WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 12, 1315-1331. Review Article ISSN 2277– 7105

REVIEW ON CORONA VIRUS (COVID-19)

Jayesh V. Ahirrao*[1] and Dr. Rishikesh S. Bacchav[2]

[1]Department of Quality Assurance Techniques, R. G. Sapkal College of Pharmacy, Anjaneri Nashik-422013.

[2]Department of Pharmacology, R. G. Sapkal College of Pharmacy, Anjaneri Nashik-422013.

Article Received on
19 August 2020,

Revised on 09 Sept. 2020,
Accepted on 29 Sept. 2020

DOI: 10.20959/wjpr202012-18868

***Corresponding Author**
Jayesh V. Ahirrao
Department of Quality Assurance Techniques, R. G. Sapkal College of Pharmacy, Anjaneri Nashik-422013.

ABSTRACT

In early December 2019, an outbreak of coronavirus disease 2019 (COVID-19), caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), arise in Wuhan City, Hubei Province, China. On January 30, 2020 the World Health Organization declared the outbreak as a International Public Health problem. As of 14 February 2020, 49,053 laboratory confirmed cases and 1,381 deaths have been reported globally. The disease is spread by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 days. The symptoms are mainly fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild in most of the people; in some gen elder patient, it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. Many people are asymptomatic. WHO and ECDC advices to avoid public places. The virus transmit faster than its two ancestors the (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), but has lower fatality rate. We conducted a literature review of publicly available information to summarize knowledge about the pathogen and the current epidemic. In this literature review, pathogenesis and immune responses, epidemiology, diagnosis, treatment and management of the disease, control and preventions strategies are all reviewed.

KEYWORDS: Corona virus, COVID-19, SARS-CoV-2, MERS-CoV-2, outbreak, novel coronavirus.

History & Origin

On December 31, 2019, the China Health Authority alerted the World Health Organization

(WHO) to many cases of pneumonia of unknown cause in Wuhan City in Hubei Province in central China. The cases had been reported since December 8, 2019, and many patients worked at or lived around the local Huanan Seafood Wholesale Market although other early cases had no exposure to this market.[1] Coronaviruses are enfold positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like preseance under the electron microscope; hence the name coronavirus.[5] There have been two events in the past two decades where in crossover of animal betacorona viruses to humans has resulted in severe disease. The first such case was observed in 2002–2003 when a new coronavirus of the beta generation and with origin in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus, delegate as severe acute respiratory syndrome corona virus affected 8422 people mostly in China and HongKong and caused 916 deaths (mortality rate 11%) before being contained.[6] Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of batorigin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%).[7] On January 7, a novel coronavirus, originally abbreviated as 2019-nCoV by WHO, was identified from the throat swab sample of a patient.[2] This pathogen was later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group[3] and the disease was named coronavirus disease 2019 (COVID-19) by the WHO. As of January 30, 7736 confirmed and 12,167 suspected cases had been reported in China and 82 confirmed cases had been detected in 18 other countries.[4] In the same day, WHO declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC).[4]

Microbiology

Corona virus is spherical or pleomorphic, single stranded, enveloped RNA and covered with club shaped glycoprotein. Corona viruses are four sub types such as alpha, beta, gamma and delta corona virus. Each of sub type corona viruses has many serotypes. Some of them were affect human of other affected animals such as pigs, birds, cats, mice and dogs.[8-12]

Types of corona virus

SARS-CoV-2 is a member of the family Coronaviridae and order Nidovirales. The family consists of two subfamilies, Coronavirinae and Torovirinae and members of the subfamily Coronavirinae are subdivided into four generation:

(a) Alphacoronavirus (229E) and (NL63) This virus contains the human coronavirus;
(b) Betacoronavirus includes HCoV-(OC43), Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), HCoV-(HKU1), and Middle Eastern respiratory syndrome coronavirus (MERS-CoV);
(c) Gammacoronavirus includes viruses of whales and birds and;
(d) Deltacoronavirus includes viruses isolated from pigs and birds.[13]

SARS-CoV-2 belongs to Betacoronavirus together with two highly pathogenic viruses, SARS-CoV and MERS-CoV. SARS-CoV-2 is an enveloped and positive-sense single-stranded RNA (+ssRNA) virus.[14]

