

Challenges and Opportunities for Covid-19 Management: An Outbreak

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Abstract

Corona virus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome corona virus 2(SARS-CoV-2). The disease was first identified in 2019 in Wuhan, the capital of Hubei, China, and has since spread globally, resulting in the 2019–20 corona virus pandemic. Common symptoms include fever, cough, and shortness of breath. Other symptoms may include muscle pain, sputum production, diarrhoea, sore throat, and loss of smell and taste. While the majority of cases result in mild symptoms, some progress to pneumonia and multi-organ failure. As of 25 March 2020, the overall rate of deaths per number of diagnosed cases is 4.5 percent, but it in fact ranges from 0.2 percent to 15 percent according to age group and other health problems. The virus is typically spread during close contact and via respiratory droplets produced when people cough or sneeze. Respiratory droplets may be produced during breathing but it is not considered airborne. It may also spread when one touches a contaminated surface and then their face. It is most contagious when people are symptomatic, although spread may be possible before symptoms appear. The virus can live on surfaces up to 72 hours. Time from exposure to onset of symptoms is generally between two and fourteen days, with an average of five days. The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. The infection can also be diagnosed from a combination of symptoms, risk factors and a chest

CT scan showing features of pneumonia. Recommended measures to prevent infection include frequent hand washing, social distancing (maintaining physical distance from others, especially from those with symptoms), covering coughs and sneezes with a tissue or inner elbow, and keeping unwashed hands away from the face. The use of masks is recommended by some national health authorities for those who suspect they have the virus and their caregivers, but not for the general public, although simple cloth masks may be used by those who desire them. There is no vaccine or specific antiviral treatment for COVID-19. Management involves treatment of symptoms, supportive care, isolation, and experimental measures. The World Health Organization (WHO) declared the 2019–20 corona virus outbreak a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and a pandemic on 11 March 2020. Local transmission of the disease has been recorded in many countries across all six WHO regions.

Keywords: - Covid- 19, Reverse transcription polymerase chain reaction (rRT-PCR), WHO, SARS-CoV-2, Pathogenic disease

INTRODUCTION

Since the beginning of the 21st Century there are very well known virus that causes certain deaths due to acute respiratory disorders in human as well as in animals like SARS-CoV (in 2003) and MERS-CoV (in 2012).[1] But a recently discovered new Pathogenic Disease was Novel Corona Virus Disease, which was known as COVID-19(in 2019), but now designated as severe acute respiratory syndrome corona virus 2 (SARS- CoV 2). In December 2019, certain deaths were seen in the city of Wuhan (China) with unknown cause which gets spread all over

the world within 1 month and causes a global health hazard. A cluster of acute respiratory disorder cases were reported worldwide due to transmission of this virus by the droplets.

Corona virus consists of a huge family of viruses that may affect humans as well as animals (bats, cats, cattle and camels). There were Seven strains of corona virus:[2]

- 29E (Alpha Corona virus)
- NL63 (Alpha Corona virus)

- OC43 (Beta Corona virus)
- HKU1 (Beta Corona virus)
- MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
- SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
- SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)

Transmission of SARS-CoV 2:

Sometimes the virus from animal infects human and further spread via human to human as SARS- CoV and MERS – CoV and now with SARS- CoV 2 i.e. COVID 19. The mode of transmission is yet incomplete. Epidemiologic investigation in Wuhan at the beginning of this outbreak identified an initial association with a seafood market where most patients had worked or visited.^[3] The seafood market also sold live snakes, rabbits, birds and many more things. The initial research concept was that the virus originated from snake but later recent studies proved that it has more similarity in bats. However, as

the outbreak progressed rapidly in a pandemic proportion, person-to-person transmission through droplets and fomites became the primary mode of transmission.

There are two modes of transmission:

Primary Mode of Transmission (Droplet

mode): The investigation study states that due to coughing, sneeze or talk, the virus is released from the respiratory secretions through an infected person. By having direct contact with mucous membrane, these droplets may infect the other. This viral infection may also occur by touching an infected surface and followed by mouth, nose and eyes. The droplets may not travel more than two meters and do not linger in the air. There is no evidence of its airborne, however still airborne precautions are recommended routinely in some countries and in the setting of specific high risk procedures. Patients are thought to be most contagious when they are symptomatic ^[4]. Some spread might be possible before symptoms appear, but this is not thought to be a common occurrence ^[5-7].

Secondary mode of transmission

(Through surface): The other mode of transmission is through touching an infected surface or object. People may

touch the surface or object having virus on it and then touching their own eyes, mouth and nose, but this is not thought to be the main reason of spreading the virus. The latest study suggests that the virus may also be spread through faces and may contaminate bathroom sinks and toilet bowls.^[8] But it needs more research to know the possibility of transmission of the virus through this mode.

In China, a newborn baby was diagnosed with COVID-19 just 30 hours after birth in month of February. The mother of baby was tested positive before it gives birth. However it is unclear how the virus gets transmitted into the worm or after birth.^[9]

MECHANISM OF ACTION

SARS-CoV-2 is a virus having spike proteins on it and structure to be like a crown, hence named as Corona Virus. It has a single stranded RNA enveloped virus that targets cell through the viral structural spike protein that may binds to be angiotensin- converting enzyme 2 (ACE2) receptors. By binding with the receptor the virus particles uses host cell receptors and endosomes to further enter into the cells. A host type 2 named as transmembrane serine protease (TMPRSS2) facilitates further cell entry via Spike (S) proteins.^[29] After entering inside the cell the viral

polyproteins were synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA in the host cell via RNA-dependent RNA polymerase. Then structural proteins are synthesized that leads to be the completion of assembly and release of viral particles.^[30-32] These lifecycle steps of virus provides potential targets for drug delivery. This potential target drug delivery may include non-structural proteins like 3-chymotrypsin-like protease, papain-like protease and RNA-dependent RNA polymerase that share homology with other novel corona viruses (nCoVs). The drug targets may also include viral entry and immune regulation pathways.

