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COVID-19 RECENT UPDATES AND THERAPEUTIC HOPE

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ARTICLE INFO	ABSTRACT
Article history	The disease caused by this virus has different names. The disease is called COVID-19,
Received 10/09/2020	Coronavirus Diseases 2019 for the year in which it first appeared globally. COVID-19 is also
Available online	known as "novel coronavirus," meaning a new type of Coronavirus not previously discovered
31/10/2020	or identified. COVID-19 is a type (strain) of Coronavirus. A virus is very small (microscopic)
	type of germ that can cause an infection. Which causes serious respiratory illness such as
Keywords	pneumonia and lung failure, was first reported in Wuhan, the capital of Hubei, China.
COVID-19,	COVID-19 is also called SARS-Cov-2 for severe acute respiratory syndrome coronavirus 2?
Antiviral Drugs	Current clinical management includes infection prevention and control measures and
(Remdesivir,	supportive care including supplemental oxygen and mechanical ventilatory support. These
Hydroxychloroquine,	drugs and therapeutic agents include antiviral agents (remdesivir, hydroxychloroquine,
Chloroquine,	chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir), and supporting agents
Azithromycin),	(Ascorbic acid, Azithromycin, Corticosteroids, Nitric oxide, IL-6 antagonists), among others.
Convalescent Plasma etc.	We hope that this review will provide useful and most updated therapeutic drugs to prevent,
	control, and treat COVID-19 patients until the approval of vaccines and specific drugs
	targeting SARS-CoV-2.

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INTRODUCTION

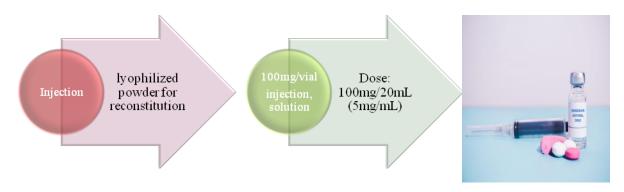
The horrific pandemic outbreak of COVID-19 (coronavirus disease 2019) around the world caught the health care systems in every country by storm, most if not all were caught off guard without proper defense mechanisms to cope with and to control such a pandemic. COVID-19, caused by a new and novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), has recently been identified and characterized. Coronaviruses are named for their crown-like spikes on their surface and there are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta. SARS-CoV-2 belongs to the beta sub-grouping, and is one of the seventh coronavirus to date infecting humans.

ANTIVIRAL DRUG

Remdesivir :-

Remdesivir is a potential drug for treatment of COVID-19.It is a phosphoramidate prodrug of an adenosine C-nucleoside and a broad-spectrum antiviral agent synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus. Infection Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) infection in cultured cells, mice and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection. Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination.

Dosage Forms :-



Hydroxychloroquine & Chloroquine :-

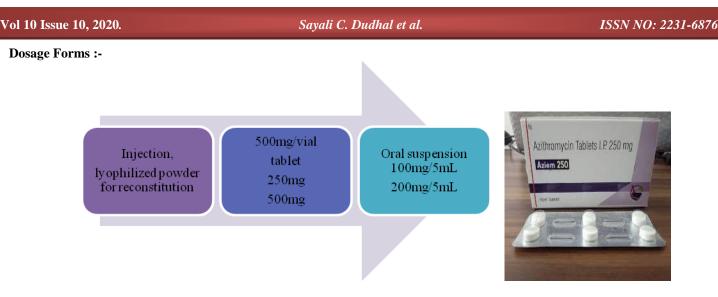
Hydroxychloroquine and Chloroquine are drugs with a long history of clinical use with similar chemical structures often used in the treatment of lupus erythematosus, rheumatoid arthritis, and malaria. Compared with chloroquine, hydroxychloroquine has a hydroxyl group, which makes it less toxic while maintaining similar activity. TheseThese medicines are manufactured in tablet form for oral administration as chloroquine phosphate 500 mg (equivalent to 300 mg chloroquine base) and hydroxychloroquine sulfate 200 mg (equivalent to 155 mg hydroxychloroquine base) active drug per tablet, respectively.

Etiology :-

Chloroquine and hydroxychloroquine bind to melanin in the retinal pigment epithelium (RPE) and cause damage to the macular cones outside of the fovea. The drugs inhibit RPE lysosome activity, reduce phagocytosis of shed photoreceptor outer segments causing an accumulation of outer receptor segments.

Azithromycin:

Azithromycin is an antibiotic that can be used to fight many different types of infections caused by susceptible bacteria, such as respiratory infections, skin infections, and sexually transmitted diseases. Moreover, it has been proven to be active in vitro against Zika and Ebola viruses and to prevent severe respiratory tract infections when treated to patients suffering viral infection. For the mechanism of action, azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA. Previously, azithromycin has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza).