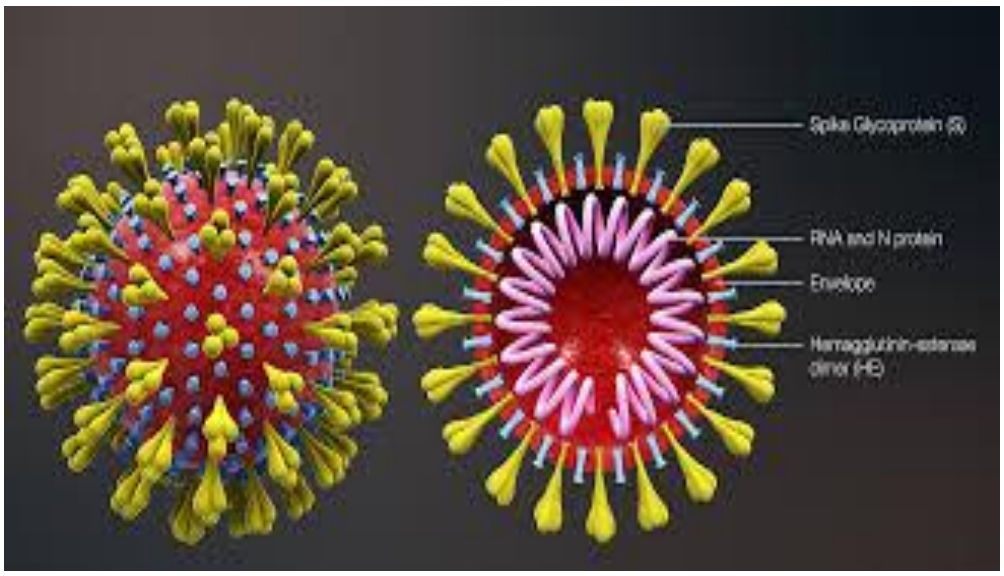

Fig. 1: Structure of corona virus.

Transmission

The initial cases were presumably linked to direct exposure to infected animals (animal-to-human transmission) at a seafood market in Wuhan, China. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and>70% similarity with the SARS CoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from there.[15] The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring.[16] Coughing and sneezing without covering the mouth can spread droplets into the air. Touching or shaking hands with a person who has

infected with the virus can pass the virus between individuals. Making contact with a object or surface that has the virus and then touching the nose, eyes, or mouth may be a large source of transmission. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick convection) were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20th Jan, 2020. By 23rd January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region.

Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries.[17] Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. the infection could be transmitted from asymptomatic people. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travellers returning from China, placed all people symptomatic or otherwise in isolation for 14 days and tested them for the virus.[18]

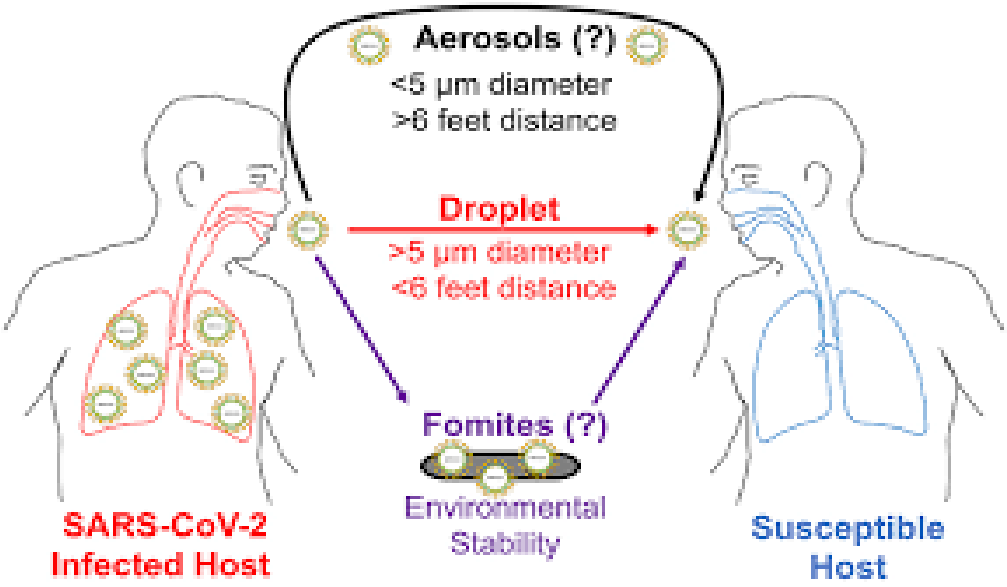

Fig. 2: Transmission of corona virus from airborn particle.

Epidemiological data of COVID-19

A large number of studies so far are reports based on experiences in China. At the beginning of the outbreak, COVID-19 cases were mostly observed among elderly people.[19] As the outbreak continued, the number of cases among people aged 65 years and older increased

further, but also some increase among children (< 18 years) was observed. The number of male patients was higher initially, but no significant gender difference was observed as case number increased. The mean incubation period was 5.2 days. The combined case-fatality rate was 2.3%.[20,21] The risk factors of in-hospital death were studied using the data of two hospitals in Wuhan. Older age, higher sequential organ failure assessment (SOFA) score and ddimer >1 μg/mL on admission were shown to be risk factors in the multi-variable analysis.[29] In the univariable analysis, the presence of coronary artery disease, diabetes and hypertension was also considered to be risk factors. The study of 85 fatal COVID-19 patients with median age of 65 years in Wuhan showed that the majority of patients died from multi-organ failure as respiratory failure, shock, and ARDS were seen in 94%, 81%, and 74% of cases, respectively.[22] As in line with the high prevalence of multi-organ failure, high d-dimer levels, fibrinogen and prolonged thrombin time were seen in severe diseases.[23]