EPIDEMIOLOGY

The first reported cases were from the city of China i.e. Wuhan in December 2019. Around 81,669 total cases of corona virus were reported in China including all laboratories confirmed before April 2020 from which 76,964 people get recovered and 3,329 deaths were observed. The rate of new cases outside of China has outpaced the rate in China which led world health organization (WHO) to declare COVID-19 as a pandemic. Increasing number of cases was seen in 5th April 2020 all over the world, from which some are shown in the table:^[10]

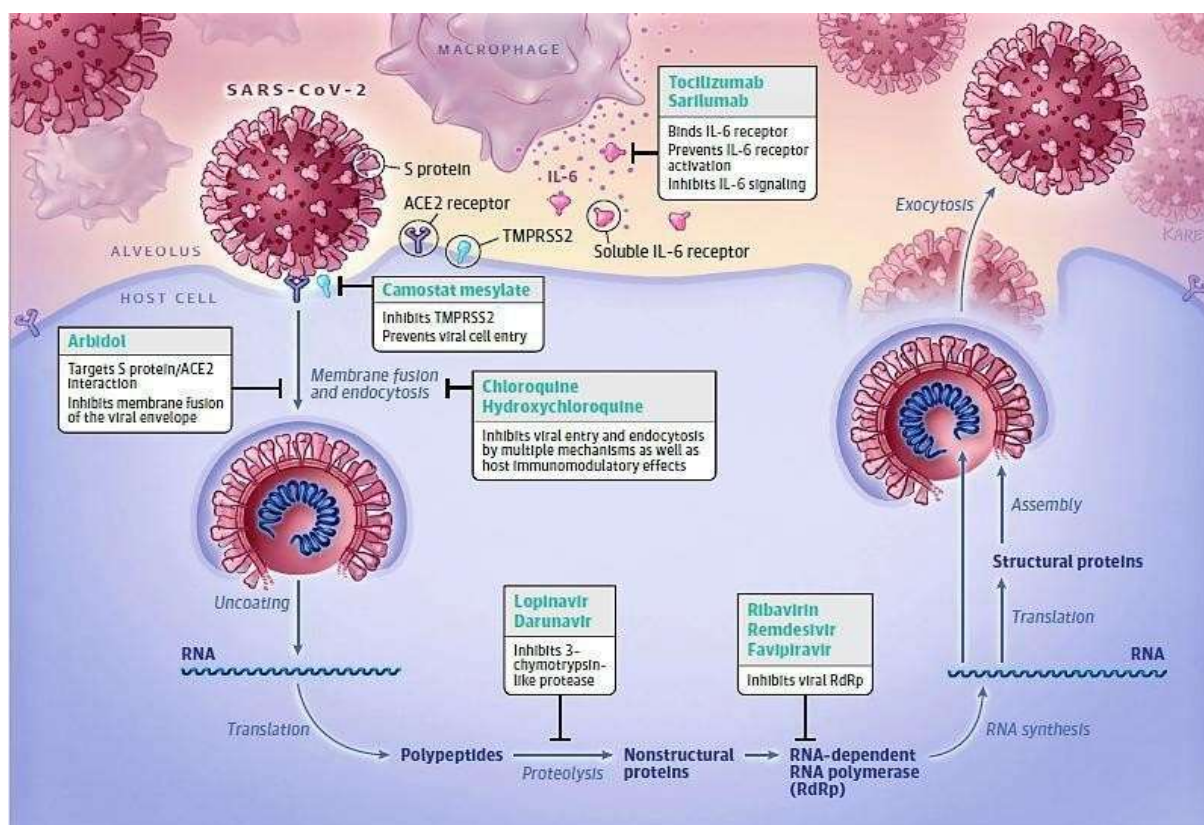


Fig.1. Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease. [33]

Table.1. Worldwide count of cases (Data upto 5th April 2020)

COUNTRIES	TOTAL CASES	TOTAL DEATHS	TOTAL RECOVERED
USA	311,637	8,454	14,828
Spain	126,168	11,947	34,219
Italy	124,632	15,362	20,996
German	96,092	1,444	26,4000
France	89,953	7,560	15,438
China	81,669	3,329	76,964
Iran	55,743	3,452	19,736
UK	41,903	4,313	135
Turkey	23,934	501	786
Switzerland	20,505	666	6,415
Belgium	18,431	1,283	3,247
Canada	14,018	233	2,603
Australia	5,635	62	32
India	3,588	99	229

