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Contemporary Evolution in The Curement of Covid 19: An Overhaul Review

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HUMAN

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ABSTRACT

In late December of 2019, the emergence of the novel coronavirus also known as COVID-19 became a matter of concern. In a short period, the virus was able to infect a large number of populations as the virus transmits from one person to another person. The novel coronavirus shows genetic similarity with the SARS and MERS. However, have a low mortality rate compared to them and the reason for such a low mortality rate lies in its pathogenesis features. The coronavirus uses ACE2 receptors as the entry path to enter the host body and so gain the excess. Since most of the ACE2 receptors exist on the lungs the first sign of infection appears in the respiratory region which includes normal inflammation sign like fever, cough, headache, and tiredness but as the infection progress, the symptom like pneumonia can also be observed. The incubation period for the symptoms to appear range from 0-14 days as the infection progress further a multi-organ damage can be observed. Studies also suggest that in some patients no symptoms were observed even though they were infected such patients were called asymptomatic. Currently, no specific medicine is there for COVID-19, and therefore treatment involves various drug therapies like Immunoenhancement therapy, Convalescent plasma therapy, Auxiliary blood purification treatment, ramdesivir, chloroquine, and hydroxychloroquine, arbidol, etc. and also many vaccines are under pre-clinical and clinical trials.

INTRODUCTION

In the late December of 2019, the first patient of novel coronavirus also known as COVID-19 was admitted to the hospital of Wuhan city, Hubei province in China and since then the virus has spread across the globe affecting around 10,321,689 people this indicates that the virus is highly transmissible and can be transferred from human to human[1-5]. The origin of the virus is thought to be related to the Huanan seafood market[6]. However, the genetic analysis shows that the virus belongs to the genus of beta coronavirus and shows similarity with the coronavirus which is found in bats. Also from different studies, it was observed that the COVID-19 has 79.577% nucleotide and 83.36% amino acid similar identity with the SARS and MERS[7-9].

Interestingly, even after showing such similarities with SARS and MERS the mortality rate of COVID-19 is less compare to them. The main reason for such a low mortality rate lies in its pathogenesis features which seem to be different from the other two strains of coronavirus[10]. After studying the bioinformatics modeling and in vitro experiments it was concluded that the virus of COVID-19 gains its excess into the host cell through the help of the ACE-2 receptor interestingly the same receptor was earlier identified for the entry of SARS-CoV and HCOV-NL63[11-13]. Basically, in coronavirus infection, the envelope spike glycoprotein protein binds with the ACE-2 receptors and because of that the virus enters the host cells and releases its viral RNA genome into the cytoplasm and hence the process of translation begins for the production of the viral genome. Furthermore, these newly formed envelope glycoproteins are placed inside the membrane of the endoplasmic reticulum or Golgi and the formation of nucleocapsid starts through the combination of genomic RNA with nucleocapsid proteins. After that, the germination of viral particles starts to occur into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), and hence virus releases when the vesicles containing virus particles merge with the plasma membrane[14-17]. Surprisingly recent studies also suggest that the ACE-2 does not only work as a receptor but has involvement in the post-infection regulation, including immune response, cytokine secretion, and viral genome replication[18].

However, the time taken by the COVID-19 virus to shows its symptoms approximately take 5.2 days and this period is called as incubation period[19]. The time range from COVID-19 infections symptoms to death generally range from 6 to 41 days making 14 days the median but this period can change as it depends on the patient's immune system. In one of the

studies, it was also observed that in the COVID-19 infection there is a drastic decrease in the lymphocyte count and also a markable elevation in the inflammatory markers which somewhere might be the reason for the elevated mortality rate[20,21]. The onset of the symptoms starts around the 14th day with the symptoms like fever, cough, fatigue, sputum production, headache, hemoptysis, diarrhea, dyspnoea, and lymphopenia also the CT scan of the patient's chest reveals some different features like RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death also some other special features shown by COVID-19 infection is that it affects the lower airway as evident by upper respiratory tract because of which symptoms such as rhinorrhoea, sneezing and sore throat can be observed and the main reason for showing such diverse symptoms may lie on the fact that ACE-2 receptors can be found on the renal, cardiovascular and gastrointestinal lung alveolar epithelial cells, enterocytes of the small intestine, arterial and venous endothelial cells and arterial smooth muscle cells from this it can also be concluded that COVID-19 infection can cause issues in heart [20,22-29]. Interestingly some people who were infected with the COVID-19 virus didn't show any symptoms therefore they were called asymptomatic patients which somewhere only acts as a carrier[30].

Sadly, until now there is no specific medicament or cure available for the treatment of this infection. However different medicines and therapies are used in combination to cure the patients and also the clinical trials of the potential drug substances are also going on[31].