Following the outbreak in China, SARS-CoV-2 has spread worldwide. As of early April 2020, the reported number of COVID19 patients is highest in the U.S., followed by Spain, Italy, Germany, France and China. Italy was significantly affected after the outbreak of China. Fatality rate was also higher in elder population as in Chinese series. The report from Italy showed the case-fatality rate of 7.2%.[20,24] which was three times as high as the one in China. Although the case-fatality rate of patients aged 70 years or older was higher in Italy, it was very similar between age 0 and 69 years in both countries. As 23% of Italian was aged 65 years or older, the high case-fatality in Italy was somewhat explained by the demographic characteristics. The data from US and other countries is available in the number of resources.[30,25] We expect to learn experiences more from individual countries in the forthcoming future.

From the beginning of this outbreak, the percentage of children within the total COVID-19 patients was small. According to the data of the Chinese Center for Disease Control and Prevention (China CDC) from February 2020, children younger than 10 years of age and within the age of 11–19 years occupied 1% each of the total cases.[20] Considering this age group represents 20% of the total population, this may indicate less prevalence of COVID-19 in pediatric population. However, this may be underestimation of actual incidence in pediatric population if less tests were undertaken in children due to less symptoms. One confounding factor is that schools in China were closed for most of the epidemic due to the Chinese New Year holidays, which might have contributed to less exposure among children. In the report

of 2134 pediatric patients with COVID-19 from the China CDC, 4.4%, 50.9%, 38.8%, and 5.9% of patients were diagnosed as asymptomatic, mild, moderate, or severe, respectively.[26] The definition of asymptomatic, mild, moderate, severe and critical is summarized in Table 1 . In contrast, 18.5% of adult patients had severe diseases.[26] Infants were most vulnerable to severe type of infection; the proportion of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1% and 3.0% for the age group of <1, 1–5, 6–10, 11–15 and ≥16 years, respectively. The case-fatality rate of age group 0–9 and 10–19 was 0% each. In Italy, COVID19 patients of age 8–18 years occupied only 1.2%.[24] The case-fatality rate of age group 0–9 and 10–19 was 0% and 0.2%, respectively, which was similar to Chinese experience. In the data from the Korean CDC on late March, 6.3% of all cases tested positive for COVID-19 were children under 19 years of age.[27] On April 6, 2020, the US CDC released the study of 2572 COVID19 cases among children younger than 18 years.[28] Of all reported cases in the US, this occupied only 1.7% of the total cases, even though this age group makes up 22% of US population. Overall, the data suggested that children were less symptomatic than adults as in Chinese reports. Among the children for whom complete information was available, only 73% developed fever, cough, or shortness of breath. That's compared to 93% of adults reported in the same time frame, between the ages of 18 and 64 years. The estimated hospitalization rate for children aged 1 to 17 was 14% at most.[28] In contrast, infant accounted for the highest percentage of hospitalization (15–62%), which was again similar to the data from Chinese CDC.

Accounted for the highest percentage of hospitalization (15–62%), which was again similar to the data from Chinese CDC. Despite the overall favorable outcome for pediatric population, a number of deaths have been reported in US and other countries, and further information needs to be obtained.

Classification of COVID-19 Patient

Type of patient	Sign & Symptoms
Mild	Symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhoea)
Moderate	Pneumonia (frequent fever, cough) with no obvious hypoxemia, chest CT with lesions.
Severe	Pneumonia with hypoxemia (SpO2 < 92%)

Critical	Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury

Mechanism of SARS-CoV-2 invasion into host cells

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses of ~30 kb. They infect a wide variety of host species.[31] They are largely divided into four genera; α, β, γ, and δ based on their genomic structure. α and β coronaviruses infect only mammals.[32] Human coronaviruses such as 229E and NL63 are responsible for common cold and croup and belong to α coronavirus. In contrast, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 are classified to β coronaviruses.

The life cycle of the virus with the host consists of the following 5 steps: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host receptors (attachment), they enter host cells through endocytosis or membrane fusion (penetration). Once viral contents are released inside the host cells, viral RNA enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released. Coronaviruses consist of four structural proteins; Spike (S), membrane (M), envelop (E) and nucleocapsid (N).[33] Spike is composed of a transmembrane trimetric glycoprotein protruding from the viral surface, which determines the diversity of coronaviruses and host tropism. Spike comprises two functional subunits; S1 subunit is responsible for binding to the host cell receptor and S2 subunit is for the fusion of the viral and cellular membranes. Angiotensin converting enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV.[34] Structural and functional analysis showed that the spike for SARS-CoV-2 also bound to ACE2.[35,36,37] ACE2 expression was high in lung, heart, ileum, kidney and bladder.[38] In lung, ACE2 was highly expressed on lung epithelial cells. Whether or not SARS-CoV-2 binds to an additional target needs further investigation. Following the binding of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage. A two-step sequential protease cleavage to activate spike protein of SARS-CoV and MERS-CoV was proposed as a model, consisting of cleavage at the S1/S2 cleavage site for priming and a cleavage for activation at the S′2 site, a position adjacent to a fusion peptide within the S2 subunit.[39,40,41] After the cleavage at the S1/S2 cleavage site, S1 and S2 subunits remain non-covalently bound and the distal S1 subunit contributes to the stabilization of the membraneanchored S2 subunit at the prefusion state.[36]

