WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 2206-2223. Review Article ISSN 2277– 7105

A REVIEW ON CORONAVIRUS (COVID-19) CLINICAL FEATURES, DIAGNOSIS, AND TREATMENT

Arshad Hasan* and Fatima Amin

Department of Pharmacology, Amity Institute of Pharmacy, Amity University Lucknow.

Article Received on
19 June 2020,

Revised on 09 July 2020,
Accepted on 29 July 2020

DOI: 10.20959/wjpr20208-18187

***Corresponding Author**
Dr. Arshad Hasan
Department of Pharmacology, Amity Institute of Pharmacy, Amity University Lucknow.

ABSTRACT

Coronavirus disease 2019 (COVID-19) originated in the city of Wuhan, Hubei Province, Central China, and has spread quickly to 72 countries to date. COVID-19 is caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [previously provisionally known as 2019 novel coronavirus (2019-nCoV)]. At present, the newly identified SARS-CoV-2 has caused a large number of deaths with tens of thousands of confirmed cases worldwide, posing a serious threat to public health. However, there are no clinically approved vaccines or specific therapeutic drugs available for COVID-19. Intensive research on the newly emerged SARS-CoV-2 is urgently needed to elucidate the pathogenic mechanisms and epidemiological characteristics and to identify potential drug targets, which will contribute to the development of effective prevention and treatment strategies. Hence, this review will focus on recent progress regarding the structure of SARS-CoV-2 and the characteristics of COVID-19, such as the aetiology, pathogenesis and epidemiological characteristics.

KEYWORDS:- Corona, covid-19, SARS-CoV-2, Vaccines, Intensive, Recent process and Treatment strategies.

INTRODUCTION

Corona virus is an infectious disease. It is also called (COVID-19) which is caused by severe respiratory syndrome coronavirus 2 (SARSCOV-2)[1] which have the ability to cause severe and life-threatening disease.[2]

This kind of virus take place back on 1965 which was introduced by Tyrrell and Bynoe who also found.[3] that this could be a transferable virus and also named this virus as B814.

It is named as COVID-19 because this disease was originated in December 2019. In 2019 this disease was identified in Wuhan, China which results in pandemic outbreak as declared by World Health Organisation (WHO).[4]

However, the first case was observed on 17 November, 2019 and till today it reaches at the peak of more than 5.9 million cases which have been reported across 187 countries including the territories. And also resulting in more than 390,000 deaths.[5]

This type of virus when enter the cell the genome which virus contain translated protein then the messenger RNAs form a unique web like structure sharing a 3' end of the mRNA. So new virus's production take place by budding from host cell membranes. So, the multiplication take place in this form.[6] Transmission usually takes place by airborne droplets to the nasal mucosa a skin layer which then virus causes cell damage and induce severe attack cause inflammation.

On 3 January 2020, a novel coronavirus was identified in a bronchial alveolar lavage fluid sample from a patient in Wuhan and that was confirmed to be the cause of the COVID-19.

This disease is a transferable disease which is transmitted to other person either by casual contact with the person who is suffering from this corona disease. Although the origin of this "SARS-CoV-2" in still under investigation, current source predict that it was transmitted to humans through the animals which was illegally sold in Huanan Seafood Wholesale Market.[7]

Till yet no vaccines or treatment is available to cure this disease.

Signs and Symptoms

It has been determined that this type of disease appears within 3 to 14 days of exposure. The time between before having the symptoms and after having the exposure is called incubation period.[8]

Following are some symptoms that may appear to confirm that a particular person suffer from corona disease as follows:

Common symptoms

- Fever
- Cough

- Tiredness

Less common symptoms

- Aches and pain
- Diarrhoea
- Muscle pain
- Joints pain
- Loss of smell and taste
- Rashes on skin
- Permanent headache

Severe symptoms

- Loss of movement
- Shortness of breath
- Chest pain
- Change in lips colour to bluish
- Sudden confusion
- Impact on brain system

Those with suffering from weak immune system may have major impact of corona disease on their health, they may also suffer from severe pneumonia or severe inflammatory disease.