Convalescent Plasma :-

COVID-19 is an infectious disease that is caused by a new coronavirus, SARS-COV-2. The outbreak has affected almost every country of the World and as of July 11, 2020, a total of 12,639,583 confirmed cases and 563,137 deaths had been reported in 188 countries. As the development of efficient and safe vaccination will require months, quick alternative treatments are sought. Passive immunisation using the plasma of recovered COVID-19 donors for the treatment of severe COVID-19 cases could offer a suitable therapeutic strategy. The plasma of recovered COVID-19 donors contains specific IgG and IgM anti–SARS-CoV-19 antibodies, which can neutralize the virus. However, implementation of a convalescent plasma transfusion programme might need comprehensive planning. The current treatment of COVID-19 caused by novel coronavirus SARS-CoV-2 has been limited to general supportive care, with provision of critical care as no vaccines are available. The clinical data for the studies involving COVID-19 are still scarce and limited to data from China, Spain, Italy, United States of America, Germany, France, The United Kingdom, and other international registries. This will be a problem when predicting treatment outcomes.

Symptoms :-



Seek immediate medical attention if you have serious symptoms. Always call before visiting your doctor or health facility. People with mild symptoms who are otherwise healthy should manage their symptoms at home. On average it takes 5-6 days from when someone is infected with the virus for symptoms to show, however it can take up to 14 days.

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CONCLUSION

All patients with COVID-19-infected received antibacterial agents, 90% received antiviral therapy, and 45% received methylprednisolone. Clinical trials are underway to investigate the efficacy of new antiviral drugs, convalescent plasma transfusion, and vaccines. The COVID-19 pandemic is a public health emergency of international concern, and all countries need a coordinated international effort to fight COVID-19. In the absence of vaccines and antivirals, isolation and quarantine are achieving remarkable results. It is necessary to strengthen the monitoring of COVID-19 and to develop drugs and vaccines against the COVID-19 infection as soon as possible.

REFERENCE

- 1. Nelemans T, Kikkert M. Viral innate immune evasion and the pathogenesis of emerging rna virus infections. Viruses. 2019;11(10). https://doi.org/10.3390/v11100961.
- 2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–3. https://doi.org/10.1038/s41586-020-2012-7.
- 3. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020;14(1):69-71. https://doi.org/10.5582/bst.2020.01020.
- 4. The US national initiative to provide COVID-19 Convalescent Plasma for use in controlled trials and in expanded access linked to those trials: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-coordinates-national-effort-develop-blood-related-therapies-covid-19.
- 5. The FDA previously provided guidance on emergency use of COVID-19 convalescent plasma: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-processcber/investigational-covid-19-convalescent-plasma-emergency-inds
- 6. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020;26:450–2. https://doi.org/10.1038/s41591-020-0820-9.
- 7. Bruckova M, McIntosh K, Kapikian AZ, Chanock RM. The adaptation of two human coronavirus strains (OC38 and OC43) to growth in cell monolayers. Proc Soc Exp Biol Med. 1970;135(2):431–5.
- 8. Hamre D, Kindig DA, Mann J. Growth and intracellular development of a new respiratory virus. J Virol. 1967;1(4):810–6.
- Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol. 2005;79(2):884– 95. https://doi.org/10.1128/JVI.79.2.884-895.2005.
- 10. Kindler E, Thiel V. SARS-CoV and IFN: too little, too late. Cell Host Microbe. 2016;19(2):139–41. https://doi.org/10.1016/j.chom.2016.01.012.
- 11. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 2016;19(2):181–93. https://doi.org/10.1016/j.chom.2016.01.007.
- 12. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523–34. https://doi.org/10.1038/nrmicro.2016.81.
- 13. 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. Lancet (LondEngl). 2020;395(10223):497–506. https://doi.org/10.1016/s0140-6736(20)30183-5.
- 14. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418–23. https://doi.org/10.1002/jmv.25681This review provides general information on coronaviruses.
- 15. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science (New York, NY). 2020;367(6485):1444–8. https://doi.org/10.1126/science.abb2762This paper described the recognition of SARS-CoV-2 by human ACE2 protein This paper described the recognition of SARS-CoV-2 by human ACE2 protein.
- 16. Fung TS, Liu DX. Human coronavirus: host-pathogen interaction. Annu Rev Microbiol. 2019;73:529– 57. https://doi.org/10.1146/annurev-micro-020518-115759.
- 17. Nelemans T, Kikkert M. Viral innate immune evasion and the pathogenesis of emerging rna virus infections. Viruses. 2019;11(10). https://doi.org/10.3390/v11100961.
- 18. CDC CfDCaP. Groups at higher risk for severe illness. Center for Disease Control and Prevention (CDC) 2020.
- 19. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020. https://doi.org/10.1164/rccm.202003-0817LE.
- 20. Fehr AR, Channappanavar R, Perlman S. Middle East respiratory syndrome: emergence of a pathogenic human coronavirus. Annu Rev Med. 2017;68:387–99. https://doi.org/10.1146/annurev-med-051215-031152.
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (LondEngl). 2020;395(10223):507– 13. https://doi.org/10.1016/s0140-6736(20)30211-7.
- 22. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. J Med Chem. 2017;60(5):1648–61. https://doi.org/10.1021/acs.jmedchem.6b01594.
- 23. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71. https://doi.org/10.1038/s41422-020-0282-0This paper evaluated the in vitro efficacy of remdesivir and chloroquine in inhibiting SARS-CoV-2.