Subsequent cleavage at the S′2 site presumably activates the spike for membrane fusion via irreversible, conformational changes. The coronavirus spike is unusual among viruses because a range of different proteases can cleave and activate it.[42] The characteristics unique to SARS-CoV-2 among coronaviruses is the existence of furin cleavage site ("RPPA" sequence) at the S1/S2 site. The S1/S2 site of SARS-CoV-2 was entirely subjected to cleavage during biosynthesis in a drastic contrast to SARS-CoV spike, which was incorporated into assembly without cleavage.[36] Although the S1/S2 site was also subjected to cleavage by other proteases such as transmembrane protease serine 2 (TMPRSS2) and cathepsin L.[41,43] the ubiquitous expression of furin likely makes this virus very pathogenic.

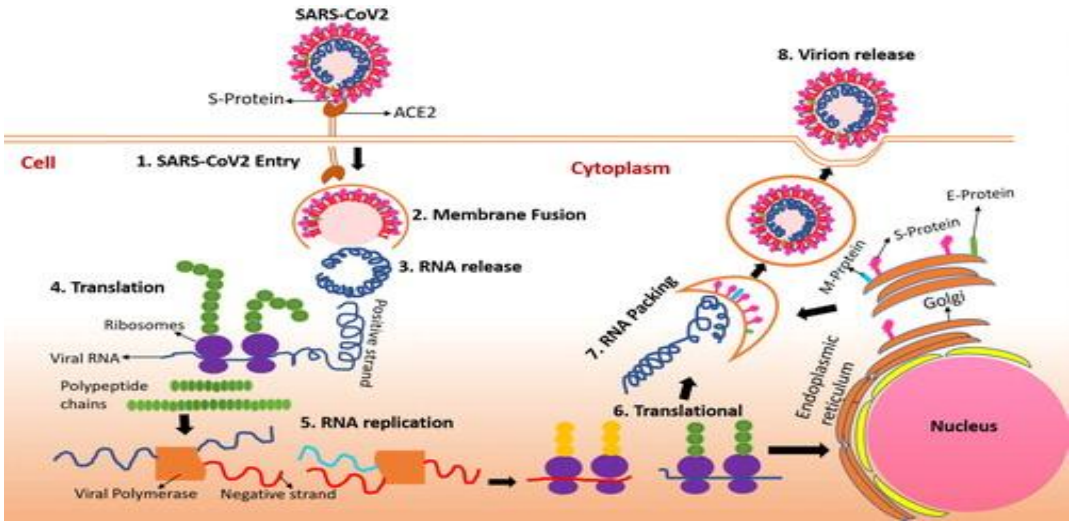

Fig. 3: Mechanism of action of corona virus.

Management

Isolation gives the most effective measure for containment of COVID-19. No definite anti-viral medication or vaccine is currently available.[44] Therefore, the remedy of COVID-19 includes symptomatic care and oxygen therapy. Patients with mild infections require early supportive management. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements, and anti-bacterial therapy.[45] Critically ill patients require high flow oxygen, extracorporeal membrane oxygenation (ECMO), glucocorticoid therapy, and convalescent plasma.[45] The administration of systemic corticosteroids is not suitable to treat ARDS.[44] Moreover, unnecessary administration of antibiotics should also be avoided. ECMO should be considered in patients with refractory hypoxemia despite undergoing protective ventilation.[44] Patients with respiratory failure may require intubation, mechanical ventilation, high-flow nasal oxygen, or non-invasive ventilation.[44] Treatment of septic shock requires hemodynamic support with the

administration of vasopressors. Other suggested anti-virals include ribavirin and a bidor.[45] The use of three or more anti-viral drugs simultaneously is not suitable or not suggested as good. Ongoing clinical studies suggest that remdesivir (GS5734) can be used for prophylaxis and therapy.[44] Furthermore, a fusion inhibitor targeting the HR1 domain of spike protein is reported to have the potential to treat COVID19.