Incubation period

It is a period which defines the exposure of the disease or the exposure of the symptoms for a particular disease.[9] According to Central of Disease Control and Prevention which defines the current status of novel coronavirus[10] is between 2 to 14 days after exposure.

Recent studies have been estimated the incubation period that the symptoms of the coronavirus develop within 11.5 days and also assumed that 106 cases out of 10,000 cases developed the symptoms after 14 days of observation.[11]

For different person the incubation period differs some people may carry the symptoms after 12 days, some after 11.5 days, or some after 14 days. Average period seems to be around 5 days. It differs according to different person.[12-13] COVID-19 symptoms start within 2 to 14 days and it also ultimately turn to severe condition as the days increase.

It is a key measure for controlling the symptoms as it will decrease the risk of being infected at severe worst condition.

Virology

Coronavirus or COVID-19 belong to a family called *C*oronaviridae and based on the recent studies this virus is positive single-stranded RNA[14] which is surrounded by an envelope protein. Its size ranges from 26 to 32 kilobases (kb). It has the larger know genetic sequence for RNA viruses.

In the present studies it is explained that this virus has a organize complex genomic structure. It contains several structural as well as non-structural image of protein including[15] spike protein (S)gene, membrane protein (M) gene, nucleocapsid protein (N) gene, envelop protein (E) gene, replicase complex (orf1ab) gene. From all this protein spike protein (S) gene have strong binding affinity towards human receptor (ACE2).[16]

According to several sources it has been determined that main proteases and spike protein both complexed with human receptor (ACE2) are important source to develop vaccines and to cure this new covid disease. In the recent studies K. Anand[17] observed that this virus has the ability which is responsible for viral replication like this virus make small polypeptide chain by the method of transcription with the help of proteolytic enzymes.

They are divided into four genera as: Alpha-, Beta-, Gamma- and Deltacoronavirus. The alpha-coronavirus (HCoV-NL63 and HCoV-229E and betacoronavirus (HCoV-OC43 and HCoV-HKU1) usually called common colds, and betacoronavirus is associated with low respiratory tract infection. SARS-CoV and MERS-CoV origin takes place which causes respiratory syndrome and even fatal condition.[18]

Some CoVs with having the ability to boost infection, which was limited to animal species barrier but still progressed to established zoonotic disease in human.

There are almost 30 identified CoVs that have the ability to infect humans, mammals, and other including animals.[19] Humans are commonly infected with alpha -CoVs and beta-CoVs. The viral infection is recognised when upper respiratory tract appears in a person.

Epidemiology and Pathogenesis

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before onset of symptoms. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people.[20] Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying in a resort in the French Alps and upon return to the UK. These infected droplets can spread 1–2 month and deposit on surfaces. The virus can remain viable on surfaces for days in favourable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them and then touching the nose, mouth and eyes.[21] The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/ feco oral route is also hypothesized. As per current information, transplacental transmission from pregnant women to Indian J Pediatr their fetus has not been described. However, neonatal disease due to post-natal transmission is described. The incubation period varies from 2 to 14 days [median 5 days]. Studies have identified angiotensin receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa. The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modelling studies.[22-23] In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009.

Clinical feature

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections.[24] In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα. The median time from onset of symptoms to dyspnea was 5 days, hospitalization 7 days and acute respiratory distress syndrome (ARDS) 8 days. The need for intensive care admission was in 25–30% of affected patients in published series.

Complications witnessed included acute lung injury, ARDS, shock and acute kidney injury. Recovery started in the 2nd or 3rd week. The median duration of hospital stays in those who recovered was 10 days. Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50–75% of fatal cases). Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range between 2 and 3%.[25]