- 24. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222. https://doi.org/10.1038/s41467-019-13940-6.
- 25. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. J Med Chem. 2017;60(5):1648–61. https://doi.org/10.1021/acs.jmedchem.6b01594.
- 26. https://clinicaltrials.gov/ct2/show/NCT04252664. Mild/Moderate 2019-nCoV Remdesivir RCT. 2020
- 27. https://clinicaltrials.gov/ct2/show/NCT04257656. Severe 2019-nCoV Remdesivir RCT. Feb 24, 2020
- 28. 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. https://doi.org/10.1056/NEJMoa2001282.
- 29. De Clercq E. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. Int J Antimicrob Agents. 2009;33(4):307–20. https://doi.org/10.1016/j.ijantimicag.2008.10.010.
- 30. Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ. 2020.
- 31. Borba M, de Almeida Val F, Sampaio VS, Alexandre MA, Melo GC, Brito M et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). medRxiv. 2020. This paper revealed the toxicity of a high dose (600 mg twice daily) of chloroquine in treating COVID-19 patients.
- 32. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020:2020.03.17.20037432. https://doi.org/10.1101/2020.03.17.20037432.
- 33. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug DiscovTher. 2020;14(1):58–60. https://doi.org/10.5582/ddt.2020.01012.
- 34. Villalaín J. Membranotropic effects of arbidol, a broad anti-viral molecule, on phospholipid model membranes. J Phys Chem B. 2010;114(25):8544–54. https://doi.org/10.1021/jp102619w.
- 35. Boriskin YS, Leneva IA, Pecheur EI, Polyak SJ. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem. 2008;15(10):997–1005. https://doi.org/10.2174/092986708784049658.
- 36. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antivir Res. 2013;100(2):446–54. https://doi.org/10.1016/j.antiviral.2013.09.015.
- 37. De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chem Asian J. 2019;14(22):3962-8. https://doi.org/10.1002/asia.201900841.
- 38. McClellan K, Perry CM. Oseltamivir. Drugs. 2001;61(2):263-83.
- 39. Rosa SGV, Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. Rev Panam Salud Publica. 2020;44.
- 40. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020;105954. https://doi.org/10.1016/j.ijantimicag.2020.105954.
- 41. Peters DH, Friedel HA, McTavish D. Azithromycin. A review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. Drugs. 1992;44(5):750–99. https://doi.org/10.2165/00003495-199244050-00007.
- 42. Retallack H, Di Lullo E, Arias C, Knopp KA, Laurie MT, Sandoval-Espinosa C, et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc Natl Acad Sci U S A. 2016;113(50):14408–13. https://doi.org/10.1073/pnas.1618029113.
- 43. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early Administration of Azithromycin and Prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. JAMA. 2015;314(19):2034–44. https://doi.org/10.1001/jama.2015.13896.
- 44. Madrid PB, Panchal RG, Warren TK, Shurtleff AC, Endsley AN, Green CE, et al. Evaluation of Ebola virus inhibitors for drug repurposing. ACS Infect Dis. 2015;1(7):317–26. https://doi.org/10.1021/acsinfecdis.5b00030.
- 45. label Ua. US azithromycin label. US azithromycin label. 2016 February Archived from the original on 23 November 2016.
- Ishaqui AA, Khan AH, Sulaiman SAS, Alsultan MT, Khan I, Naqvi AA. Assessment of efficacy of oseltamivir-azithromycin combination therapy in prevention of influenza-A (H1N1)pdm09 infection complications and rapidity of symptoms relief. Expert Rev Respir Med. 2020:1–9. https://doi.org/10.1080/17476348.2020.1730180.
- Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020. https://doi.org/10.1016/j.medmal.2020.03.006.
- 48. Kim Y, Kim H, Bae S, Choi J, Lim SY, Lee N, et al. Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-alpha/beta at the initial stage of influenza A virus (H3N2) infection. Immune Netw. 2013;13(2):70–4. https://doi.org/10.4110/in.2013.13.2.70.
- 49. Carr AC, Maggini S. Vitamin C and immune function. Nutrients. 2017;9(11). https://doi.org/10.3390/nu9111211.
- 50. Medicine USNLo. ClinicalTrials.gov. US National Library of Medicine. 2020 doi:(https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=ascorbic+acid&cntry=&state=&city=&dist=.
- 51. Cheng R. Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? Med Drug Discov. 2020;100028. https://doi.org/10.1016/j.medidd.2020.100028.

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- 52. Villar J, Belda J, Anon JM, Blanco J, Perez-Mendez L, Ferrando C, et al. Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: study protocol for a randomized controlled trial. Trials. 2016;17:342. https://doi.org/10.1186/s13063-016-1456-4.
- 53. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020. https://doi.org/10.1001/jamainternmed.2020.0994.
- 54. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020;395(10225):683-4. https://doi.org/10.1016/S0140-6736(20)30361-5.
- 55. Villar J, Ferrando C, Martinez D, Ambros A, Munoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8(3):267–76. https://doi.org/10.1016/S2213-2600(19)30417-5.