Control & prevention

COVID-19 is evidently a serious disease of international concern. By some estimates it has a higher reproductive number than SARS,[46] and more people have been reported to have been infected or died from it than SARS.[47] Similar to SARS-CoV and MERS-CoV, disrupting the chain of transmission is considered key to stopping the spread of disease.[48] Different strategies should be implemented in health care settings and at the local and global levels. Health care settings can unfortunately be an important source of viral transmission.[48] Suspected cases presenting at healthcare facilities with symptoms of respiratory infections (e.g. runny nose, fever and cough) must wear a face mask to contain the virus and strictly adhere triage procedure. They should not be permitted to wait with other patients seeking medical care at the facilities. They should be placed in a separated, fully ventilated room and approximately 2 m away from other patients with convenient access to respiratory hygiene supplies.[49] In addition, if a confirmed COVID-19 case require hospitalization, they must be placed in a single patient room with negative air pressure – a minimum of six air changes per hour. Exhausted air has to be filtered through high efficiency particulate air (HEPA) and medical personnel entering the room should wear personal protective equipment (PPE) such as gloves, gown, disposable N95, and eye protection. Once the cases are recovered and discharged, the room should be decontaminated or disinfected and personnel entering the room need to wear PPE particularly facemask, gown, eye protection.[49]

In a community setting, isolating infected people are the primary measure to interrupt the transmission. For example, immediate actions taken by Chinese health authorities included isolating the infected people and quarantining of suspected people and their close contacts.[50] Also, as there are still conflicting assumptions regarding the animal origins of the virus (i.e. some studies linked the virus to bat.[51,52] while others associated the virus with snake,[53] contacts with these animal fluids or tissues or consumption of wild caught animal meet should be avoided. Moreover, educating the public to recognize unusual symptoms such as chronic cough or shortness of breath is essential therefore that they could seek medical care

for early detection of the virus. If large-scale community transmission occurs, mitigating social gatherings, temporary school closure, home isolation, close monitoring of symptomatic individual, provision of life supports (e.g. oxygen supply, mechanical ventilator), personal hand hygiene, and wearing personal protective equipment such as facemask should also be enforced.[54] In global setting, locking down Wuhan city was one of the immediate measure taken by Chinese authorities and hence had slowed the global spread of COVID-19.[54] Air travel should be limited for the cases unless severe medical attentions are required. Setting up temperature check or scanning is mandatory at airport and border to identify the suspected cases. Continued research into the virus is critical to trace the source of the outbreak and provide evidence for future outbreak.[54]

Treatment

Yet, there is no vaccine for treatment of COVID-19. Many country are conducted a clinical trials for COVID-19 vaccine. Many Anti-viral drug are under clinical trials. There are various treatment for coronavirus which mainly inhibit the action of virus.

- **Remdesivir**

REMDISIVIR was developed for the treatment of EBOLA VIRUS. Remdesivir is an adenosine analogue that incorporates into nascent viral ribonucleic acid (RNA) chains and results in premature termination, preventing virus replication.[55] It is widely distributed in the human body and is predominantly eliminated renally.[56] remdesivir was approved for use in Japan and is now available in all over the world as an emergency use authorisation.[57,58,59] Gilead has increased production of remdesivir to meet the demand for use in COVID-19 trials, but there is concern that many countries will simply not be able to afford this.[60]

- **Favipiravir**

The CDSCO has issued an accelerated approval to manufacture and market favipiravir for the treatment of mild to moderate COVID-19 disease under restricted emergency use. Favipiravir, also known as T-705, is an antiviral drug developed in Japan in 2002 that inhibits viral RNA-dependent RNA polymerase, preventing the virus from replication.[61] Favipiravir is available as 200mg tablets and the WHO has reviewed the available evidence to consider whether favipiravir (either a loading dose of 1600mg or 1800mg followed by either 600mg three times per day or 800mg twice per day for 14 days) should be included in the Solidarity trial. At the time of the WHO's consultation, which was published on 10 April 2020, it was felt that additional pre-clinical data were required. Favipiravir may have some benefits in

combination with other antivirals to boost antiviral activity or decrease resistance; however, given the potential regimen, consideration needs to be given to the number of tablets a patient would have to take in a day and whether this is practical.[62]

- **Tocilizumab**

Tocilizumab is an immunosuppressive drug, mainly for the treatment of rheumatoid arthritis (RA).[63] Tocilizumab is a humanized immunoglobulin that blocks the IL-6 receptor. It is licensed in the US and Europe for chimeric antigen receptor Tcell- induced severe or life-threatening cytokine release syndrome. It is hypothesized to be effective in suppressing the cytokine storm syndrome associated with severe or critical COVID-19.[64] The NHC guidelines recommended the use of tocilizumab in severe COVID-19 with extensive bilateral lung disease and elevated IL-6.[65]

- **Hydroxychloroquine**

Hydroxycholorquine is approved as a treatment in mild cases and as prophylactic. The collective data from multiple large clinical trials such as WHO's SOLIDARITY and UK's RECOVERY trials show hydroxycholorquine does not show benefits in treatment. USFDA canclled Emergency Use Authorisation, India shifted the drug out of treatment protocol for severe cases. Side-effects of hydroxychloroquine is Severe heart arrhythmia.[66]