Interestingly, disease in patients outside Hubei province has been reported to be milder than those from Wuhan. Similarly, the severity and case fatality rate in patients outside China has been reported to be milder. This may either be due to selection bias wherein the cases reporting from Wuhan included only the severe cases or due to predisposition of the Asian population to the virus due to higher expression of ACE_2 receptors on the respiratory mucosa. Disease in neonates, infants and children has been also reported to be significantly milder than their adult counterparts. In a series of 34 children admitted to a hospital in Shenzhen, China between January 19th and February 7th, there were 14 males and 20 females.[26] The median age was 8-year 11 month and in 28 children the infection was linked to a family member and 26 children had history of travel/residence to Hubei province in China. All the patients were either asymptomatic (9%) or had mild disease. No severe or critical cases were seen. The most common symptoms were fever (50%) and cough (38%). All patients recovered with symptomatic therapy and there were no deaths.[27] One case of severe pneumonia and multiorgan dysfunction in a child has also been reported. Similarly, the neonatal cases that have been reported have been mild.

Diagnosis

So many diagnoses[28] procedures have been implemented to test this covid disease which are already available in the laboratory. One of the best standard testing methods for this disease is Reverse Transcription Polymerase Chain Reaction (RT-PCR). Recent studies data suggested that RT-PCR is the only effective method to acute infection, the main criteria for testing a person is:

- Location
- Age
- Duration of symptom
- Contact to virus history
- Medical factors and risk determination.

Provide information on the above basis then

- Collect and the upper respiratory tract samples and test the same by using a nasophyrangeal swab.
- If a severe cough is evident han a particular specimen should collect.
- If a person is receiving invasive ventilation then a sample of broncho- alveolar and lower respiratory tract should be collected.

The diagnosed image should be useful with good access of imaging technology and poor access to laboratory testing in quick form, so that it can be useful in identifying patients with corona disease. Some perform the chest X-ray in order to check the initial stage of corona disease with sensitivity details. However, CT scan or X-ray is not a method of diagnosis for this Corona disease as it can be easily confused with other diseases such as: MERS, SARS, H1N1 and seasonal flu.[29] Like all this method lung ultrasound is also recommended valuable testing procedure in diagnosis. According to the recent CDC recommendation that viral testing is the only effective method for diagnosis of Covid disease.

Some test for diagnosis of this disease given below

- **Swab test**: in which a swab is used to take the samples from throat or nose.
- **Sputum test**: it is a thick mucus form which comes out with a cough that is already accumulated in lungs. Swab is used to collect the sample from nose.
- **Blood test:** a blood sample is taken from vein present in arm to diagnose the disease
- **Nasal aspirate**: in this method a sample of saline solution is injected in nose and then the sample will be collected by a light suction.

Antibody samples is also collected in order to determine several factors like age, medication, infection etc. The diagnosis method should be done under proper care.

Treatment

Since now, no specific medication or vaccine has been developed for COVID-19. The treatment currently available is symptomatic and oxygen therapy act as the chief treatment intervention for sufferers with acute infection. Mechanical ventilation might be required for patients with respiratory failure as well as hemodynamic support is required for handling septic shock.

Nowadays researchers are working a lot to develop effective medicine for COVID-19.

Therapies, which are currently in use to treat patients include medications[30] that are used to treat malaria and few autoimmune diseases; some antivirals that were originally developed to treat some other viruses, and antibodies of people who already have beaten COVID-19.

Chloroquine/Hydroxychloroquine

Reports that came in beginning from China and France advised that the sufferer with severe symptoms of coronavirus showed promising and quick results in recovering[31] when treated with chloroquine or hydroxychloroquine. Few physicians used a combination including azithromycin and hydroxychloroquine with some effective results.

Chloroquine and hydroxychloroquine drugs are generally used to treat malaria as well as some inflammatory diseases, involving lupus and rheumatoid arthritis. Azithromycin is primarily prescribed antibiotic drug[32] for strep throat and bacterial pneumonia. Both of these medicines are easily available and inexpensive.

In the laboratory, both hydroxychloroquine and chloroquine have shown to kill the coronavirus. These drugs might be working through two mechanisms. Firstly, they make it difficult for the virus to bind itself to the cell, preventing the entry of the virus into the cell and dividing inside it. Second, when the virus can't get inside of the cell, the drugs kill it before dividing.