CLINICAL FEATURES

AGE and SEX : In beginning, the most of cases reported with COVID-19 in Wuhan were adults patients, however, all of these cases had pneumonia.^[11-13] It was observed in two recent non-peer- reviewed studies i.e. one study with 1099 patients from 552 hospitals in 31 provinces in China, in which the median age was seen to be 47.0 years and 55.1% of patients having COVID-19 was between the age of 15-49 years, and the second study which contains 4021 confirmed cases in 30 provinces in China, the mean age was observed to be 49 years and 50.7% patients were between the age group of 20-50 years.^[14,15] So by this we can say that mostly middle aged (>30 years) and elderly persons are more prone to this infection. The symptomatic infection in children appears to be uncommon, but when it occurs, it is usually mild.^[16] These studies may involve serious cases of ARD and pneumonia. In Korea, the studies found that the most of the patients with COVID-19 were between the ages of 25-60 years.^[17] Regarding children with COVID-19, one study shows that only 9 patients which get infected are under the age group of 0-14 years while the other study count is 14 with patients of >10 years of age.^[12, 13] On the other hand regarding sex ratio, male sex comprises

more than half of the cases in COVID-19 infection and the proportion rises from 51.4% to 73.2%.^[11-15] As many cases demonstrate human to human transmission of COVID-19 but till now there are no evidence was found for intrauterine infection caused by vertical transmission of women who contract COVID-19 pneumonia during late pregnancy.^[18] One study in the Wuhan University showed that about 12% of the medical staff get infected during the treatment of the patients with COVID-19 as they are directly exposed to it while hospitalization which also includes health workers.^[13]

Incubation period: It is very important to know the incubation period as it is the time elapse between the exposure of the infectious agent and the signs and symptoms of the infection. It helps in the control as well as guidance of the isolation period. The initial data collected from the 10 confirmed cases in Wuhan was used to describe the isolation period that was 5.2 days.^[19] Using the travel history and confirmed cases data that were detected outside the Wuhan in the early phase of this pandemic another study suggests that the mean isolation period was 6.4 days ranging from 2.1 to 11.1 days.^[20] So, the exact incubation period was not known but it is assume to be between 2 to 14 days

within exposure to infectious agent, even in most cases occurring within 5 days also after exposure.

Illness severity: As compare to the various infections, COVID-19 cause severe illness in elderly population or in people having chronic medical problems. As per the studies from Chinese reports that includes approximately 44,500 confirmed cases shows estimation of disease severity as ^[21]

- Overall case fatality rate was between 2.3 to 5%
- Severe illness (Hypoxemia, >50% lung involvement on imaging within 24 to 48 hours) in 14%
- Critical Disease (Respiratory failure, shock, multi-organ dysfunction syndrome) was reported in 5 percent
- Mild illness was reported in 81% patients

Clinical Presentation: The study data containing 1099 confirmed cases of COVID-19 in Wuhan shows the most common clinical features at the onset of illness i.e. ^[22]

- Myalgias in 14.9%

- Dyspnea in 18.7%
- Fatigue in 38%
- Dry cough in 67%
- Fever in 88%

In the beginning of the infection patient shows symptoms similar like cold and flu but later on patient develop breathing difficulty after a median of five days of illness. Pneumonia appears to be the most common manifestation of the infection. Later on acute respiratory distress syndrome appears in 3.4% of the patients.

Other symptoms

- Headache
- Rhinorrhea
- Gastrointestinal symptoms
- Sore throat

About 6% of the cases, patients were died due to critical illness like respiratory failure, multiple organ dysfunction or failure, septic shock. However, only 13% of the cases have shown severe symptoms of diseases like dyspnea, respiratory frequency ≥ 30 /minute, blood oxygen saturation $\leq 93\%$, PaO₂/FiO₂ ratio < 300 , and/or lung infiltrates $> 50\%$ of the lung field within 24-48 hours. On the other hand about 80% of the patients with

confirmed COVID-19 cases show moderate illness.

Effect on Pediatric population: There are very few pediatric cases with COVID-19 with milder symptoms and better prognosis as compare to the confirmed adult cases of COVID-19. The children recover more frequently and rapidly after the onset of symptoms, even within one to two weeks and no death has been reported from February 2020. Also, children are less frequently exposed to the main mode of transmission.

Reasons why COVID-19 is less affected in children:

- During the time period of outbreak, there was winter vacation in most of the schools, colleges, universities and kinder gardens. So everyone is in their houses with families which are equivalent to isolation itself.
- Hormonal and cellular immune development is not fully developed in children so this may be one of the mechanisms that may lead to absence of severe immune diseases in children.
- COVID-19 exploits the ACE 2 Receptor to enter into the cell but thin

children ACE2 receptors are immature, so this is another reason for the less affect.

Reported symptoms in children shows cold-like symptoms, such as fever, dry cough, sore throat, runny nose, and sneezing. Gastrointestinal manifestations including vomiting and diarrhea have also been reported from the case studies.

As per the laboratory finding, in the early stage of the infection, the total number of peripheral white blood cells is normal or decreased, the lymphocytic count gets reduced, and some children may show signs of increased liver enzymes, lactate dehydrogenase (LDH), muscle enzyme gets reduced and myoglobin in some ill patients like troponin, ferritin and D-dimer gets increased . Similar like adults, the children already having severe and critical illness may be accompanied by elevated levels of inflammatory factors such as interleukin (IL)-6, IL-4, IL-10, and tumor necrosis factor (TNF).^[23]

DIAGNOSIS

As per the WHO-China joint commission report, the diagnosed cases are defined into following categories: ^[24]

a) Suspected case: A patient with acute respiratory illness (symptoms like dry cough, fever, shortness breath) and had a travel history or residence to the country/area reported to be local or community transmission during the 14 days prior to onset of symptoms, or having in close contact with the confirmed COVID-19 diagnosed case in last 14 days before the onset of symptoms.

b) Probable case: A suspected case for whom virus testing for causing COVID-19 is inconclusive (according to the reported laboratory test results) or for whom testing was positive on a pan-coronavirus assay.

c) Confirmed case: A person who results positive or conformation of COVID-19 in laboratory tests irrespective of its signs and symptoms.