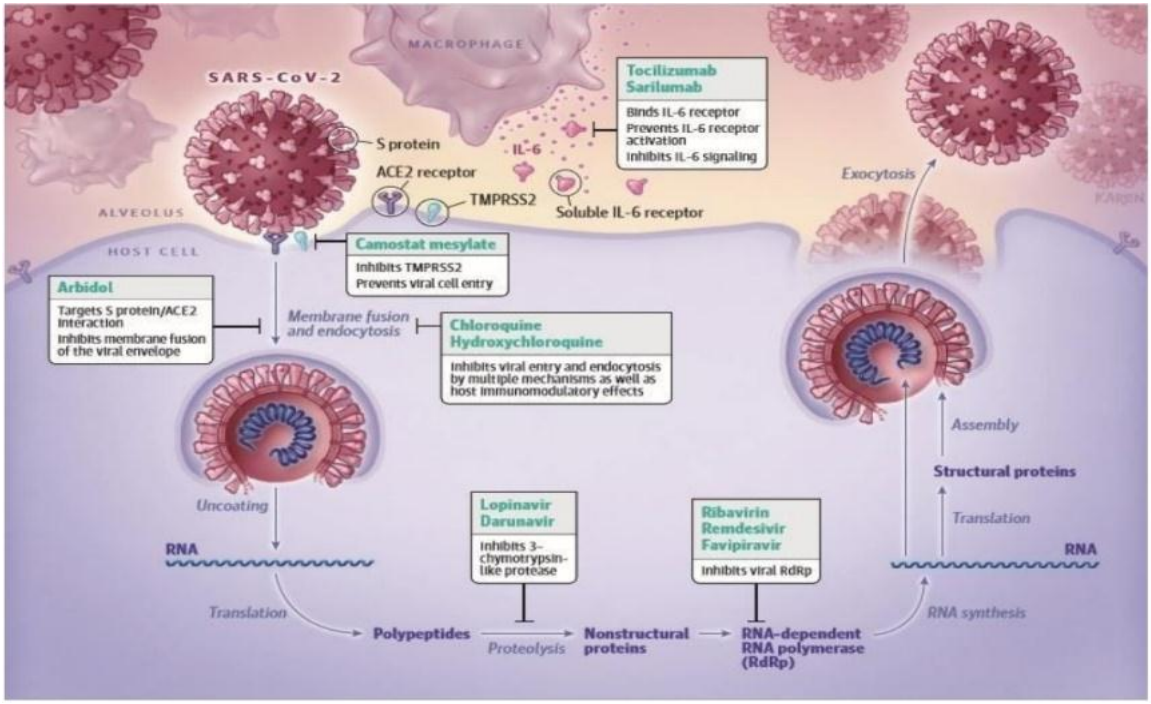

Fig. 4: Drug acting on corona virus.

CONCLUSION

Corona virus was spreading human to human transmission by close contact via airborne droplets generation by coughing, sneezing, kissing. The current COVID-19 pandemic is clearly an international public health problem. No confirm medication and vaccine has been developed. There is an urgent need to develop a targeted therapies. As per WHO & ECDC guideline avoid the contact with sick person and also avoid the market or public places as possible. There is no anti corona virus vaccine to prevent or treatment but some therapy works. Till only `distance is rescue`. Healthcare personnel must wear Personal Protective Equipment (PPE) kit such as N95 mask, gown, hand gloves, eye protection.

REFERENCES

1. H. Lu, C.W. Stratton, Y.W. Tang Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle J Med Virol.
2. D.S. Hui, I.A. E, 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 Int J Infect Dis, 2020; 91: 264-266.
3. A.E.A. Gorbalenya Severe acute respiratory syndrome-related coronavirus: the species and its viruses – a statement of the Coronavirus Study Group BioRxiv, 2020.
4. T.K. BurkiCoronavirus in China Lancet Respir Med, 2020.
5. Richman DD, Whitley RJ, Hayden FG. Clinical Virology, 4th ed. Washington: ASM Press, 2016.
6. Chan-Yeung M, Xu RH. SARS: epidemiology. Respirology, 2003; 8: S9–14.
7. Middle East Respiratory Syndrome Coronavirus. Available at: https://www.who.int/emergencies/mers-cov/en/. Accessed 16 Feb 2020.
8. Mailles A, Blanckaert K, Chaud P, van der Werf S, Lina B, Caro V, et al. First cases of Middle East respiratory syndrome Coronavirus (MERS-CoV) infections in France, investigations and implications for the prevention of human-to-human transmission, Euro Surveill, 2013; 18: 20502.
9. Buchholz U, Müller MA, Nitsche A, Sanewski A, Wevering N, Bauer-Balci T, et al. Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October-November 2012. Euro Surveill, 2013; 18: 20406.
10. Saif LJ. Animal coronaviruses: what can they teach us about the severe acute respiratory syndrome? Rev Sci Tech, 2004; 23: 643–60.