Azithromycin has never been used to treat viral infections. However, this drug has some inflammatory metabolism. There have been assumptions, which are never proven, that this drug might assist to dampen an overactive immune response to the coronavirus infection.[33]

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.[34-35] 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).[36] Currently, many trials are testing the effect of azithromycin conjunction with hydroxychloroquine on the course of disease in people with SARS-CoV-2. For example, Pfizer has announced positive data for the use of its azithromycin (Zithromax) drug, along with hydroxychloroquine, in a COVID-19 clinical trial that was performed in France. In brief, the clinical trial was conducted to assess hydroxychloroquine in 20 patients, 6 of which were co-administered with azithromycin. Compared with 16 controls and 14 hydroxychloroquine alone group, the 6 patients treated with hydroxychloroquine + azithromycin presented[37] with highest virologic cure rate following 6-day treatment. Three other clinical studies used azithromycin (500 mg on day 1, then 250 mg daily on days 2–5) co-treated with 10- day regimen of hydroxychloroquine (600 mg daily) in an open-label non-randomized study in France (6 pts), open-label uncontrolled study in France (11 pts), and uncontrolled observational study in France (80 pts). Specifically, Gautret et al. reported a 100% viral clearance in nasopharyngeal swabs in their 6 patients after co-treated of hydroxychloroquine and azithromycin. But the findings reported by Molina et al. stand in contrast with those reported by Gautret. Molina et al. repeated the experiments, thought the rapid and full viral clearance was quite unexpected and found 8 of 11 patients had significant comorbidities. Based on those results, data presented to date are insufficient to evaluate possible clinical benefits of azithromycin[38] in patients with COVID-19. Furthermore, one must consider the additive cardiac toxicity of hydroxychloroquine and azithromycin. Both agents are known to prolong the QT interval and may potentiate the risk for cardiac events in a population known to have cardiac-related comorbidities.

Remdesivir

Researchers around the globe are examining the effectiveness of a few drugs that were earlier developed to treat some other viral infections[39] for the treatment of COVID-19.

Remdesivir is one drug that has received a lot of attention from the researchers as this drug was used to treat diseases such as SARS and MERS, whose viruses closely resemble the virus that causes COVID-19. Some evidence from the laboratories as well as animal studies suggested that remdesivir might help in limiting the reproduction and spreading of these viruses in the host's body. In fact, an important fragment of all these three viruses, which can be targeted by remdesivir drug and that important fragment s responsible for making a vital enzyme[40] that, the virus requires to reproduce. This fragment is almost identical in all the three coronaviruses; remdesivir drug successfully targeted that critical fragment in viruses

that caused SARS and MERS and is possibly effective against the COVID-19 virus.

Remdesivir was originally developed for the treatment of viral diseases, which was also effective for the disease caused by the Ebola virus (which was not a coronavirus). It prevents the virus to make copies of itself by preventing its capability to reproduce; when the virus can't reproduce it won't be able to spread and cause infection to other cells or parts of the body.[41]

Favipiravir

A Japanese influenza drug, which was clinically tried on 300 patients in Wuhan and Shenzen. The patients were found to kill the virus after four days of medication, in comparison to those who did not take medications were found to kill the virus in around 11 days. The drug seemed to have lessened the duration of the disease.[42]

Favipiravir, also known as Avigan, is an antiviral drug. It is designed to focus on the RNA viruses comprising the COVID-19 virus an influenza virus. This drug works by disturbing the path these viruses take to divide inside the cells.

Nitric Oxide and Epoprostenol

Since patients with pre-existing pulmonary conditions are at higher risk of COVID-19 and should be closely monitored Curr Pharmacol Rep and cared, pulmonary vasodilator agents.[43] have been used in some patients for hypoxemia refractory to conventional treatments, but no study has been performed specifically on COVID-19 patients. The Surviving Sepsis Campaign suggested a trial of inhaled pulmonary vasodilator method as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies. Inhaled nitric oxide (iNO) and inhaled epoprostenol (iEPO, a naturally occurring prostaglandin) are two common pulmonary vasodilators that have been widely studied.[44-45] Experience in patients with ARDS indicates that iNO can substantially reduce mean pulmonary artery pressure and improve oxygenation in such patients. Furthermore, in vitro evidence of direct antiviral activity against SARS-CoV was studied and the genetic similarity between SARS-CoV and SARS-CoV-2 suggests their potential effectiveness against SARS-CoV-2.[46-47] For iEPO, dosages up to 50 ng/kg per minute have been used.[48,49.50] Previous studies reported that to provide a clinically important increase in PaO2 and reduction in pulmonary artery pressure, the most effective and safe dosage appears to be 20– 30 ng/kg per minute in adults and 30 ng/kg per minute in pediatric

patients.[51] For iNO, therapy was given for ≥ 3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, then weaned on day 4) in a pilot study on SARS-CoV.[52] Additionally, clinical trials evaluating iNO for treatment or prevention of COVID-19 are planned or underway (NCT04305457, NCT04306393, NCT04312243).[53-54] And on March 20, 2020, FDA granted emergency expanded access allowing its iNO delivery system (INOpulse®) to be immediately used for the treatment of COVID-19. Finally, additional studies are needed to evaluate the potential role of iEPO and iNO in the treatment of COVID-19 patients.

Vitamin-C (Ascorbic Acid)

To hasten recovery in some severely ill patients of COVID-19, high doses of intravenous (IV) vitamin C have been given. However, it is not a standard part for treating COVID-19 and also there is no clear evidence for the same.[55] Researches have been going on in China that will decide whether this medication is useful for sufferers with critical COVID-19.

The idea of using Vitamin C for treating infections is not new. Studies have shown that high dose IV vitamin C treatment (with thiamine and corticosteroids) have avoided deaths in people with sepsis (an infection causing dangerously low blood pressure and organ failure) and acute respiratory distress syndrome (ARDS) where fluid fills in the lungs.[56] Although, neither of the studies showed any special reason for this medication to be given to severely infected COVID-19 patients but these conditions (sepsis and ARDS) are primarily responsible for leading a sufferer to Intensive Care Unit (ICU) admission, ventilator support, or death among people with critical COVID-19 infections.

Ibuprofen

A few French Doctors have advised the use of ibuprofen for COVID-19 symptoms.

The WHO[57] initially advised the use of acetaminophen instead of ibuprofen for reducing symptoms such as fever and aches associated with COVID-19 infection, but now it states that either of the two drugs can be used. Rapidly changing recommendations have created uncertainty.

Convalescent Plasma

It's actually plasma of patients recovered from COVID-19. It's been in use for a period of more than 100 years to treat various illnesses such as measles, polio, chickenpox, and SARS. In the current scenario,[58] plasma-containing antibodies from a recovered patient are taken

and transfused into the patient suffering from COVID-19. The donated antibodies help the sufferer to fight against the illness, which might be reducing the duration or severity of the disease.

Though this therapy is in use for many years, and has a good success rate and shown promising results, still not much is known as how effective this technique is for treating COVID-19.[59]

Thiazolidinediones

Studies have demonstrated that thiazolidinedione and its derivatives, which are type 2 diabetes mellitus drugs, show efficacious effect against pulmonary disease induced by respiratory syncytial virus (RSV) or H1N1 influenza infection.[60] But their role as a therapeutic drug against coronavirus is not yet explored. Interestingly, it is known that thiazolidinediones may have the potential to upregulate ACE2 receptor, which is identified as a binding target for SARS-CoV-2 in host cells.[61-62] However, lack of clinical evidence makes it uncertain to determine its therapeutic efficacy against coronavirus infections.

Indomethacin

Amici et al. have demonstrated that indomethacin, a wellknown NSAID and a potential cyclooxygenase (COX) inhibitor, exhibits antiviral activity against SARS-CoV and canine coronavirus (CCoV).[63] In vitro studies suggest that indomethacin exhibits dose-dependent response in Canine A72 cell monolayers infected with CCoV with an IC50 of 5 uM after 24 hrs of exposure. Also, remarkable inhibition against SARSCoV-infected Vero cells by more than 99% at concentrations that were non-toxic for uninfected cells is also observed. In addition, indomethacin significantly blocks viral RNA[64] synthesis in dogs infected with CCoV following oral administration of the drug (1 mg/kg). This suggests probable efficacy of indomethacin against SARS-CoV-2.