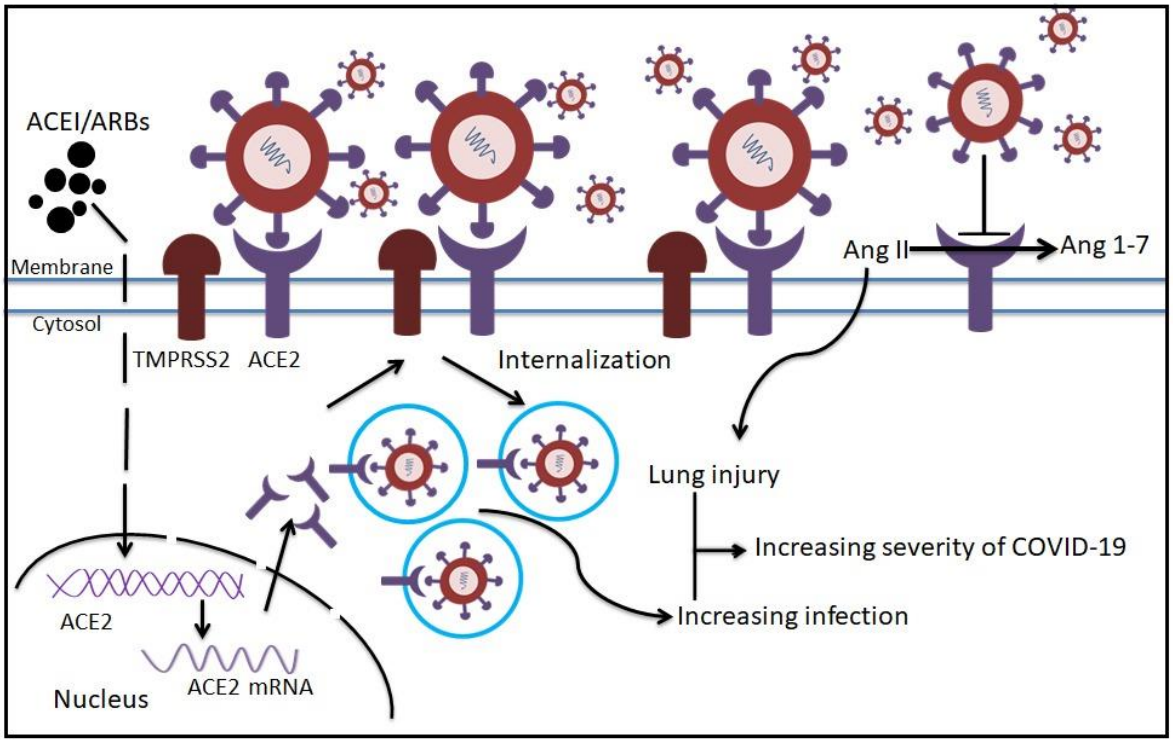

Figure No. 1: Diagrammatic Representation of Covid-19 Infection through ACE2 Receptors[18]

TREATMENT

Corticosteroids: - are the drug families which are used to treat inflammation. They also suppress the immune system. In the era of the COVID-19 pandemic, they are used in the treatment of COVID-19 patients. A study suggests that corticosteroids should not be used in the treatment of COVID-19 induced lung injury but can be used in clinical trials. They are known to reduce mortality and the need for ventilators in pneumonia patients. There is a potential risk linked with high doses of corticosteroids like long-term complications and prolong virus shedding. Basic procedures must be followed when using corticosteroids. They are considered a double edge sword. Hence, its liberal use is restricted and low-to-moderate doses are recommended[32].

Traditional Chinese medicines (TCM): - These are plants that are reported to have medicinal properties and promoted for general prescription in the treatment of COVID-19 patients in China[33]. *qingfeipaidu* decoction is reported to have a 90% recovery rate in COVID-19 patients. It works via multi-component and multi-target regulation. The pharmacological target site is the lung, a decoction of 16 herbs reported to have specificity

for lung diseases. ACE-2 receptor is commonly expressed with potential target sites. The same receptor is the target for the COVID-19 treatment. Multiple ribosomal proteins are inhibited and hence COVID-19 replication is blocked[34]. QPD is reported to elevate immune response and eliminate inflammation by regulating cytokine action pathways and pathways related to the immune system. In silico analysis has shown that ergosterol, shionone, and patchouli alcohol formulations possess anti-COVID-19 activity, which provides a novel molecular structure for drug development[35-37].

Immunoenhancement therapy: - Elevation of the immune response system is the best procedure for SARS treatment. Interferon induces innate and adaptive response which inhibits viral infection. Recombinant alpha interferon was reported to be effective in the treatment of SARS patients[38]. Interferons are found to be effective replication inhibitors of MERS-CoV[39]. These studies pave the path for the potential use of interferons in the COVID-19 treatment. Thymosin alpha-1 works as an immune booster for SARS patients. Immunoglobulin injected intravenously was observed to be the safest immunomodulator for long-term use. Hence, they can be used for the treatment of COVID-19[40-42].

Convalescent plasma therapy: - This therapy is given when there is no specific vaccine or drug is sufficient for the treatment. This is one of the effective ways to alleviate the course of disease for the patients who are infected severely. The patients suffering from SARS treated with convalescent plasma therapy and few doses of hormonal shock, convalescent plasma therapy found to be more effective as compared to hormonal shock. There was decreased hospital stays and mortality rate. The patients recovered from COVID-19 produced specific antibodies against it and plasma from them can be used to treat limit viral production in the initial infection phase and help to eliminate the virus which results in rapid recovery of the patients[43-46]. Hence further considerations are required to ensure the safety of the plasma globulin products[42].