d) Close contacts: This can be defined as-

- A person living in the same house with confirmed COVID-19 case.
- A person having unprotected direct contact with the infectious secretions of COVID-19 confirmed case like being coughed on, touching used tissue paper with bare hands etc.
- A person having directly in physical contact with the COVID-19 suspected case like shaking hands.
- A person having face-to-face contact with the confirmed case within 2 meters and less than 15 minutes.
- A person who was in a closed area like meeting room, hospital rooms and classrooms with the infectious case for 15 minutes and is in a distance of less than 2 meters.
- A laboratory worker, healthcare worker who are taking care of the COVID-19 case and having a direct contact with any recommended personal protective equipment (PPE).
- A person travelling in an aircraft had sharing a seat with infectious case or the crew members serving in the section of aircraft where the index case was seated. ^[24]

LABORATORY INVESTIGATION

White blood cell count: As per the recorded data the laboratory findings shows that-

- The count of WBC may vary. It does not provide an accurate confirmation about COVID-19. [25]
- About 80% of the patients more commonly show Leukopenia.
- Leukopenia, leukocytosis, and lymphopenia have been reported.
- Mild thrombocytopenia has also been reported but it is considered as a poor prognostic sign. [25, 26]

Inflammation markers:

- C-reactive protein (CRP): It indicates the severity of the disease and prognosis. COVID-19 increases the level of CRP. An alternative diagnosis should also be sought for the patients suffering with severe respiratory failure with a normal CRP level. [25,26]
- Serum Procalcitonin: It is normal at the time of admission but increases in patients who require ICU care. A study

show high D-Dimer and lymphopenia is associated with poor prognosis. [25,26]

SUGGESTIONS FOR SAMPLE COLLECTION

- The described method for collection of the specimen sample for SARS-CoV-2 test was from the upper respiratory tract (nasopharyngeal and oropharyngeal swab).
- Sputum samples should not be recommended for testing.
- Bronchoscopy is an option for testing but it an aerosol generating procedure that may get the potential to transmit the infection to others. So it is preferably avoid performing it and limit its usage. It can only be used by clearing the secretions/ mucus plugs in intubated patients. [16]
- Additional samples of specimen like blood, urine, stool can also be collected to confirm the results.
- All the samples of specimen's collection from respiration should be taken in a negative pressure room.

CURRENT DIAGNOSTIC MODALITY FOR COVID-19

- The RNA of SARS-CoV-2 is detected for polymerase chain reaction (RT-PCR).
- The results are generated within few hours to 2 days.
- A single positive test should be confirmed by a second RT-PCR assay targeting a different SARS-CoV-2 gene.
- If initial testing was found to be negative but still the person shows signs for the infection the WHO recommends re-sampling and testing from the multiple respiratory tract sites.
- The specimen collected from the documented COVID-19 case should not be submitted for viral collection.
- The sample collected should also be tested for other viral as well as bacterial pathogens.

COVID-19 TESTING KIT

This rapid test kit gives qualitative detection for antibodies IgM and IgG to

SARS-CoV-2 present in human whole blood, plasma and serum. This test applies lateral flow immuno-chromatography and is a tool to help in the diagnosis of SARS-CoV-2 infections. The IgM-IgG combined assay has better and rapid utility and sensitivity compared with a single IgM or IgG test. It can be used for the rapid screening of SARS-CoV-2 carriers, symptomatic or asymptomatic, in test laboratories, clinics, and hospitals as well. [27]

INITIAL MANAGEMENT OF COVID-19

At the initial stage the best and only way to prevent the transmission of infection to isolate the patient. The therapeutic strategies to deal with this pandemic infection are only supportive and preventive, aimed to reduce transmission in the community is the best weapon against it. It has been seen in many countries which are affected by the virus the only treatment they followed is social distancing and self-isolation or quarantine method to prevent the community transmission, even most of the countries decide for the lockdown until the number of infected cases with COVID-19 may get reduced. The person who found to be suspected case should be isolated for at least 14 days of time period. Any

healthcare worker who is in directly contact with the confirmed case or may showing the symptoms such as dry cough, fever, difficulty in breathing, should also be isolated immediately.

Many wards in government authorized hospitals are converted into separate isolation wards. The laboratory confirmed cases should be kept separately in isolation rooms with ventilator facility and a close eye should be kept on them. Other than that patients may also be quarantine in their homes. The isolation ward may ensure proper hand washing facility and hand-hygiene supplies must always available. The alcohol-based hand rub or sanitizers should always be available near point of care and room door. The door of ward should be labelled with sign of Isolation room and the ventilation of that area should be proper. The sanitization of the ward is also an important issue, so there should be no extra furniture at the site and there should be only essential furniture in the room which can be easily cleaned or sanitized. Only healthcare workers and medical staff are allowed in the isolation ward and no visitors must come to meet the infected person.

A stock of PPE supply must be in linen outside the isolation area. The healthcare workers and medical staff must wear Personal Protective Equipment (PPE) while visiting in the isolation room. There must be a trolley holding PPEs on it outside the isolation ward. The waste-bins are must in the isolation room and it should be touch-free. Cleansing of room as well as equipment's should be done with disinfectants. A telephone is available in the isolation room for the communication with the other workers and medical staff so that minimal entry of staff and number of usage of PPE must be controlled.