Prevention

Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. The WHO has advised against close contact with[65] patients, farm animals, and wild animals. Patients and the general public must cover coughs and sneezes to help prevent aerosol transmission. Frequent handwashing with soap and water is also required. As an alternative measure, hand sanitizers can also be used. Immunocompromised individuals are advised to avoid public gatherings. Emergency

medicine departments must apply strict hygiene measures for the control of infections.[66] Healthcare personnel must use personal protective equipment such as N95 masks, FFP3 masks, gowns, eye protection, gloves, and gowns.

CONCLUSION

The COVID-19 pandemic is spreading across the globe at an alarming rate. It has caused more infections and deaths as compared with SARS or MERS. Based on R0 values, it is deemed that SARS-CoV-2 is more infectious than SARS or MERS. Elderly and immunocompromised patients are at the greatest risk of fatality. The rapid spread of disease warrants intense surveillance and isolation protocols to prevent further transmission. No confirmed medication or vaccine has been developed. Current treatment strategies are aimed at symptomatic care and oxygen therapy. Prophylactic vaccination is required for the future prevention of COV-related epidemic or pandemic.

REFERENCES

1. Banerjee A, Kulcsar K, Misra V, Frieman M, Mossman K. Bats and coronaviruses. Viruses, 2019; 11 pii: E41. doi: 10.3390/v11010041.
2. Yang D, Leibowitz JL. The structure and functions of coronavirus genomic 3 and 5 ends. Virus Res, 2015; 206: 120–33. doi: 10.1016/j. virusres.2015.02.025.
3. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, et al. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses, 2019; 11 pii: E59. doi: 10.3390/ v11010059.
4. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. Nat Rev Microbiol, 2013; 11: 836–48. doi: 10. 1038/nrmicro3143.
5. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet, 2015; 386: 995–1007. doi: 10.1016/S0140-6736(15)60454-8.
6. Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Infect Dis, 2018; 18: e 217–27. doi: 10.1016/S1473-3099(18)30127-0.
7. Su S, Wong G, Liu Y, Gao GF, Li S, Bi Y. MERS in South Korea and China: a potential outbreak threat? Lancet, 2015; 385: 2349–50. doi: 10.1016/ S0140-6736(15)60859-5.

8. Li Q, Guan X, Wu P, et al.: Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia [Epub ahead of print]. N Engl J Med, 2020; 10.1056/NEJMoa2001316.
9. Novel Coronavirus (2019-nCoV) Situation Report-7 - World Health Organization (WHO), January 27, 2020
10. China's National Health Commission news conference on coronavirus - Al Jazeera, 2020; 26.
11. Symptoms of Novel Coronavirus (-nCoV) – CDC, 2019.
12. Novel coronavirus (-nCoV) - Australian Government Department of Health, 2019.
13. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany - The New England Journal of Medicine, 2020; 20.
14. Yoneyama M, Onomoto K, Jogi M, Akaboshi T, Fujita T. Viral RNA detection by RIG-I-like receptors. Curr Opin Immunol, 2015; 32: 48- 53.
15. Yoneyama M, Fujita T. Recognition of viral nucleic acids in innate immunity. Rev Med Virol. Wiley Online Library CAS PubMed Web of Science®Google Scholar, 2010; 20(1): 4- 22.
16. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell, 2010; 140(6): 805- 820.
17. Weber M, Gawanbacht A, Habjan M, et al. Incoming RNA virus nucleocapsids containing a 5′-triphosphorylated genome activate RIG-I and antiviral signaling. Cell Host Microbe, 2013; 13(3): 336- 346.
18. Goubau D, Schlee M, Deddouche S, et al. Antiviral immunity via RIG-I-mediated recognition of RNA bearing 5'-diphosphates. Nature, 2014; 514(7522): 372- 375.
19. Civril F, Bennett M, Moldt M, et al. The RIG-I ATPase domain structure reveals insights into ATP-dependent antiviral signalling. EMBO Rep., 2011; 12(11): 1127- 1134.
20. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019nCoV infection from an asymptomatic contact in Germany. N Engl J Med., 2020. https://doi.org/10.1056/NEJMc2001468.
21. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med., 2020. https://doi.org/10.1056/NEJMoa2001316.
22. Cheng ZJ, Shan J. 2019 novel coronavirus: where we are and what we know. Infection, 2020; 1–9. https://doi.org/10.1007/s15010-02001401-y.

23. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med., 2020. https://doi.org/10.1056/NEJMc2001737.
24. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020; 395: 507–13.
25. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel corona virus–infected pneumonia in Wuhan, China. JAMA, 2020. https://doi.org/10.1001/jama.2020. 1585.
26. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ, 2020; 368: m606.
27. Wang XF, Yuan J, Zheng YJ, et al. Clinical and epidemiological characteristics of 34 children with 2019 novel corona virus infection in Shenzhen. [Article in Chinese]. Zhonghua Er Ke Za Zhi., 2020; 58: E008.
28. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus [2019-nCoV] infected pneumonia [standard version]. Mil Med Res., 2020; 7: 4.
29. Huang P, Liu T, Huang L, et al. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology, 2020. https://doi.org/10.1148/radiol. 2020200330.
30. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med., 2020. https://doi.org/10.1056/ NEJMoa2007016.
31. Rynes R. Antimalarial drugs in the treatment of rheumatological diseases. Rheumatology, 1997; 36(7): 799–805.
32. Schultz K R, Gilman A L. The lysosome tropicamines,chloroquine and hydroxychloroquine: a potentially novel therapy for graftversus-host disease. Leuk Lymphoma, 1997; 24(3–4): 201–10.
33. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema K-J, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy, 2018; 14(8): 1435– 55.
34. 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.

35. 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.
36. 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.
37. 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.
38. label Ua. US azithromycin label. US azithromycin label. 2016 February Archived from the original on, 2016; 23
39. 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/s41467019-13940-6.
40. 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/s41422-020-0282-0.
41. Holshue M L, De Bolt C, Lind quist S, Lofy K H, Wiesman J, Bruce H, et al. First case of 2019novel coronavirus in the United States. N Engl J Med, 2020; 382(10): 929–36. https://doi.org/10.1056/ NEJMoa2001191.
42. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc J pn A cad Ser B Phys Biol Sci., 2017; 93(7): 449–63. https://doi.org/10.2183/pjab. 93.027.
43. Cherian SV, Kumar A, Akasapu K, Ashton RW, Aparnath M, Malhotra A. Salvage therapies for refractory hypoxemia in ARDS. Respir Med., 2018; 141: 150–8. https://doi.org/10.1016/j. rmed.2018.06.030.
44. [44] Khan TA, Schnickel G, Ross D, Bastani S, Laks H, Esmailian F, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. J Thorac Cardiovasc Surg., 2009; 138(6): 1417–24. https://doi.org/10.1016/j.jtcvs.2009.04. 063.

45. Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolised prostacyclin in adult respiratory distress syndrome. Lancet (Lond Engl), 1993; 342(8877): 961–2. https://doi.org/10. 1016/0140-6736(93)92004-d.
46. Searcy RJ, Morales JR, Ferreira JA, Johnson DW. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis., 2015; 9(6): 302–12. https://doi.org/ 10.1177/1753465815599345.
47. Chen L, Liu P, Gao H, Sun B, Chao D, Wang F, et al. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. Clin Infect Dis., 2004; 39(10): 1531–5. https://doi.org/10.1086/425357.
48. Medicine USNLo. U.S. National Library of Medicine. Clinical Trials gov, 2020; 2. doi: https://clinicaltrials.gov.
49. Biospace. Mallinckrodt evaluates the potential role for inhaled nitric oxide to treat COVID-19 associated lung complications, engages with scientific, governmental and regulatory agencies. From the Biospace website. 2020 Mar 24. https://www.biospace. com/article/releases/mallinckrodt-evaluates-the-potential-role-forinhaled-nitric-oxide-to treat-covid-19-associated-lungcomplications-engages-with-scientific-governmental-and regulatory-agencies/.
50. Seto B. Rapamycin and mTOR: a serendipitous discovery and implications for breast cancer. Clin Transl Med., 2012; 1(1): 29. https://doi.org/10.1186/2001-1326-1-29.
51. Seto B. Rapamycin and mTOR: a serendipitous discovery and implications for breast cancer. Clin Transl Med., 2012; 1(1): 29. https://doi.org/10.1186/2001-1326-1-29.
52. Alessandri F, Pugliese F, Ranieri VM. The role of rescue therapies in the treatment of severe ARDS. Respir Care., 2018; 63(1): 92– 101. https://doi.org/10.4187/respcare.05752.
53. Cherian SV, Kumar A, Akasapu K, Ashton RW, Aparnath M, Malhotra A. Salvage therapies for refractory hypoxemia in ARDS. Respir Med., 2018; 141: 150–8. https://doi.org/10.1016/j. rmed.2018.06.030.
54. Carr AC, Maggini S. Vitamin C and immune function. Nutrients, 2017; 9(11). https://doi.org/10.3390/nu9111211. 78. Kim Y, Kim H, Bae S, Choi J, Lim SY, Lee N, et al.
55. Vitamin C is an essential factor on the anti-viral immune responses through the production ofinterferon-alpha/beta atthe initial stageof influenza A virus (H3N2) infection. Immune Netw., 2013; 13(2): 70–4. https://doi.org/10.4110/in.2013.13.2.70.

56. van Gorkom GNY, Klein Wolterink RGJ, Van Elssen C, WietenL, Germeraad WTV, Bos GMJ. Influence of Vitamin C on lymphocytes: an overview. Antioxidants (Basel)., 2018; 7(3). https://doi. org/10.3390/antiox7030041.
57. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med., 2005; 11(8): 875–9. https://doi.org/10.1038/nm1267.
58. Casadevall A, Scharff MD. Serum therapy revisited: animal models of infection and development of passive antibody therapy. AntimicrobAgentsChemother., 1994; 38(8):1695–702.https://doi. org/10.1128/aac.38.8.1695.
59. van Erp EA, Luytjes W, Ferwerda G, van Kasteren PB. Fcmediated antibody effector functions during respiratory syncytial virus infection and disease. Front Immunol, 2019; 10: 548. https:// doi.org/10.3389/fimmu.2019.00548.
60. Arnold R, Neumann M, Konig W. Peroxisome proliferator activated receptor-gamma agonists inhibit respiratory syncytial virus-induced expression of intercellular adhesion molecule-1 in human lung epithelial cells. Immunolog, 2007; 121(1): 71–81. https://doi.org/10.1111/j.1365-2567.2006.02539.x.
61. Bauer CM, Zavitz CC, Botelho FM, Lambert KN, Brown EG, Mossman KL, et al. Treating viral exacerbations of chronic obstructive pulmonary disease: insights from a mouse model of cigarette smoke and H1N1 influenza infection. PLoS One, 2010; 5(10): e13251. https://doi.org/10.1371/journal.pone. 0013251.
62. DinarelloCA.OverviewoftheIL-1family in innate inflammation and acquired immunity. Immunol Rev., 2018; 281(1): 8–27. https:// doi.org/10.1111/imr.12621.
63. Amici C, Di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther., 2006; 11(8): 1021–30.
64. Leung YY, Yao Hui LL, Kraus VB. Colchicine–update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum, 2015; 45(3): 341–50. https://doi.org/10.1016/j.semarthrit.2015.06. 013.
65. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD: Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing, Treasure Island, FL, 2020.
66. Chan JF, To KK, Tse H, Jin DY, Yuen KY: Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol, 2013; 21: 544-555. 10.1016/j.tim.2013.05.005