Auxiliary blood purification treatment: - ACE2 receptors are highly expressed in human kidneys approximately 100 times as compares to lungs. It is the key receptor needed by COVID-19 for its replication in the host. Hence, kidneys might be the main target for the COVID-19. The blood purification treatment can decrease the renal workload and assist in renal function recovery. The serious cases of COVID-19 might suffer from cytokine storms. The immune system can get damaged due to an imbalance of pro-inflammatory and anti-inflammatory factors. Blood purification technology can be used to eliminate inflammatory

factors and cytokine storms, maintain electrolyte and acid-base balance to control patient's capacity in an effective manner[48, 49]. In this manner, symptoms in patients can be improved and blood oxygen level might be increased[42].

Remdesivir: - Gilead Science Inc. has developed a nucleotide prodrug which is a novel experimental drug. It is an antiviral unapproved drug that was developed for the treatment of Ebola and SARS. A clinical case study in the US on a COVID-19 patient who was first administrated with remdesivir, on the 11th day lower load of virus particles observed in nasopharyngeal and or pharyngeal samples. Hence clinical conditions of patients are improved[49]. Further controlled clinical trials are required to ensure its safety and efficacy in COVID-19 patients[50,51].

Antiviral Drugs: - Favorable clinical response was observed when lopinavir and ribavirin are used to treat COVID-19 patients. In vitro antiviral activity of both the drugs reported against SARS-associated coronavirus[52, 53].

Chloroquine and Hydroxychloroquine: - are used to treat malaria, systemic lupus erythematosus, and rheumatoid arthritis by preventing viral entry into the host cells by preventing glycosylation of host receptors, proteolysis, and acidification of endosomes. They were also reported to attenuate cytokine production, inhibit autophagy and lysosomal activity. Hence, they have an immunomodulator effect. In the low micro molar range, chloroquine inhibits COVID-19 with a half-maximal effective concentration in vitro. Hydroxychloroquine showed lower EC50 as compared to chloroquine in vitro after 24 hours. A report from china shows chloroquine used in the successful treatment of approximately 100 COVID-19 cases. However, no evidence exists that proves the efficacy of chloroquine and hydroxychloroquine against SARS and MERS. Chloroquine and hydroxychloroquine resulted in low virus numbers, enhanced radiological findings, and decreased progression of diseases. Both of these drugs cause rare and serious adverse effects like QTc prolongation, hypoglycemia, neuropsychiatric effects, retinopathy, and cardiac arrest[54-61].

Arbidol: - It is one of the promising antiviral agents which works with a unique mechanism that targets the S protein/ ACE 2 interaction resulting in inhibition of viral envelop fusion with membrane[62].

Favipiravir: - It is ribofuranosyl-5' triphosphate, a prodrug of purine nucleotide. The active compound inhibits the RNA polymerase, which interferes with viral replication. The

preclinical data were obtained from the trials of this drug against Ebola and influenza. It also showed a broad range of activity against other RNA viruses. The EC50 value of favipiravir against SARS-CoV-2 was found to be 61.88 μM/L in Vero E6 cells. Depending upon the indication of the infection dosing regimens are proposed. A lower dose is prescribing for influenza as compared to SARS-CoV-2 and Ebola. Higher doses are (higher value of therapeutic window) are considered for the COVID-19 patients. A loading dose is given followed by a maintenance dose every 12 hours. This drug has a half-life of about 5 hours. Even though the drug is well tolerated it shows some mild adverse effects. It is used for influenza treatment in Japan, but unavailable for clinical use in United States[63-71].

Tocilizumab (TCZ): - An alternative treatment approach for COVID-19 patients with cytokine storms risk is Tocilizumab, a monoclonal antibody specifically against interleukin-6. In serious patients, a single dose of Tocilizumab was found very beneficial with a 10-fold increase in interleukin-6. Interleukin-6 is eliminated through IL-6R–mediated clearance.IL-6R binds with TCZ which inhibits IL-6 mediated clearance, leading to serum accumulation. Interestingly this study might explain the elevated IL-6 levels in TCZ-treated COVID-19 patients and then the gradual decrease in IL-6 levels which is caused by the inhibition of the inflammatory activity of TCZ which finally results in improved clinical outcome[72,73].

JAK inhibitors: - the receptors of COVID-19 are a cell surface protein ACE2, which is expressed by the cells of the heart, kidney lungs, and blood vessels. This virus enters the cell via endocytosis. Out of all known regulators of endocytosis, one is AP-2 associated protein kinase1. Virus entry into the cell can be interrupted by inhibiting AP-2 associated protein kinase. A well-known JAK inhibitor and AP-2 associated protein kinas inhibitor are Baricitinib, which also a possible drug candidate for the treatment of COVID-19 patients. To reach the plasma concentration 2mg or 4mg therapeutic dose once daily was enough. Jack inhibitors tend to inhibit multiple inflammatory cytokines such as INF-a, which plays a necessary role in curbing virus activity. To confirm the efficacy of Baricitinib, clinical trials needed to be studied in detail. However, a prospective, single-blind, randomized controlled clinical trial was carried out on an inpatient that was severely affected with covid-19 pneumonia by treating them with a combination of ruxolitinib with mesenchymal stem cells[74, 75].