TREATMENT OF COVID-19

Trails are ongoing to find out the particular drug for the treatment on SARS-CoV-2 or COVID-19. On the basis of previously found viruses of this family like MERS-CoV, and SARS-CoV, various agents were used but it doesn't show any positive results on COVID-19. Currently anti-malarial drug hydroxychloroquine and chloroquine are showing some effects in the patients having severe symptoms of COVID-19. The drugs used for the treatment are listed below in the table:

Table.2. Drugs used in the treatment

DRUG	DOSE	TARGET	CONTRAINDICATION
Hydroxy-chloroquine Sulphate	200mg-400mg	Inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells	Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative, or any component of the formulation
Chloroquine Phosphate	250mg-500mg	Blockade of viral entry by Inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immune modulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells	Hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of formulation. Presence of retinal or visual field changes of any etiology (unless benefit outweighs risk)
Umifenovir	50mg-200mg	S protein/ACE2, membrane fusion Inhibitor	Known hypersensitivity to umifenovir
Lopinavir/ritonavir	50mg-400mg	3CL protease	Hypersensitivity to lopinavir/ritonavir or any of its ingredients, including ritonavir. Co-administration with drugs highly dependent on CYP4503A. Co-administration with potent CYP450 3A inducers
Remdesivir	100mg-200mg	RNA polymerase inhibitor	Exclusion criteria based on specific protocols
Favipiravir	200mg	RNA polymerase inhibitor	Exclusion criteria based on specific protocols

Hydroxychloroquine and Chloroquine: It is well known drug for prevention of malarial and treatment of inflammatory diseases like Rheumatoid arthritis. It helps to block entry of virus into the cells by inhibiting glycosylation of host receptors, proteolytic processing and endosomal

acidification. The drug also shows immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in the host cell. [34,35] Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal concentration (E50) in a low

micromolar range. On the other hand Hydroxychloroquine has in vitro activity with lower E50 for SARS-CoV-2 as compared with Chloroquine after 24hrs of growth.^[36]

However, there is no such high-quality evidence exists for the effect of hydroxychloroquine and chloroquine for the treatment of SARS and MERS. The recent studies from China has reported the use of hydroxychloroquine and chloroquine for using in more than 100 case series that may results in reducing disease progression.^[37]

A recent open-label nonrandimized French study on 36 patients shows very effective results by using 200mg of hydroxychloroquine with supportive medical care. Within 6 days virological clearance is noted from nasopharyngeal swab. In addition, the authors also reported that addition of azithromycin to hydroxychloroquine in 6 patients resulted in numerically superior viral clearance compared with hydroxychloroquine monotherapy.^[38]

Chloroquine dose for treatment of COVID-19 consists of 500mg orally twice a day.^[39,40] While hydroxychloroquine dose for SLS is 400mg daily. The

consequences of thier safety and efficacy are still not properly clear in case of COVID-19 and needs a data over it. Both the agents are safe but still the adverse effects of the drug may also be seen in some patients like hypoglycaemia, neuropsychiatric effects, QTc prolongation and retinopathy.^[41,42]

Antiretrovirals- Lopinavir/Ritonavir: This combination is FDA approved and is a effective agent against HIV and also showing action against novel coronaviruses by inhibiting 3 chymotrypsin –like protease.^[43,44] However, there is no clear research evidence about its effect on COVID-19 patients. A study is carried out on a group of 199 infected patient comparing the efficacy of Lopinavir/Ritonavir vs standard care with median time from the onset of symptoms to 14 days isolation period, with no group difference. The patients may show very slow response to the treatment even after 28 days. The delayed recovery of patients may indicate the ineffectiveness of the drug. Hence, this treatment is not as much effective in treatment of COVID-19.^[45]

The most commonly used dosing regimen of Lopinavir/Ritonavir for COVID-19 is 400mg/100mg daily twice a day upto 14

days.[45,46] The adverse effects of treatment are also been seen including gastrointestinal distress such as nausea and diarrhea, and hepatotoxicity.^[47] In recent study it has been seen that on treatment with Lopinavir/Ritonavir about 50% of patients shows adverse effects and about 14% of the patients discontinue the therapy due to gastrointestinal distress.^[45] Due to hepatotoxicity Lopinavir/Ritonavir treatment may also results to limit patients ability to access other drugs.[48] Other antiretroviral drugs which may act as a protease inhibitors and integrate stand transferase inhibitors are identified for SARS - CoV-2 activity during their screening.[49] Agent like Darunavir is effectively showing results against SARS-CoV-2 during in-vitro ongoing trail studies in China.^[48]

RIBAVIRIN: It is a guanine analogue that inhibits viral RNA dependent RNA polymerase. As previously used agent in novel corona viruses, it may shortlisted as an agent for the treatment of COVID-19. However, the in-vitro activity of Ribavirin is seemed to be limited and required high concentration for SARS-CoV to inhibit viral replication. IV administration is seen to be suitable while treatment in previous studies.[50] No evidence for use of ribavirin exists by inhalation method for

nCoV treatment, and data with respiratory syncytial virus suggest inhaled administration offers no benefit over intravenous administration.^[51]

It is used for the treatment of MERS in combination with interferones but doesn't demonstrate discernible effects on viral clearance.^[52,53] The adverse effects seen while treatment are severe hematologic or liver toxicity. About 60% of the patients may results in haemolytic anemia due to high dose of Ribavirin while treating SARS and near about 40% of patients may need blood transfusions while treating MERS due to intake of Ribavirin with interferons.^[53,54] Ribavirin is also a well-known teratogen and contraindicated in pregnancy.^[55] The substantial toxicity of Ribavirin suggest that it has limited value for its use in treatment of COVID-19 and if used, combination therapy provides best chances for clinical efficacy of the drug.

Antiviral Agents - Oseltamivir: It is a neuraminidase inhibitor used in the treatment of influenza virus but it has no in vitro documented activity for the treatment of SARS-CoV-2. In China, the outbreak of COVID-19 occurs during the peak season of influenza so a large number of patients may receive the therapy with Oseltamivir until the discovery of SARS-CoV-2 as the

cause of COVID-19.^[56] But its agent has no effect in management of COVID-19 once influenza has been excluded.

Umifenovir: It is also known as Arbidol. This antiviral agent is used for the treatment of influenza with unique mechanism of action by targeting S-protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope.^[57] The clinical trials are ongoing for its use in treatment of COVID-19 based on its in vitro data suggestions for activity against SARS.^[58] The current dose of Umifenovir is 200mg orally every 8 hrs for influenza virus is being studied for the treatment of COVID-19. A study in China on 67 patients shows that those who receive Umifenovir for treatment of COVID-19 for median duration of 9 days may result in lower mortality rate and higher discharge date.^[59] This makes it point of interest for research in treatment of COVID-19.

SELECTED INVESTIGATIONAL Drugs

Favipiravir: Previously this agent is known as T-705 and is a prodrug of purine nucleotide favipiravir ribofuranosyl-5'-triphosphate. Its mechanism of action is to inhibit RNA polymerase hence resulting in halting viral

replication. Most of the data collected is due to its activity on influenza and Ebola virus, but it also shows action against activity of RNA viruses.^[60] The described E50 value from clinical data of Favipiravir for influenza and Ebola viruses is low while for treatment of SARS-CoV-2 the dose concentration required should be high.^[61,62] The recommended dose is 2400mg to 3000mg for every 12hrs twice a day, followed by maintenance dose 1200mg to 1800mg every 12hrs. The half-life of the drug is approximately 5 hours.^[63] This drug is having very low adverse effects and is well tolerated at higher doses, even shows very minor adverse effects at higher doses.^[64,65] On the basis of clinical reports when Favipiravir is compared with Arbidol for the treatment of moderate to severe COVID-19 infection, it may show recovery within 7 days in moderate infections. No significant recoveries were seen in moderate and severe (combined) cases.^[66]

Remdesivir: It is also named as GS-5734 which is a monophosphate prodrug that may undergoes metabolism to active C-adenosine nucleoside triphosphate analogue. It may discover during screening process for antimicrobials with activity against RNA viruses such as Coronaviridae and Flaviviridae. Its

development is during the outbreak of Ebola virus. This agent may shows very effective results against Ebola virus at low concentrations.^[67] Due to broad spectrum of Remdesivir, currently it is a choice of drug for treatment of COVID-19. It has a potent activity against many nCoVs, including SARS-CoV-2 with E50 and E90 values of 0.77 μ M and 1.76 μ M respectively.^[68,69] The safety, efficacy and pharmacokinetics of remdesivir is evaluated by single and multidose regimen study in phase I of clinical trial.^[70] the IV infusions recommended is of 3mg and 225mg which are well tolerated by the patients without any evidence of kidney or liver toxicity. At this range remdesivir shows liner pharmacokinetics and the intracellular half-life is of greater than 35 hours. The first clinical use of this agent was against Ebola virus however now successfully showing results against COVID-19.^[71-73] Clinical trials are ongoing for safety, efficacy and antiviral activity of remdesivir for severe to moderate patients of COVID-19.

COMPLIMENTARY THERAPIES

Due to lack of treatment and no particular drug for SARS-CoV-2, the supportive care is recommended for the patients for fast recovery ranging from symptomatic outpatient management to full intensive

care support. There are three adjuvant therapies i.e. corticosteroids, anticytokine or immunomodulatory agent and plasma therapy/immunoglobulin therapy.

Corticosteroids: They are well known to decrease host inflammatory responses in lungs which may results to acute lung injury and acute respiratory distress syndrome (ARDS). However this benefit is underestimated due to adverse effects like delay viral clearance and increased risk of secondary infections. Limited evidence was seen for the direct use of corticosteroids for the treatment of COVID-19. In the previous observational studies for the patients with SARS and MERS infection, corticosteroids had no association with the improved survival but has a association with the delayed viral clearance from respiratory tract and blood with high rate of complications like hyperglycaemia, avascular necrosis and psychosis.^[50,53] The benefits of corticosteroids are related with bacterial infections rather than viral infections. Therefore the potential harms and lack of data for proven benefits of corticosteroids cautions against their routine use in patients with COVID-19.

Anticytokine or Immunomodulatory Agent: This is another class of

complimentary therapy for the patients of COVID-19 as they are monoclonal antibodies against key inflammatory cytokines and other aspects of immunological response. The reason behind their use is that the underlying pathophysiology of significant organ damage in lungs and other organs caused due to immune response and cytokine release.^[73] Based on earlier cases in China, IL-6 appears to be a key driver for this dysregulated inflammation.^[74] Tocilizumab is a monoclonal antibody against IL-6 receptor antagonist which is FDA approved to treat RA and cytokine release syndrome followed by chimeric antigen receptor T-cell therapy. A report during early phase shows use of Tocilizumab with dose of 400mg associated with clinical improvement in 91% of patients with COVID-19 measured with improved respiratory function, rapid defervescence and successful discharge as compared with the patients receiving 1 dose.^[75] An another IL-6 antagonist named Sarilumab approved for RA is also been in clinical trials of phase 2nd/3rd for hospitalized patients with severe and moderate COVID-19.^[76] Other monoclonal antibodies or immunomodulator agents like bevasizumab, fingolimod and eculizumab are also in clinical trial phase for the treatment of COVID-19.

Plasma Therapy/ Immunoglobulin

Therapy: Another effective therapy for the treatment of COVID-19 is the use of convalescent plasma or hyperimmune immunoglobulins.^[77] The reason for this treatment is that antibodies from coronavirus recovered patients may help with both free virus and infected cell immune viral clearance. This therapy may shows very effective results previously in case of SARS and MERS, hence selected in the treatment of COVID-19.^[78,79] In previously treated viral infection the convalescent plasma plays very effective role like in 2009, H1N1 influenza A, reports may suggests that the patients who receive plasma therapy with effective drugs may shows recovery rate high and reduction in mortality as compared to the patients who are just on single therapy. While treatment on SARS, this therapy may shows results within 7 to 10 days of infection, when viremia is at its peak and primary immune response has not yet occurred. Although, due to lack of current commercial immunoglobulin preparations likely lack protective antibodies to SARS-CoV-2. This may warrants to test its safety and efficacy trial as the number of patients who recovered from COVID-19 increases worldwide. The first use of convalescent plasma was in China when COVID-19 is at stage I.^[80] Also a case of 5 patients in

Wuhan treated with the plasma therapy are recently published.^[81] Even FDA also released some guidelines for requesting an emergency investigational new drug application and screening donors for COVID-19 convalescent plasma on March 26, 2020.^[82] Also there are early preprint reports suggesting clinical development of human monoclonal antibodies against a common epitope to block SARS-CoV-2 infection.^[83]

CONCLUSION

It's not been first time that an outbreak of infectious disease takes place in this world. Before that many pandemics due to infectious diseases happens like SARS, MERS, H1N1 Influenza virus etc. The corona virus outbreak comes from the city of Wuhan, China but the main reason behind its origin is not yet found. This may transmit from person to person via droplets so social distancing is only weapon to control it from community transmission. The other ways to stop its transmission is to quarantine himself or self-isolation in home, washing hands with soap for at least 20 sec and not to touch nose, eyes and mouth with hands when you are out of home. Pneumonia is also a common symptom among the patients with COVID-19. There is no specific drug for the treatment of COVID-19 till yet but

hydroxychloroquine is showing some curing effects on patients having severe conditions. Clinical trials are ongoing for the vaccines to recovery this COVID-19 outbreak. There is a need to develop such kind of immunity enhancing vaccines so that no such kind of infectious diseases may affect the human body. Containment and prevention is best options to overcome this infection as at present there is no such therapy for it.

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REFERENCES & BIBLIOGRAPHY

- I. Kamal Kant Sahu, Ajay Kumar Mishra, Amos Lal; Comprehensive update on current outbreak of novel coronavirus infection (2019-nCoV); February 2020.
- II. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases.

- III. World Health Organization. Novel coronavirus situation report -2. January 22, 2020.
- IV. Li Z, Yi Y, Luo X, et al. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. J Med Virol 2020.
- V. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med 2020; 382:970.17.
- VI. Kupferschmidt K. Study claiming new coronavirus can be transmitted by people without symptoms was flawed. Science. February 3, 2020.
- VII. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19 JAMA 2020.
- VIII. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. Sean Wei Xiang Ong, MBBS1; Yian Kim Tan, PhD2; Po Ying Chia, MBBS1; et al.
- IX. <https://nypost.com/2020/03/13/second-newborn-baby-tests-positive-for-coronavirus/>
- X. <https://www.worldometers.info/coronavirus/#countries>
- XI. 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 2020;395:507e13.
- XII. 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 2020;395:497
- XIII. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. J Am Med Assoc 2020 Feb 7.
- XIV. Guan WJ, Ni ZY, Hu Y, Laing WH, Ou CQ, He JX, et al. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv 2020 Feb 9.
- XV. Yang Y, Lu Q, Liu M, Wang Y, Zhang A, Jalali N, et al. Epidemiological and clinical features of the 2019 novel

- coronavirus outbreak in China. medRxiv 2020 Feb 11.
- XVI. Momen M. Wahidi, Carla Lamb, Septimiu Murgu, American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients with Suspected or Confirmed COVID-19 Infection.
- XVII. Ryu S, Chun BC. An interim review of the epidemiological characteristics of 2019 novel coronavirus. Epidemiol Health 2020.
- XVIII. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020 Feb 12.
- XIX. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel corona virus infected pneumonia. N Engl J Med 2020 Jan 29.
- XX. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. Euro Surveill 2020;25(5).
- XXI. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.
- XXII. Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen.
- XXIII. National Health Commission of the People's Republic of China. Diagnosis and treatment plan of novel coronavirus pneumonia, Version 7, EB/OL,(2020-03-04
- XXIV. <https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov>
- XXV. Clinical Characteristics of Coronavirus Disease 2019 in China. W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L.

- Li, G. Zeng, K.-Y. Yuen, R. Chen
<https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25727>
Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis.
- XXVI. International pulmonologists consensus on COVID-19, Dr. Tinku Joseph, Dr. Mohammad Ashken Moslehi, 2020.
- XXVII. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. Published online March 4, 2020.
- XXVIII. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol*. 2020;92(4):418-423.
- XXIX. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol*. 2015;1282:1-23.
- XXX. Fung TS, Liu DX. Coronavirus infection, ER stress, apoptosis and innate immunity. *Front Microbiol*. 2014;5:296.
- XXXI. James M. Sanders et.al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review, American Medical Association, April 13, 2020.
- XXXII. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of Hydroxyl chloroquine in preventing infection and progression. *J Antimicrob Chemother*. 2020;dkaa114.
- XXXIII. . Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. Published online March 11, 2020.
- XXXIV. . Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2.
- XXXV. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical

- studies. *Biosci Trends*. 2020; 14(1):72-73.
- XXXVI. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. Published online March 20, 2020. doi:10.1016/j.ijantimicag.2020.105949
- XXXVII. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020.105932
- XXXVIII. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. Accessed March 18, 2020.
- XXXIX. Kalil AC. Treating COVID-19 off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA*. Published March 24, 2020.
- XL. Interview with David Juurlink. Coronavirus (COVID-19) update: chloroquine/hydroxychloroquine and azithromycin. *JAMA*. March 24, 2020. Accessed April 3, 2020.
- XLI. Chu CM, Cheng VC, Hung IF, et al; HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256.
- XLII. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother*. 2014;58(8):4875-4884.
- XLIII. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med*. Published online March 18, 2020.
- XLIV. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. Accessed March 18, 2020.
- XLV. Lopinavir/ritonavir Hudson (OH): Lexicomp Inc; 2016. Accessed March 17, 2020.
- XLVI. ClinicalTrials.gov. Accessed March 18, 2020.
- XLVII. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease

- 2019 (COVID-19). *Drug Discov Ther.* 2020;14(1):58-60.
- XLVIII. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med.* 2006;3(9):e343.
- XLIX. Foolad F, Aitken SL, Shigle TL, et al. Oral versus aerosolized ribavirin for the treatment of respiratory syncytial virus infections in hematopoietic cell transplant recipients. *Clin Infect Dis.* 2019;68(10):1641-1649.
- L. MorraME, Van Thanh L, Kamel MG, et al. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. *Rev Med Virol.* 2018;28(3):e1977.
- LI. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis.* Published online June 25, 2019.
- LII. Altınbas S, Holmes JA, Altınbas A. Hepatitis C virus infection in pregnancy: an update. *Gastroenterol Nurs.* 2020;43(1):12-21.
- LIII. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* Published online February 7, 2020.
- LIV. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proc Natl Acad Sci USA.* 2017;114(2):206-214
- LV. Khamitov RA, Loginova SIa, Shchukina VN, Borisevich SV, Maksimov VA, Shuster AM. Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures [in Russian]. *Vopr Virusol.* 2008;53(4):9-13.
- LVI. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis.* Published online March 16, 2020.
- LVII. 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.

- LVIII. Mentre F, Taburet AM, Guedj J, et.al. Dose regimen of favipiravir for Ebola virus disease. *Lancet Infect Dis.* 2015;15(2):150-151.
- LIX. Sissoko D, Laouenan C, Folkesson E, et al; JIKI Study Group. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea published correction appears in *PLoS Med.* 2016;13(4):. *PLoS Med.* 2016;13(3):e1001967.
- LX. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. [published online February 22, 2020]. *Pharmacol Ther.* 2020;107512.
- LXI. Chinello P, Petrosillo N, Pittalis S, Biava G, Ippolito G, Nicastri E; INMI Ebola Team. QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient. *PLoS Negl Trop Dis.* 2017;11(12):e0006034.
- LXII. Kumagai Y, Murakawa Y, Hasunuma T, et al. Lack of effect of favipiravir, a novel antiviral agent, on QT interval in healthy Japanese adults. *Int J Clin Pharmacol Ther.* 2015;53(10):866-874.
- LXIII. Chen C, Huang J, Cheng Z, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. *medRxiv.* Preprint posted March 27, 2020.
- LXIV. Siegel D, Hui HC, Doerffler E, 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):1648-1661.
- LXV. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. *Travel Med Infect Dis.* Published online March 5, 2020.
- LXVI. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-271.
- LXVII. World Health Organization. WHO R&D blueprint: ad-hoc expert consultation on clinical trials for Ebola therapeutics. Published October 2018.
- LXVIII. Jacobs M, Rodger A, Bell DJ, et al. Late Ebola virus relapse causing

- meningoencephalitis: a case report. Lancet. 2016;388(10043):498-503.
- LXIX. Holshue ML, DeBolt C, Lindquist S, et al; Washington State 2019-nCoV Case Investigation Team. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-936.
- LXX. Kujawski SA, Wong K, Collins JP, et al. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. medRxiv. Preprint posted March 9, 2020.
- LXXI. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immuno suppression. Lancet. 2020;395(10229):1033-1034.
- LXXII. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
- LXXIII. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. chinaXiv. Preprint posted March 5, 2020.
- LXXIV. Sanofi. Sanofi and Regeneron begin global Kevzara (sarilumab) clinical trial program in patients with severe COVID-19 [news release]. Published March 16, 2020. Accessed March 18, 2020.
- LXXV. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20(4):398-400.
- LXXVI. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methyl prednisolone treatment in SARS patients. Clin Microbiol Infect. 2004;10(7):676-678.
- LXXVII. Arabi Y, Balkhy H, Hajeer AH, et al. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. Springerplus. 2015;4:709.
- LXXVIII. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020. Published online March 27, 2020.
- LXXIX. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with

- coronavirus disease 2019. Open Forum Infect Dis. Published online March 21, 2020.
- LXXX. US Food and Drug Administration. Investigational COVID-19 Convalescent plasma: emergency INDs. Updated April 3, 2020.
- LXXXI. Wang C, Li W, Drabek D, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. bioRxiv. Preprint posted March 11, 2020. doi:10.1101/2020.03.11.987958.2020.

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