11. Gwaltney JM Jr. Virology and immunology of the common cold. Rhinology, 1985; 23: 265.
12. Tyrrell DAJ, Myint SH. Chapter 60: Coronaviruses. In Barson 1 S, editor. Medical microbiology. 4th edition. Galveston: University of Texas Medical Branch at Galveston, 1996.
13. C. Burrell, C. Howard, F. Murphy Fenner and White's medical virology (5th ed.), Academic Press, United States, 2016.
14. Kramer, I. Schwebke, G. KampfHow long do nosocomial pathogens persist on inanimate surfaces? A systematic review BMC Infect Dis, 2006; 6: 130.
15. Xinhua. China's CDC detects a large number of new corona viruses in the South China seafood market in Wuhan. Available at: https:// www.xinhuanet.com/2020-01/27/c_1125504355.htm.Accessed20 Feb 2020.
16. 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.
17. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019nCoV infection from an asymptomatic contact in Germany. N Engl J Med, 2020.
18. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med, 2020.
19. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., Qiu Y., Wang J., Liu Y., Wei Y., Xia J., Yu T., Zhang X., Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020; 395: 507–513. Wu Z., McGoogan J.M. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020 doi: 10.1001/jama.2020.2648.
20. Onder G., Rezza G., Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA, 2020. doi: 10.1001/jama.2020.4683.
21. Du Y., Tu L., Zhu P., Mu M., Wang R., Yang P., Wang X., Hu C., Ping R., Hu P., Li T., Cao F., Chang C., Hu Q., Jin Y., Xu G. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational Study. Am J Respir Crit Care Med, 2020. doi: 10.1164/rccm.202003-0543OC.
22. Gao Y., Li T., Han M., Li X., Wu D., Xu Y., Zhu Y., Liu Y., Wang X., Wang L. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol, 2020. doi: 10.1002/jmv.25770.

23. Livingston E., Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. Journal, 2020. doi: 10.1001/jama.2020.4344.
24. Tcfc Information. Journal. Dong Y., Mo X., Hu Y., Qi X., Jiang F., Jiang Z., Tong S. Epidemiological characteristics of 2143 Pediatric patients with 2019 coronavirus disease in China. Journal, 2020. doi: 10.1542/peds.2020-0702.
25. Brodin P. Why is COVID-19 so mild in children? Journal, 2020. doi: 10.1111/apa.15271.
26. CfDCa Prevention. Journal. Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z., Xiang J., Wang Y., Song B., Gu X., Guan L., Wei Y., Li H., Wu X., Xu J., Tu S., Zhang Y., Chen H., Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, 2020; 395: 1054–1062. [PMC free article] [PubMed] [Google Scholar].
27. JHUoMCr center Journal. 2020 https://coronavirus.jhu.edu/map.html [Google Scholar] Channappanavar R., Zhao J., Perlman S. T cell-mediated immune response to respiratory coronaviruses. Journal, 2014; 59: 118–128. [PMC free article] [PubMed] [Google Scholar].
28. Rabi F.A., Al Zoubi M.S., Kasasbeh G.A., Salameh D.M., Al-Nasser A.D. SARS-CoV-2 and Coronavirus disease 2019: what we know so far. Journal, 2020; 9. [PMC free article] [PubMed] [Google Scholar].
29. Bosch B.J., van der Zee R., de Haan C.A., Rottier P.J. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. Journal, 2003; 77: 8801–8811. [PMC free article] [PubMed] [Google Scholar]
30. Li W., Moore M.J., Vasilieva N., Sui J., Wong S.K., Berne M.A., Somasundaran M., Sullivan J.L., Luzuriaga K., Greenough T.C., Choe H., Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Journal, 2003; 426: 450–454. [PMC free article] [PubMed] [Google Scholar].
31. Chen Y., Guo Y., Pan Y., Zhao Z.J. Structure analysis of the receptor binding of 2019-nCoV. Journal, 2020. doi: 10.1016/j.bbrc.2020.02.071. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
32. Walls A.C., Park Y.J., Tortorici M.A., Wall A., McGuire A.T., Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Journal, 2020. doi: 10.1016/j.cell.2020.02.058.
33. Letko M., Marzi A., Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Journal, 2020; 5: 562–569.