VACCINES

Subunit vaccines: - A subunit vaccine efficacious in many studies based on recombinant S protein of MERS-CoV S and ARS-CoV[76-79]. A vaccine is under development by Clover Biopharmaceuticals based on Trimer-Tag technology [80]. SARS-CoV-2 protein binding to ACE2 receptor domain was found to exhibit higher binding affinity as compared to SARS-CoV protein binding to ACE2 receptor[81]. Hence, this knowledge is used by various organizations with international collaborations to develop a receptor-binding domain vaccine[82]. To potentiate heterosubtypic immunity for influenza pulmonary surfactant biometric nanoparticles are used and can also be used as an adjuvant for the enhancement of immunogenicity of COVID-19 subunit vaccines[83].

Inactivated or live-attenuated vaccines: - It represents one of the traditional methods for vaccine development. Researchers from Hong Kong University developed a live influenza vaccine that expresses SARSCoV-2 proteins. To attenuate the virus codon deoptimization technology used by Codagenix. Many more companies are exploring strategies to develop COVID-19 vaccine[84, 85].

Virus vector-based vaccine: - High level of expression of the protein, long-term stability, and strong induction of immune response offered by vaccines which are based on viral vectors [86]. An adenovirus vector vaccine is developed by Jonson and Jonson Company via AdVac® /PER.C6® platform for vaccine[87]. The first adenovirus vector-based COVID-19 vaccine developed by a group of Chen Wei group entered the human trial phase 1 with unprecedented rapidity on 16 march 2020 (NCT04313127). In Wuhan, China March 2020 one more phase 1 safety trial of an adenovirus recombinant candidate for the vaccine (Cansino Biologics Inc., Tianjin, China), Ad5-nCoV, recruited 108 healthy adults[88]. Shenzhen Geno-Immune Medical Institute developed two lentivirus vector-based vaccine candidates, COVID-19/aAPC (by applying lentivirus modification, including SARS-CoV2 small genes) and LVSMENP- DC (by modifying DC with lentivirus vectors expressing SARS-CoV2 minigenes and immune-modulatory genes)[89].

Vaccine candidates in the clinical phase

Worldwide currently 31 vaccines are in the clinical trial phase. The vaccines can be broadly classified into five categories like Non-replicating viral vector, inactivated, RNA, DNA, and protein subunit. The routes of administration of these vaccines are intramuscular except for

one vaccine which is developed by Cadila Healthcare Limited which administered intradermally. The following table represents the five categories of vaccines along with their manufacturer[90].

Non-Replicating Viral Vector	Inactivated	RNA	DNA	Protein Subunit
•University of Oxford/AstraZeneca •CanSino Biological Inc./Beijing Institute of Biotechnology •Janssen Pharmaceutical Companies •Gamaleya Research Institute •ReiThera/LEUKOCARE/Univercells •Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme (Replicating Viral Vector)	•Sinovac •Wuhan Institute of Biological Products/Sinopharm •Beijing Institute of Biological Products/Sinopharm •Institute of Medical Biology, Chinese Academy of Medical Sciences •Bharat Biotech	•Moderna/NIAID •BioNTech/Fosun Pharma/Pfizer •Curevac •Arcturus/Duke-NUS •Imperial College London •People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech.	•Inovio Pharmaceuticals/ International Vaccine Institute •Osaka University/ AnGes/ Takara Bio •Cadila Healthcare Limited •Genexine Consortium	•Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences •Novavax •Kentucky Bioprocessing, Inc •Clover Biopharmaceuticals Inc./GSK/Dynavax •Vaxine Pty Ltd/Medytox •University of Queensland/CSL/ Seqirus •Medigen Vaccine Biologics Corporation/NIAID/Dynavax •Instituto Finlay de Vacunas, Cuba •FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo

Vaccines candidates in the pre-clinical phase

Worldwide around 174 vaccine candidates are in the pre-clinical phase. These vaccines can be classified into eight different categories like DNA, RNA, VLP, Non-replicating viral vector, replicating viral vector, protein subunit, Inactivated, live attenuated virus. The following data represent the vaccine type along with the developer.

DNA

- DIOSynVax Ltd / University of Cambridge
- Ege University
- Scancell/University of Nottingham/ Nottingham Trent University
- Karolinska Institute / Cobra Biologics
- Chula Vaccine Research Center
- BioNet Asia
- Mediphage Bioceuticals/University of Waterloo
- Entos Pharmaceuticals
- Symvivo
- Takis/Applied DNA Sciences/Evvivax
- Immunomic Therapeutics, Inc./EpiVax, Inc./PharmaJe

Inactivated

- KM Biologics
- Selcuk University
- Erciyes University
- National Research Centre, Egypt
- Beijing Minhai Biotechnology Co., Ltd.
- Osaka University/ BIKEN/ NIBIOHN
- Sinovac/Dynavax
- Valneva/Dynavax
- Research Institute for Biological Safety Problems, Rep of Kazakhstan

Live attenuated virus

- Mehmet Ali Aydinlar University / Acıbadem Labmed Health Services A.S.
- Codagenix/Serum Institute of India
- Indian Immunologicals Ltd/Griffith University

