronaviridae family, containing single stranded RNA with crown shape peplomers. Virus has high mutation rate which, occurs during transcription which makes coronavirus more lethal.[4]

Still there is no proper medication to cure COVID-19 disease infected patients. Scientists are priority base working on development of therapeutics for treatment of patients.[5] There are many general treatment methods used to medicate the patients. For medication purpose ritonavir, lopinavir with ribavirin, corticosteroids with interferon alfa, corticosteroids, ribavirin and convalescent plasma to cure the patients.[6] Current literature review summarized various diagnostic methods and different medication approaches used to cure COVID-19 patients.

DIAGNOSIS OF COVID-19

Clinical diagnosis of COVID-19 disease is based on physical examination, viral nucleic acid detection method, CT/X-ray imaging and rapid diagnosing kits based on immune identification (point-of-care testing (POCT) of IgM/IgG and enzyme linked immunosorbent assay (ELISA).

Physical examination: Clinical sign and symptoms of COVID-19 patients are mild fever, cough with spasm, dyspnea, dullness in percussion and increased or decreased tactile speech tremor however in severe condition the clinical sign and symptoms are shortness of breath, weakened breath sound and moist rales in lungs.

Nucleic-acid-detection-method: Coronavirus nucleic acid is detected with help of high-throughput sequencing method and RT-qPCR (real time quantitative polymerase chain reaction) method. Viral samples are taken from nasopharynx or trachea extract, nasal swabs, sputum, lung tissue, blood and feces.

Most accurate methods for diagnosis of COVID-19 are virus blood culture and high-throughput sequencing methods, due to equipment dependency and high cost, its applications are limited. Most common and acceptable method is RT-qPCR for viral detection from respiratory and blood samples. After COVID-19 outbreak Chinese companies make an effort for development of rapid diagnosing RT-qPCR test kits that was approved by CDC (Chinese Center for Disease Control and Prevention)[4,7] however other rapid diagnosing kits were based on antigen or antibodies such as POCT of IgM/IgG and ELISA kits have been developed.[8]

CT/X-ray imaging: CT/X-ray image of lungs is important technique for COVID-19 diagnosis purpose, for false negative result of PCR, clinicians proposed CT scan that's results vary with immunization status, drug interventions, and disease stage.[4] At initial stage of infection, CT scan shows small patchy-shadows in chest, however in severe condition, infiltrating-shadow and pulmonary consolidation with infrequent pleural effusion.[3,9] Pulmonary lesions are more clearly shown in CT scan than X-ray image [8,10]

TREATMENT OF COVID-19

There is no specific medication used at the current moment for treatment of current pandemic. Meanwhile the number of patients with the life-threatening situation is 5-10%. To protect the world from the current pandemic, researches throughout the world are working together hand in hand for the clinical trials of different drugs against COVID-19 declared by WHO (2020).[12] The medications that are currently used for COVID-19 are as follows.

Remdesivir: Remdesivir was the first drug to be approved by FDA for the treatment of COVID-19. Another name used for Remdesivir is GS-5734 which was initially used for Ebola and Marburg disease as an antiviral agent. This drug was indicated for treatment of COVID-19 patients whose age were above 12 years and hospitalized. This drug is broad-spectrum antiviral agent and[1] when enters in the body then it metabolizes to makes adenosine triphosphate which is a nucleotide analogue that selectively targets the polymerases enzyme.[13] This drug doesn't cause any toxicity in the body because it only targets viral polymerase enzyme.[14] Remdesivir was used for the treatment of Covid-19 for the very first time on an American 35 years old male patient. The patient was normal and no serious side effects were observed against Remdesivir.[15] This drug was used on two other COVID-19 patients as well and they recovered normally. The current dose of Remdesivir which is under investigation is 200 mg on the first day which is administered intravenously followed by 100 mg for ten days.[13]

Ritonavir/Lopinavir: They are inhibitor of protease enzyme which is required for the viral replication. Protease enzyme process the polyprotein and when this enzyme is inhibited then viral replication is also halted. These both drugs were initially developed to regulate the progression of human immunodeficiency virus (HIV) infection.[13] A study was conducted on 18 patients of Singapore by Young et al in which Lopinavir/ritonavir was used as a treatment method in only 5 patients. Out of those 5 patients 2 died due to respiratory failure while 3 had decreased in the requirement of oxygen.[16] Other cases of use of Lopinavir/ritonavir were also reported but there was inclusion of other therapies as well such as corticosteroids. Therefor the data couldn't be interpreted properly.[17-19]

There was another study led by Cao et al where the patients treated with Ritonavir/Lopinavir were compared with the ones that received standard care but in result no significant difference was found. The number of patients under study were 199. In which 99 received Lopinavir/ritonavir while 100 patients were given standard care. Mortality rate was almost same 19.2% and 25% with standard care and lopinavir/ritonavir respectively within 28 days of observation.[20]

Nucleoside analogues: Nucleoside analogues are anti metabolites under study.[21] The examples include favipiravir, remdesivir and ribavirin.[23] These drugs or chemical compounds ones enter in the body then copy the nucleosides which are involved in the synthesis of DNA or RNA, causing chain termination ultimately cell death. They also cause inhibition of enzymes which synthesize purines and pyrimidines.[22] Ribavirin and remdesivir are under clinical trial for SARS-CoV-2. Remdesivir as an adenine nucleoside is in phase III clinical trial for COVID-19 which was initially synthesized for Ebola and Marburg disease.[26]

When this drug was tested in-Vitro and on mice for SARS and MERS disease then it showed satisfactory activity [27]. Remdesivir was also effective in removing virus from lungs and improving lung function.[25] On the other hand, Ribavirin that was previously used for the treatment of hepatitis C and had been tested for SARS and MERS corona virus disease is a guanine analogue.[23] According to molecular data this drug targets RNA dependent RNA polymerase of the virus and found to be effective against current pandemic.[25] But some side effects were also observed such as anemia. For most effective treatment, the drug is taken in combination with pegylated interferons in lower doses to cause immunization.[24]

Neuraminidase inhibitor: Neuraminidase inhibitor inhibits the neuraminidase activity of virus. Oseltamivir and baloxavir which are neuraminidase inhibitor has been approved for influenza virus. These inhibitors inhibit the neuraminidase of virus by blocking virus release from cell. The corona virus doesn't utilize neuraminidase therefor no such enzyme is used to inhibit the activity of neuraminidase. Therefor if a patient is proved to have no influenza then use of neuraminidase inhibitor should be avoided. Also, there is no data available for the usage of this inhibitor in COVID patients.[13]

Corticosteroid therapy: Corticosteroid therapy is used at that time when lung is injured due to inflammation of lungs caused by lung infection. This therapy is used at that time when there is no alternative drug because usage of this therapy delays the removal of virus from lungs by increasing the chance of secondary infection. This mode of therapy has also been used for COVID-19 patients and different results were obtained in different analysis.[26] In one study in critical patients, the use of this therapy has decreased the death rate[27] while in another study the use of corticosteroid had worst outcome and delayed the cleansing of virus.[28] When using this therapy for COVID patients then one must be very careful regarding the dosage of corticosteroid. Each patient should be checked individually by measuring the risk and benefit ratio. The dosage of methylprednisolone prescribe by Chinese thoracic society is 0.5-1 mg/kg/day for seven days in selected patients.[29]

Peptide EK1: Spike protein is common in all human corona virus and this virus utilize S protein to enter in the human cell. The S protein of SARS-CoV-2 consists of two subunits: S1 and S2. HCoV utilizes the receptor binding domain (RBD) of S1 to bind with host membrane to cause changes in the confirmation of S2 by inserting the fusion peptide in the cell membrane of host. The heptad repeats 1 (HR1) of S2 subunit forms three highly conserved and hydrophobic grooves and expose it on the surface. The HR1 and HR2 fuses with one another through these grooves. This fusion cause viral membrane and host in proximity for entry of virus due to formation of six helix bundle formation (6-HB).[30] Many pharmaceutical companies used the S protein as target site for the development of their drug against SARS-CoV-2 in order to prevent the entry of virus into host cell.[31] However, for development of broad-spectrum antiviral drug this site is not an ideal target because this part of the virus is highly mutable.[31] Among the HCoV, as compare to RBD of S1, the HR region of S2 subunit is highly conserved. According to studies when peptides from HR1 interact/bind with HR2 then viral infection is inhibited because these peptides inhibit formation of 6-HB and prevent binding of both viral and host membranes. The OC43-HR2P peptide has a broad- spectrum activity. There is another peptide EK1 that is modified form of OC43-HR2P is more capable of giving better results. The results were satisfying when EK1 was tested in-Vivo and administered through nasal route.[32]

Arbitol: This drug is synthesized by a Russian pharmaceutical company named Russian research chemical pharmaceutical institute.[34] This drug has a broad-spectrum antiviral activity and was initially used to prevent from influenza virus.[33] This drug is used in Russia and China for the treatment of respiratory infections.[33] According to studies report, this drug is effective in case of hepatitis B and C virus as well[36] by preventing the interaction of virus with the host. In Jan 2020 in Wuhan city of China a clinical study was conducted including 67 COVID-19 patients in which 30 patients remained as controlled group with no treatment while 36 patients were given 400 mg of umifenovir (arbitol) for three times a day for nine days. In this study decrease in mortality was observed 16% in arbitol group than

control.[37] There was another study led in Guangdong, China in Feb 2020 which included 33 COVID-19 patients. In which 17 patients served as control group receiving 400 mg of lopinavir and 100 mg of ritonavir after every 12 hours while other 16 patients received the same treatment with lopinavir and ritonavir but along with that they also received 200 mg of arbitol after every 8h. Both control and arbitol groups were kept under observation for 14 days. Then samples were taken from patients and detected through RT-PCR. 94 % negative results were obtained in arbitol group while 53 % in control group.[38,39]

Antibiotic medications: Antibiotic medications that are found to be effective for SARS-CoV-2 is teicoplanin. This drug is a glycopeptide antibiotic normally prescribed for the treatment of infection against Gram + bacteria such as staphylococcus and streptococcus bacteria.[40] When the S protein of virus bind with the ACE2 of host cell then due to conformational changes in S protein, TMPRSS1 becomes activated[40,42] and virus enters the host cell through process of endocytosis and in late endosome another enzyme cathepsin L is required for entry of virus in cell cytoplasm.[41] The teicoplanin inhibit this cathepsin L thus prevents the entrance of virus.[42]

CONCLUSION

For the treatment of COVID-19 clinical trials, different drugs have been used in different areas of the world. No treatment method has been approved yet, therefore at the current moment the best we can do is to protect our self from exposure to COVID-19 and by following the safety measures given by WHO 2020.

Conflict of Interest: There is no conflict of interest to disclose.

Authors' affiliation

Hayat Ullah,
Department of Bio-informatics & Bio-technology, Faculty of Life Science, Government College University Faisalabad

Asad Ullah,
Department of Microbiology, Faculty of Life Science and Informatics, Balochistan University of Information Technology Engineering and Management Sciences, Quetta, Pakistan

Anbareen Gull,
Department of Biotechnology, Quaid-i-Azam University, Islamabad

Muhammad Waseem Khan
Department of Biotechnology, Faculty of Life Science and Informatics, Balochistan University of Information Technology Engineering and Management Sciences, Quetta, Pakistan

REFERENCES

1. Ullah H, Ullah A, Gull A, Mousavi T, Khan MW. Novel Coronavirus 2019 (COVID-19) Pandemic Outbreak: A Comprehensive Review of the Current Literature. Vacunas. 2020.
2. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J. Gen. Intern. Med. 2020:1-5.
3. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020:200370.
4. Sahin AR, Erdogan A, Agaoglu PM, Dineri Y, Cakirci AY, Senel ME, et al. 2019 novel coronavirus (COVID-19) outbreak: a review of the current literature. EJMO. 2020;4(1):1-7.
5. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-9.
6. Gull A, Ullah H, Iqbal N, Ullah A, Raziq A, Khan NM, et al. 1. Diagnosis and treatment of novel Coronavirus 2019 (COVID-19): A comprehensive review of the current literature. Pure appl. biol. 2020;10(1):46-53.
7. Amrane S, Tissot-Dupont H, Doudier B, Eldin C, Hocquart M, Mailhe M, et al. Rapid viral diagnosis and ambulatory management of suspected COVID-19 cases presenting at the infectious diseases referral hospital in Marseille, France,-January 31st to March 1st, 2020: A respiratory virus snapshot. Travel Med Infect Dis. 2020:101632.
8. Adhikari SP, Meng S, Wu Y-J, Mao Y-P, Ye R-X, Wang Q-Z, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19)

during the early outbreak period: a scoping review. Infect Dis Poverty. 2020;9(1):1-12.

9. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology. 2020;295(1):202-7.
10. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, 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.
11. YAVUZ S, Ünal S. Antiviral treatment of COVID-19. Turk J Med Sci. 2020;50(SI-1):611-9.
12. McCreary EK, Pogue JM, editors. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infectious Diseases; 2020: Oxford University Press US.
13. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9(396).
14. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N. Engl. J. Med. 2020.
15. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. Jama. 2020;323(15):1488-94.
16. Lim J, Jeon S, Shin H-Y, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020;35(6).
17. Han W, Quan B, Guo Y, Zhang J, Lu Y, Feng G, et al. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019. J Med Virol. 2020;92(5):461-3.
18. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci. Trends. 2020.
19. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N. Engl. J. Med. 2020.
20. Cheson B, editor New antimetabolites in the treatment of human malignancies. Seminars in oncology; 1992.
21. Galmarini C, Mackey J, Dumontet C. Nucleoside analogues: mechanisms of drug resistance and reversal strategies. Leukemia. 2001;15(6):875-90.
22. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. Int J Infect Dis. 2014;20:42-6.
23. Ahn D-G, Shin H-J, Kim M-H, Lee S, Kim H-S, Myoung J, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). J. Microbiol. Biotechnol. 2020;30(3):313-24.
24. Khan S, Attar F, Bloukh SH, Sharifi M, Nabi F, Bai Q, et al. A review on the interaction of nucleoside analogues with SARS-CoV-2 RNA dependent RNA polymerase. Int. J. Biol. Macromol. 2021 Mar 22.
25. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006;3(9).
26. Chen R-c, Tang X-p, Tan S-y, Liang B-l, Wan Z-y, Fang J-q, et al. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest. 2006;129(6):1441-52.
27. Lee N, Chan KA, Hui DS, Ng EK, Wu A, Chiu RW, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J. Clin. Virol. 2004;31(4):304-9.
28. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet (London, England). 2020;395(10225):683.
29. Xia S, Liu Q, Wang Q, Sun Z, Su S, Du L, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) entry inhibitors targeting spike protein. Virus Res. 2014;194:200-10.
30. Jiang S, Lu L, Liu Q, Xu W, Du L. Receptor-binding domains of spike proteins of emerging or re-emerging viruses as targets for development of antiviral vaccines. EMERG MICROBES INFEC. 2012;1(1):1-8.
31. Xia S, Yan L, Xu W, Agrawal AS, Algaissi A, Tseng C-TK, et al. A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. Sci. Adv. 2019;5(4):eaav4580.

32. Blaising J, Polyak SJ, Pécheur E-I. Arbidol as a broad-spectrum antiviral: an update. Antivir. Res. 2014;107:84-94.

33. Shi L, Xiong H, He J, Deng H, Li Q, Zhong Q, et al. Antiviral activity of arbidol against influenza A virus, respiratory syncytial virus, rhinovirus, coxsackie virus and adenovirus in vitro and in vivo. Arch. Virol. 2007;152(8):1447-55.

34. Boriskin Y, Leneva I, Pecheur E-I, Polyak S. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. Curr. Med. Chem. 2008;15(10):997-1005.

35. Boriskin YS, Pécheur E-I, Polyak SJ. Arbidol: a broad-spectrum antiviral that inhibits acute and chronic HCV infection. Virol. J. 2006;3(1):56.

36. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.

37. Uyeki TM. Oseltamivir treatment of influenza in children. Oxford University Press US; 2018.

38. Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J. Infect. 2020.

39. Parenti F, Beretta G, Berti M, Arioli V. Teichomycins, new antibiotics from Actinoplanes teichomyceticus nov. sp. J. Antibiot. 1978;31(4):276-83.

40. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proceedings of the National Academy of Sciences. 2009;106(14):5871-6.

41. Glowacka I, Bertram S, Müller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J. Virol. 2011;85(9):4122-34.

42. Zhou N, Pan T, Zhang J, Li Q, Zhang X, Bai C, et al. Glycopeptide antibiotics potently inhibit cathepsin L in the late endosome/lysosome and block the entry of Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV). J. Biol. Chem. 2016;291(17):9218-32.