34. Zou X., Chen K., Zou J., Han P., Hao J., Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Journal, 2020. doi: 10.1007/s11684-020-0754-0.
35. Belouzard S., Chu V.C., Whittaker G.R. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Journal, 2009; 106: 5871–5876.
36. Millet J.K., Whittaker G.R. Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein. Journal, 2014; 111: 15214–15219.
37. Ou X., Liu Y., Lei X., Li P., Mi D., Ren L., Guo L., Guo R., Chen T., Hu J., Xiang Z., Mu Z., Chen X., Chen J., Hu K., Jin Q., Wang J., Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Journal, 2020; 11: 1620.
38. Belouzard S., Millet J.K., Licitra B.N., Whittaker G.R. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Journal, 2012; 4: 1011–1033.
39. Hoffmann M., Kleine-Weber H., Schroeder S., Kruger N., Herrler T., Erichsen S., Schiergens T.S., Herrler G., Wu N.H., Nitsche A., Muller M.A., Drosten C., Pohlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Journal, 2020. doi: 10.1016/j.cell.2020.02.052.
40. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD: Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing, Treasure Island, FL, 2020.
41. Wang Y, Wang Y, Chen Y, Qin Q: Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures [Epub ahead of print]. J Med Virol, 2020. 10.1002/jmv.25748.
42. Y. Liu, A. Gayle, A. Wilder-Smith JR.The reproductive number of COVID-19 is higher compared to SARS coronavirus J TravelMed, 2020.
43. E. MahaseCoronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rateBMJ, 2020; 368: 641.
44. J.F.W. Chan, S.K.P. Lau, K.K.W. To, V.C.C. Cheng, P.C.Y. Woo, K.-Y. YuenMiddle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease Clin Microbiol Rev, 2015; 28(2): 465-522.
45. Centers for Diseases Control and PreventionCoronavirus disease 2019 (COVID-19), 2020.

46. C. Wang, P.W. Horby, F.G. Hayden, G.F. GaoA novel coronavirus outbreak of global health concern Lancet, 2020.
47. D. Paraskevis, E.G. Kostaki, G. Magiorkinis, G. Panayiotakopoulos, G. Sourvinos, S. Tsi odrasFull-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event Infect Genet Evol, 2020; 104212.
48. G.S. Randhawa, M.P.M. Soltysiak, H. El Roz, C.P. De Souza, K.A. Hill, L. KariMachine learning analysis of genomic signatures provides evidence of associations between Wuhan 2019-nCoV and bat betacoronaviruses BioRxiv, 2020.
49. W. Ji, W. Wang, X. Zhao, J. Zai, X. LiHomologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human J Med Virol, 2020.
50. D.L. Heymann, N. ShindoCOVID-19: what is next for public health? Lancet, 2020.
51. Wang M, Cao R, Zhang L, Yang X *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res, 2020; 30(3): 269–271.
52. University of Liverpool. Interactions with experimental COVID-19 therapies, 2020. Available at: https://www.covid19-druginteractions.org/ (accessed June 2020).
53. Gilead. Gilead Announces Approval of Veklury (remdesivir) in Japan for Patients With Severe COVID-19, 2020. Available at: https://www.gilead.com/news-and-press/press-room/press-releases/2020/5/gilead-announces-approval-of-veklury-remdesivir-in-japan-for-patients-with-severe-covid19 (accessed June 2020).
54. MHRA. Early access to medicines scheme (EAMS) scientific opinion: Remdesivir in the treatment of patients hospitalised with suspected or laboratory-confirmed SARS-CoV-2 infection who meet the clinical criteria, 2020. Available at: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-remdesivir-in-the-treatment-of-patients-hospitalised-with-suspected-or-laboratory-confirme (accessed June 2020).
55. US Food and Drug Administration. Remdesivir EUA Letter of Authorization, 2020. Available at: https://www.fda.gov/media/137564/download (accessed June 2020).
56. Gilead. Working to supply remdesivir for COVID-19. 2020. Available at: https://www.gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-remdesivir-for-covid-19 (accessed June 2020).

57. Furuta Y, Komeno T & Nakamura T. Favipiravir (T-705), a broad-spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys Biol Sci*, 2017; 93(7): 449–463.
58. World Health Organization. WHO R&D Blueprint. COVID-19 Informal consultation on the potential inclusion of Favipiravir in a clinical trial, 2020. Available at: http://origin.who.int/blueprint/priority-diseases/key-action/RDBlueprintbtxexpertgrouponFavipiravircallApril10th2020.pdf (accessed June 2020).
59. *Venkiteshwaran, Adith "Tocilizumab". mAbs, 2009; 1(5): 432–438. doi:10.4161/mabs.1.5.9497. PMC 2759492. PMID 20065633.*
60. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet, 2020; 395(10229): 1033–4.
61. https://www.cnbctv18.com/healthcare/covid-19-treatment-update-here-is-a-list-of-all-drugs-used-in-india-their-pros-and-cons-6322301.htm
    Another reference (figure)-
62. https://commons.wikimedia.org/wiki/File:3D_medical_animation_corona_virus.jpg
63. https://doi.org/10.3389/fpubh.2020.00163.
64. https://www.researchgate.net/figure/The-schematic-diagram-of-the-mechanism-of-COVID-19-entry-and-viral-replication-and-viral_fig1_340790860.
65. https://www.google.com/search?q=PATHOPHYSIOLOGY+OF+DRUG+ACTING+ON+COVID+19&source=lnms&tbm=isch&sa=X&ved=2ahUKEwjk2Zzpz_TqAhUs6XMBHarNB8wQ_AUoAXoECAwQAw&biw=1024&bih=664#imgrc=RFi0KmxZGTKEGM.