VLP

- Bezmialem Vakif University
- Middle East Technical University
- VBI Vaccines Inc.
- IrsiCaixa AIDS Research/IRTA-CReSA/Barcelona Supercomputing Centre/Grifols
- Mahidol University/ The Government Pharmaceutical Organization (GPO)/Siriraj Hospital
- Navarrabiomed, Oncoimmunology group
- Saiba GmbH
- Imophoron Ltd and Bristol University's Max Planck Centre
- Doherty Institute
- OSIVAX
- ARTES Biotechnology
- Univ. of Sao Paulo

Protein subunit

- Farmacológicos Veterinarios SAC (FARVET SAC) / Universidad Peruana Cayetano Heredia (UPCH)
- Research Institute for Biological Safety Problems, Rep of Kazakhstan
- Mynvax
- Izmir Biomedicine and Genome Center
- Bogazici University
- University of Virginia
- Helix Biogen Consult, Ogbomoso & Trinity Immonoefficient Laboratory, Ogbomoso, Oyo State, Nigeria.
- National Research Centre, Egypt
- University of San Martin and CONICET, Argentina
- Chulalongkorn University/GPO, Thailand
- AdaptVac (PREVENT-nCoV consortium)
- ExpreS2ion
- IMV Inc
- WRAIR/USAMRIID
- National Institute of Infectious Disease, Japan/Shionogi/UMN Pharma
- Osaka University/ BIKEN/ National Institutes of Biomedical Innovation, Japan
- Univ. of Pittsburgh
- Vaxil Bio
- Biological E Ltd
- Flow Pharma Inc
- AJ Vaccines
- Generex/EpiVax
- ImmunoPrecise/LiteVax BV
- Intravacc/Epivax
- Neovii/Tel Aviv University
- Intravacc/Epivax

Protein subunit

- EpiVax/Univ. of Georgia
- EpiVax
- Sanofi Pasteur/GSK
- Heat Biologics/Univ. Of Miami
- FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo
- Baylor College of Medicine
- iBio/CC-Pharming
- Saint-Petersburg scientific research institute of vaccines and serums
- Innovax/Xiamen Univ./GSK
- VIDO-InterVac, University of Saskatchewan
- OncoGen
- MIGAL Galilee Research Institute
- LakePharma, Inc.
- Baiya Phytopharm/ Chula Vaccine Research Center
- Quadram Institute Biosciences
- BiOMViS Srl/Univ. of Trento
- Lomonosov Moscow State University
- University of Alberta
- AnyGo Technology
- Yisheng Biopharma
- Vabiotech
- Applied Biotechnology Institute, Inc.
- Axon Neuroscience SE
- MOGAM Institute for Biomedical Research, GC Pharma

Replicating viral vector

- KU Leuven
- Cadila Healthcare Limited
- FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo
- DZIF – German Center for Infection Research/CanVirex AG
- Tonix Pharma/Southern Research
- BiOCAD and IEM
- FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo
- Fundação Oswaldo Cruz and Instituto Buntantan
- University of Hong Kong
- IAVI/Merck
- University of Manitoba
- University of Western Ontario
- Aurobindo
- FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo
- Israel Institute for Biological Research/Weizmann Institute of Science
- UW–Madison/FluGen/Bharat Biotech
- Intravacc/ Wageningen Bioveterinary Research/Utrecht Univ.
- The Lancaster University, UK

RNA

- Gennova
- Selcuk University
- Translate Bio/Sanofi Pasteur
- CanSino Biologics/Precision NanoSystems
- Fudan University/ Shanghai JiaoTong University/RNACure Biopharma
- Fudan University/ Shanghai JiaoTong University/RNACure Biopharma
- Centro Nacional Biotecnología (CNB-CSIC), Spain
- University of Tokyo/ Daiichi-Sankyo
- BIOCAD
- RNAimmune, Inc.
- FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo
- China CDC/Tongji University/Stermina
- Chula Vaccine Research Center/University of Pennsylvania
- eTheRNA
- Greenlight Biosciences
- IDIBAPS-Hospital Clinic, Spain

SUMMARY

Even though there is no specific drug to treat the novel coronavirus the combined therapy of drugs shows that we can avoid the mortality rate to a great extent. Most of such drugs act on the symptoms to give some relief to the patient. Even though precautions and measures were taken to slow the transmission rate the need for a promising drug is a need of an hour. As even though we can cure the patients with already existing drugs the after-effects of the coronavirus on the human body is a matter of concern as even after being cured of the virus the patient shows the sign and symptoms like low oxygen level, headache, difficulty in breathing and are responsible for some deaths. However, the best treatment for COVID-19 is still combined therapy along with drugs but the vaccines which are in the clinical trial phase might prove more effective than the current therapies.

CONFLICT OF INTEREST: The authors have no conflicts of interest to declare.

REFERENCES:

1) Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020; published online Feb 3. DOI:10.1038/s41586-020-2008-3.
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) World Health Organization. "Coronavirus disease 2019 (COVID-19): situation report, 72." (2020).
4) https://covid19.who.int/
5) Chan, Jasper Fuk-Woo, et al. "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster." The Lancet 395.10223 (2020): 514-523.
6) D.S. Hui, I.E. Azhar, T.A. Madani, F. Ntoumi, R. Kock, O. Dar, et al., The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—the latest 2019 novel coronavirus outbreak in Wuhan, China, International Journal of Infectious Diseases 91 (2020) 264–266.
7) Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID 19) (PDF) (Report). World Health Organization (WHO). 16–24 February 2020. Archived (PDF) from the original on 29 February 2020. Retrieved 21 March 2020
8) Lu R, Zhao X, Li J, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; published online Jan 29. https://doi.org/10.1016/ S0140-6736(20)30251-8.
9) Sardar, Rahila, et al. "Comparative analyses of SAR-CoV2 genomes from different geographical locations and other coronavirus family genomes reveals unique features potentially consequential to host-virus interaction and pathogenesis." bioRxiv (2020).
10)Petrosillo, Nicola, et al. "COVID-19, SARS and MERS: are they closely related?." Clinical Microbiology and Infection (2020).
11)N. Dong, X. Yang, L. Ye, K. Chen, E.W.-C. Chan, S. Chen, Genomic and protein structure modelling analysis depicts the origin and pathogenicity of 2019-ncov, a new coronavirus which caused a pneumonia outbreak in wuhan, China, F1000Res. 9 (2020) 121
12)W. Li, J. Sui, I.-C. Huang, J.H. Kuhn, S.R. Radoshitzky, W.A. Marasco, H. Choe, M. Farzan, The s proteins of human coronavirus nl63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ace2, Virology 367 (2007) 367–374.

13) L. He, Y. Ding, Q. Zhang, X. Che, Y. He, H. Shen, H. Wang, Z. Li, L. Zhao, J. Geng, Expression of elevated levels of pro-inflammatory cytokines in sars-cov-infected ace2+ cells in sars patients: relation to the acute lung injury and pathogenesis of sars, J. Pathol.: J. Pathol. Soc. Great Britain and Ireland 210 (2006) 288–297.

14)Li, Xiaowei, et al. "Molecular immune pathogenesis and diagnosis of COVID-19." Journal of Pharmaceutical Analysis (2020).

15)F. Wu, S. Zhao, B. Yu, et al., A new coronavirus associated with human respiratory disease in China, Nature (2020). https://doi.org/10.1038/s41586-020-2008-3

16)E. de Wit, N. van Doremalen, D. Falzarano, et al., SARS and MERS: recent insights into emerging coronaviruses, Nat. Rev. Microbiol. 14 (2016) 523-534. https://doi.org/10.1038/nrmicro.2016.81

17)S. Perlman, J. Netland Coronaviruses post-SARS: update on replication and pathogenesis, Nat. Rev. Microbiol. 7 (2009) 439-450. https://doi.org/10.1038/nrmicro2147

18)Li, Guoping, et al. "Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19." Journal of autoimmunity (2020): 102463.

19)Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al., Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2001316

20)W. Wang, J. Tang, F. Wei, Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, J. Med. Virol. 92 (4) (2020) 441–447, https://doi.org/10.1002/jmv.25689.

21)Cao, Wei, and Taisheng Li. "COVID-19: towards understanding of pathogenesis." Cell Research 30.5 (2020): 367-369.

22)L.L. Ren, Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, et al., Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study, Chinese Med J (2020), https://doi.org/10.1097/CM9.0000000000000722.

23)C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

24)W.G. Carlos, C.S. Dela Cruz, B. Cao, S. Pasnick, S. Jamil, Novel wuhan (2019-nCoV) coronavirus, Am. J. Respir. Crit. Care Med. 201 (4) (2020) 7–8, https://doi.org/10. 1164/rccm.2014P7.

25)A. Assiri, J.A. Al-Tawfiq, A.A. Al-Rabeeah, F.A. Al-Rabiah, S. Al-Hajjar, A. Al- Barrak, et al., Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study, Lancet Infect. Dis. 13 (2013) 752–761.

26) N. Lee, D. Hui, A. Wu, P. Chan, P. Cameron, G.M. Joynt, et al., A major outbreak of severe acute respiratory syndrome in Hong Kong, N. Engl. J. Med. 348 (2003) 1986–1994.

27)Dan, H.; Gilbert, M.; Borman, R.; Clark, K.L. Quantitative mrna expression profiling of ace 2, a novel homologue of angiotensin converting enzyme. FEBS Lett. 532, 0- 110.

28)Tipnis, S.R.; Hooper, N.M.; Hyde, R.; Karran, E.; Christie, G.; Turner, A.J. A human homolog of angiotensin-converting enzyme: cloning and functional expression as a captopril-insensitive carboxypeptidase. J. Biol. Chem. 275, 33238-33243.

29) I. Hamming, W. Timens, M.L.C. Bulthuis, A.T. Lely, H.V. Goor, Tissue distribution of ace2 protein, the functional receptor for sars coronavirus. A first step in understanding sars pathogenesis, J. Pathol. 203 (2004) 631–637.

30)Bai, Yan, et al. "Presumed asymptomatic carrier transmission of COVID-19." Jama 323.14 (2020): 1406-1407

31)https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19#:~:text=No%20pharmaceutical%20products%20have%20yet,%2Dlabel%E2%80%9D%20use.

32)Shang, Lianhan, et al. "On the use of corticosteroids for 2019-nCoV pneumonia." Lancet (London, England) 395.10225 (2020): 683.

33)National Health Commission of the People's Republic of China.<Guideline on diagnosis and treatment of COVID-19 (Trial 6th edition). http://www.nhc.gov.cn/xcs/zhengcwj/202002/8334a8326dd94d329df351d7da8aefc2.shtml (accessed Feb 23, 2020; in Chinese).

34) Z. Xu, L. Shi, Y.J. Wang, J.Y. Zhang, L. Huang, C. Zhang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. (2020), https://doi.org/10.1016/S2213-2600(20)30076-X.
35) J. Zhao, S.S. Tian, J. Yang, J.F. Liu, W.D. Zhang, Investigating the mechanism of Qing-Fei-Pai-Du-Tang for the treatment of Novel Coronavirus Pneumonia by network pharmacology, Chinese Traditional and Herbal Drugs, http://kns.cnki.net/kcms/ detail/12.1108.R.20200216.2044.002.html.
36)H. Wu, J.Q. Wang, Y.W. Yang, T.Y. Li, Y.J. Cao, Y.X. Qu, Y.J. Jin, C.N. Zhang, Y.K. Sun, Preliminary exploration of the mechanism of QingfeiPaidu decoction agains novel coronavirus pneumonia based on network pharmacology and molecular docking technology, Acta Pharmaceutica Sinica. DOI: 10.16438/j.0513-4870.2020-0136.
37)Ren, Jun-ling, Ai-Hua Zhang, and Xi-Jun Wang. "Traditional Chinese medicine for COVID-19 treatment." Pharmacological research 155 (2020): 104743.
38)LoutfyMR , Blatt LM , Siminovitch KA , Ward S , WolffB , Lho H , et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a prelim- inary study. JAMA 2003;290:3222–8 .
39)Mustafa S ,Balkhy H , Gabere MN . Current treatment options and the role of peptides as potential therapeutic components for Middle East respiratory syn- drome (MERS): a review. J Infect Public Health 2018;11:9–17 .
40)GilardinL ,Bayry J , Kaveri SV . Intravenous immunoglobulin as clinical im- mune-modulating therapy. CMAJ 2015;187:257–64 .
41)Kumar V , Jung YS , Liang PH . Anti-SARS coronavirus agents: a patent review (2008–present). Expert OpinTher Pat 2013;23:1337–48 .
42)Wang, Li-sheng, et al. "A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence." International journal of antimicrobial agents (2020): 105948.
43) Mair-Jenkins J , Saavedra-Campos M , Baillie JK , Cleary P , Khaw FM , Lim WS , et al. The effectiveness of convalescent plasma and hyperimmune im- munoglobulin for the treatment of severe acute respiratory infections of vi- ral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211:80–90 .
44)Soo YO , Cheng Y , Wong R , Hui DS , Lee CK , Tsang KK , et al. Retrospective com- parison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10:676–8 .
45)Baron S, editor. Medical microbiology. 4th edition. Galveston, TX: University of Texas Medical Branch; 1996 .
46)Cheng Y , Wong R , Soo YO , Wong WS , Lee CK , Ng MH , et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44–6 .
47)ZarbockA , Kellum JA , Schmidt C , Van Aken H , Wempe C , Pavenstadt H , et al. Effect of early vs delayed initiation of renal replacement therapy on mor- tality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA 2016;315:2190–9 .
48)Lim CC , Tan CS , Kaushik M , Tan HK . Initiating acute dialysis at earlier Acute Kidney Injury Network stage in critically ill patients without traditional in- dications does not improve outcome: a prospective cohort study. Nephrology 2015;20:148–54 .
49)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. DOI: 10.1056/NEJMoa2001191.
50)Wu, Yi-Chi, Ching-Sung Chen, and Yu-Jiun Chan. "The outbreak of COVID-19: An overview." Journal of the Chinese Medical Association 83.3 (2020): 217.
51)Al-Tawfiq, Jaffar A., Ali H. Al-Homoud, and Ziad A. Memish. "Remdesivir as a possible therapeutic option for the COVID-19." Travel medicine and infectious disease (2020).
52)Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al.; HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252–6.
53) Pradhan P, Pandey AK, Mishra A, Gupta P, Tripathi PK, Menon MB, et al. Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1 gp120 and Gag. bioRxiv 2020. Available at https://www. biorxiv.org/content/10.1101/2020.01.30.927871v2. Accessed February 7, 2020. (withdrawn)
54)Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3(11):722-727. doi:10.1016/S1473-3099(03)00806-5

55) Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. [published online March 20, 2020].JAntimicrob Chemother. 2020;dkaa114. doi:10.1093/jac/dkaa114
56)Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. Published online March 11,2020. doi:10.1016/j.ijantimicag.2020.105938
57)Yao X, Ye F, ZhangM, 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. Published online March 9, 2020. doi:10.1093/cid/ciaa237
58) Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020; 14(1):72-73. doi:10.5582/bst.2020.01047
59)Kalil AC. Treating COVID-19—off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA. Published March 24, 2020. doi:10.1001/jama.2020.4742
60) Interview with David Juurlink. Coronavirus (COVID-19) update: chloroquine/ hydroxychloroquine and azithromycin. JAMA. March 24, 2020. Accessed April 3, 2020. https://edhub. ama-assn.org/jn-learning/audio-player/18337225
61)https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or
62)Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc Natl Acad Sci U S A. 2017;114(2):206-214. doi:10.1073/pnas.1617020114
63)Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc JpnAcad Ser B Phys Biol Sci. 2017; 93(7):449-463. doi:10.2183/pjab.93.027
64)Mentre F, Taburet AM, Guedj J, et al. Dose regimen of favipiravir for Ebola virus disease. Lancet Infect Dis. 2015;15(2):150-151. doi:10.1016/S1473-3099(14)71047-3
65) Sissoko D, Laouenan C, Folkesson E, et al; JIKI Study Group. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea [published correction appears in PLoS Med. 2016;13(4): e1002009]. PLoS Med. 2016;13(3):e1001967. doi:10.1371/journal.pmed.1001967
66)Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. [published online February 22, 2020]. PharmacolTher. 2020;107512. doi:10.1016/j. pharmthera.2020.107512
67)Chinello P, Petrosillo N, Pittalis S, Biava G, Ippolito G, Nicastri E; INMI Ebola Team. QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient. PLoSNegl Trop Dis. 2017;11(12):e0006034. doi:10.1371/journal.pntd.0006034
68)Kumagai Y, Murakawa Y, Hasunuma T, et al. Lack of effect of favipiravir, a novel antiviral agent, on QT interval in healthy Japanese adults. Int J Clin PharmacolTher. 2015;53(10):866-874. doi:10.5414/CP202388
69)WangM, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.Cell Res. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0
70)Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug DiscovTher. 2020;14(1):58-60. doi:10.5582/ddt.2020.01012
71)Sanders, James M., et al. "Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review." Jama 323.18 (2020): 1824-1836.
72)Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008;112(10):3959-3964.
73)Luo, Pan, et al. "Tocilizumab treatment in COVID-19: A single center experience." Journal of medical virology 92.7 (2020): 814-818.
74)P. Richardson, I. Griffin, C. Tucker, D. Smith, O. Oechsle, A. Phelan, J. Stebbing, Baricitinib as potential treatment for 2019-nCoV acute respiratory disease, Lancet. 395 (2020) e30-e31.

75)Zhang, Wen, et al. "The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China." Clinical Immunology (2020): 108393.
76)Du L, Yang Y, Zhou Y, Lu L, Li F, Jiang S. MERS-CoV spike protein: a key target for antivirals. Expert OpinTher Targets 2017;21:131e43.
77) Wang Q, Wong G, Lu G, Yan J, Gao GF. MERS-CoV spike protein: targets for vaccines and therapeutics. Antivir Res 2016;133:165e77.
78)Du L, Tai W, Yang Y, Zhao G, Zhu Q, Sun S, et al. Introduction of neutralizing immunogenicity index to the rational design of MERS coronavirus subunit vaccines. Nat Commun2016;7:13473.
79)Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV–a target for vaccine and therapeutic development. Nat Rev Microbiol 2009;7: 226-36.
80)Clover Biopharmaceuticals. Clover initiates development of recombinant subunit-trimer vaccine for Wuhan coronavirus (2019-nCoV). 2020.
81)Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol 2020. https://doi.org/10.1038/s41423-020-0400-4 [Epub ahead of print].
82)Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 vaccine pipeline: an overview. Curr Trop Med Rep 2020. https://doi.org/10.1007/s40475-020-002016 [Epub ahead of print].
83)Wang J, Li P, Yu Y, Fu Y, Jiang H, Lu M, et al. Pulmonary surfactant-biomimetic nanoparticles potentiate heterosubtypic influenza immunity. Science 2020;367.
84)Cheung E. China coronavirus: Hong Kong researchers have already developed vaccine but need time to test it, expert reveals. South China Morning Post. https://www.scmp.com/news/hong-kong/health-environment/article/ 3047956/china-coronavirus-hongkong-researchers-have. Accessed 28 Feb 2020.
85)Shieber J. Codagenix raises $20 million for a new flu vaccine and other therapies. Tech Crunch. https://techcrunch.com/2020/01/13/codagenix-raises- 20-million-for-a-new-flu-vaccine-and-othertherapies/. Accessed 28 Feb 2020.
86)Thanh Le T, Andreadakis Z, Kumar A, G_omezRom_an R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov2020;19:305e6.
87) J&J working on coronavirus vaccine. thepharmaletter; 2020. https://www.thepharmaletter.com/art icle/j-j-working-on-coronavirusvaccine. [Accessed 28 February 2020].
88)IVI, INOVIO, and KNIH to partner with CEPI in phase 1/2 clinical trial of INOVIO's COVID-19 DNA vaccine in South Korea. 2020. http://ir.inovio.com/ news-and-media/news/press-release-details/2020/IVI-INOVIO-and-KNIH-to- Partner-with-CEPI-in-Phase-12-Clinical-Trial-of-INOVIOs-COVID-19-DNAVaccine-in-South-Korea/default.aspx. [Accessed 22 April 2020].
89)Zhang, Naru, et al. "Current development of COVID-19 diagnostics, vaccines and therapeutics." Microbes and Infection (2020).
90)https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines