COVID-19
A Preventative and Treatment Approach

Allybocus Zubair Akbar,
M.S Gynecology and Obstetrics, Molecular Genetics and Cytogenetics
Republic of Mauritius

Abstract—The year 2020's pandemic is caused by a novel coronavirus, SARS-CoV-2, which binds to human ACE2 receptors via SARS-CoV-2 virus Spike glycoproteins. ACE2 receptors being present on multiple human tissues, act as an entry port for the virus in human cells, and consequently result in a myriad of symptoms suggestive of COVID-19. Once a person is tested and confirmed positive for the presence of SARS-Cov-19 in his/her body, a series of preventive and treatment protocols are initiated. Hydroxychloroquine with azithromycin and other compassionate drugs such as Remdesivir, Avastin, Angiotensin Receptor Blocker, Angiotensin Converting Enzyme inhibitor, and Ivermectin help to reinforce the active immunity of COVID-19 patients while passive immunity conferred via plasma exchange for protective antibodies against SARS-Cov-2 is also an option to fight COVID-19 infection. Oxygen therapy, via Non-Invasive or Invasive forms, is available for moderate to severe cases of respiratory failure or acute respiratory distress syndrome. In this paper, we shall have an overview of SARS-Cov-2 related symptoms, diagnosis and few "promising" medications to manage to COVID-19 infection.

Index Terms— SARS-Cov-2, Covid-19, Hydroxychloroquine, Remdesivir, Avastin, Plasma Exchange, Oxygen Therapy.

1 COVID-19 /SARS-CoV-2

COvid19 or SARS-CoV-2, of the Coronavirus family, has over a few months brought the world to a standstill. Its origin is debatable, neither does the virus has a previously used virus backbone to call it a manipulated virus nor is it identical to the bat/pangolin betacoronaviruses, which make it a pure product of natural selection [1]. SARS-CoV-2 has a genomic sequence comprising of around 28 000 bases The outer surface of the virus is covered with Spike proteins that contain Receptor Binding Domain (RBD), which is the most variable part of the virus. The virus entry port in human host cell is via high-affinity binding to human receptor ACE2. Multiple tissues in the body contain these transmembrane proteins, ACE2, to which the virus can interact thereafter producing multiple symptoms and organ damage. Once inside the host cell, viral mRNA replication starts thereby increasing viral load leading to viremia that will cause the infected person to exhibit symptoms of Covid-19. With the number of newly infected cases and death rates escalating daily, this pandemic finds a comfortable place among some deadliest pandemic experienced in history. It is an ongoing race against time to manage the spread of the virus and simultaneously save maximum lives. The transmission routes of the virus, associated symptoms, prevention, and medication to manage COVID-19 are briefly communicated.

2. Transmission

SARS-CoV-2 is primarily transmitted between people through respiratory droplets (size >5-10 um diameter) or droplet nuclei (size <5um diameter), aerosol, and contact routes. We can classify its transmission as (i) 'Direct transmission' where an infected person with respiratory symptoms (sneezing, coughing) infects other people within 1m of his/her vicinity after the later inhaled these virus-containing-respiratory droplets, and (ii) 'Indirect transmission' when a person comes in contact with surfaces/clothes/belongings recently used by an infected person [2]. The virus has a different survival period on different surfaces and contact transmission occur if one touches his/her mouth, nose, or eyes immediately after touching this surface. Re-applying a used face mask is also a common mistake. Viral transmission may also occur in medical interventional procedures such as nebulisation, manual ventilation, intubation, cardiopulmonary resuscitation as the healthcare personal is within one meter of the patient and respiratory droplets are abundant. Can the Viral mRNA survive in the air and for how long is it viable to cause further transmission?

International Journal of Scientific & Engineering Research, Volume 11, Issue 4, April-2020
ISSN 2229-5518

3. Symptoms

Once a person has hosted the SARS-CoV-2 virus, his/her active immunity plays a major defensive role and he/she may either be asymptomatic or symptomatic. Following exposure to the virus, by day 4-5 the earliest symptoms manifest as fever, tiredness, dry cough among others as listed by CDC, and these symptoms are ranged from mild symptoms to severe illness. In an immunologically resistant person or with minimal medical assistance, symptoms usually fade/disappear by the 14th day. Experiencing trouble breathing, persistent chest pain, confusional state, and cyanosis are among the emergency warning signs requiring immediate medical attention [3]. The elderly patient and immunocompromised patient are more vulnerable to SARS-CoV-2 attack and require closer monitoring with a more aggressive treatment plan. Unfortunately in many cases, critically ill patients will not make it through.

4. Diagnosis

All potential patients should undergo a baseline physical examination before receiving treatment. Right now everybody should be regarded as a potential carrier of SARS-CoV-2 until proven otherwise. Basically at the clinic, the patient symptoms should draw attention to whether or not to suspect COVID-19. Routine blood tests including full blood count, urea and creatine, Erythrocyte Sedimentation Rate are performed. Then an oro/nasopharyngeal swab must be taken to rule out COVID19.
Abnormal lung sounds on auscultation may further provide evidence of COVID-19. If he/she is tested negative for SARS-CoV-2, he/she can go home otherwise if found positive then he/she is taken to the isolation centre for treatment.

4.1 rRT-PCR

Symptoms are subjective to a person and are not diagnostic on their own. Quick and accurate diagnostic tests would provide actionable results in lesser time along our treatment pathway. Currently, laboratory molecular and serological antibodies diagnostic technics are being used to diagnose Covid-19. In laboratory settings, when a respiratory (oro/nasopharyngeal swab) sample of a person is sent to a given laboratory, a technic called real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) is used to extract viral mRNA from that sample. This mRNA is used as a template backbone for synthesising a complementary DNA (cDNA) sequence and the later is amplified in a stepwise manner producing thousands of copies of cDNA under established protocols. These copies have fluorescent markers attached to them which when detected by a computer tracking method will provide data that can be interpreted as a negative or positive result. The procedure may last 6-24 hours depending on institutions' protocols.

4.2 Serological test

Post-exposure to the SARS-CoV-2 virus, a person's immune system will produce antibodies to fight this foreign virus and these antibodies in the person's blood can be detected by performing serological testing. Venous blood sample from a patient is taken and a technic called Enzyme-linked immunosorbent assay (ELISA) is used to detect the presence of antibodies to coronavirus namely immunoglobulin (IgM, IgG) in this blood sample. The presence of these IgM or/and IgG in a blood sample not only is indicative that the person is infected and that his/her immune system is fighting the virus but also whether this is an active infection or past infection. ELISA test is not routinely performed as the antibodies will be present in the human body 5-10 days post-infection when the patient has developed antibodies thereby giving false-negative results at day 1-2. Serology testing should not be the sole diagnostic test for SARS-CoV-2. The presence of antibodies in the blood cannot ensure that the patient is immune to reinfection and how long this immunity will last.

4.3 Promising Test Kit

The development of Covid19 on spot test Kit will be helpful as the result will be available within 30min and in case of positive result; the patient is taken care of earlier. Some documented portable devices using molecular test methods include MicrosensDx RapiPrep@COVID-19 test, MesaBioTech Accula Test, Cepheid Xpert SARS-CoV-2, GenMark Eplex, and Abbot IDNow Covid-19 test. Documented antibody-based Test Kits include BioMedomics rapid test, Surescreen rapid test cassette, Goldsite diagnostic kit, Assay Genie rapid POC kit, and VivaDiag COVID-19 IgG-IgM test. Massachusetts Institute of Technology recently produced a paper-based COVID Test Kit, E25Bio's COVID 19 diagnostic kit [4]. Singapore also has developed the SARS-CoV-2 assay kit VitaPCR™ that can supposedly give results in 20 minutes [5]. UC San Francisco and Mammoth Biosciences have developed CRISPR-based COVID-19 Test Kit that can provide a diagnostic result within one hour [6]. The urge to develop a quick and accurate diagnostic test kit is escalating and hopefully, these will be helpful in rapid detection and management of the patient to halt the spread of the virus.

4.4 Chest CT Scan

A patient's condition may degenerate from moderate to severe or critically ill patient. Pneumonia commonly develops in these patients and leads to acute respiratory distress syndrome. Inflammation in the lung causes (i) exudates to fill the alveolar spaces, (ii) transxudate to fill the interstitial lung space causing alveolar collapse, (iii) lung vasculature enlargement and (iv) lung consolidation which gives ground-glass opacities on chest CT scan. This lung architectural dis-

International Journal of Scientific & Engineering Research, Volume 11, Issue 4, April-2020
ISSN 2229-5518

tortion, pleural effusion, bronchial distortion reflect the viral load and can be used to evaluate the severity of pneumonia in the respective patients [7].

5 Preventative measures

5.1 Precautionary Sanitary Measures

Precautionary measures range from governmental to a personal level. The government should firstly sensibilise the population about the virus and how to tackle it together. Sanitary measures have to be well communicated and upon their implementation, the population should abide by these regulations. A lockdown, partial or complete, is a righteous approach from the government to minimize the spread of the virus in the population. An interdisciplinary team including medical personals, police force, and other frontliners, works for the safety of the population. At an individual level, proper hygiene is fundamental to prevent the spread of the virus. Washing hands regularly, washing food properly before eating, and avoid touching surfaces outside. In society, the wearing of protective face mask is a must and social distancing with an interval of 1 to 2 metre(s) between people to prevent droplet borne viral transmission.

5.2 Quarantine

Any person who (i) presents with symptoms of COVID-19, (ii) has recently travelled to high-risk countries, (iii) has been in direct contact with another infected person should be isolated from the rest of the population for a minimum period of at least 14 days. During his/her isolation period, the person's symptoms progression or regression, and his/her viral load are monitored at regular intervals. By day 14 of isolation, he/she can be discharged home if judged asymptomatic by medical staffs and consecutive laboratory test shows negative for SARS-CoV-2.

5.3 Death and Corpse disposal

Unfortunately, some patients who (i) are old and vulnerable, (ii) immunologically compromised, (iii) have other chronic comorbidities (chronic diabetes, cardiovascular problem, kidney problem, autoimmune problems), or (iv) long time intubated/ventilated may not make it through. The virus is believed to stay in the corpse even a few days after death and any family member who touches the corpse may potentially be infected. Therefore for COVID-19 related death, corpse disposal is undertaken by the authorised death management team to ensure effective cremation or burial under preset protocols.

6 Medications

In the context of the Covid-19 pandemic, there is an urgency to find a safe and effective treatment plan. There is to-date neither a vaccine nor drugs specific to fight Covid-19. Different countries have adopted different treatment protocols and we shall consider some drugs briefly.

6.1 Hydroxychloroquine

Hitherto known for its antimalarial and arthritic anti-inflammatory properties, Hydrochloroquinine (HCQ) has since this 2020 pandemic been the 'game-changer' drug in controlling COVID-19 infection. HCQ works by altering the pH of lysosomes in antigen-Presenting cell thereby modifying a series of the immunological pathway that results in decrease inflammatory process. HCQ blocks virus infection by altering the endolysosomal pH required for virus/cell fusion and also interferes with glycosylation of cellular receptors of SARS-CoV-2 and is, therefore, a promising silver bullet to this pandemic. HCQ is used alone or in combination with Azithromycin (AZI) as the first-line treatment option while simultaneously ongoing clinical trials are being performed to confirm its efficacy. In one study, a dosing regimen of 600mg HCQ+ 500mg AZI daily for 10 days showed a fall in viral load of the infected patient by day 6 of treatment and thereafter prioritised the use of HCQ+AZI in combination[8]. Some studies noted that neither HCQ alone nor HCQ+AZI showed evidence of reduced risk of death and/or mechanical ventilation. National Institute of Health and Centers for Disease Control and Prevention have also back-off from the support of HCQ+AZI as first-line treatment option and therefore to-date we do not have a consensual Protocol [9,10]. More studies are against HCQ+AZI use because of its associated toxicities [11]. However due to limited anecdotal evidence, unless a new "magical" drug emerges overnight, several countries will continue using HCQ + AZI as first-line treatment option.

6.2 Ivermectin

Ivermectin is a semi-synthetic derivative of avermectin family that is used to kill parasites and pests. In the body of parasites, ivermectin works by binding to some specific ivermectin-sensitive ions channels on cell surface causing an influx of Cl^- ions through cell membranne and these results in hyperpolarisation which leads to muscle paralysis. How an antiparasitic drug gained overnight recognition? Well, credit goes to a team of scientists from Melbourne's Monash University, led by Dr. Kylie Wagstaff, who found that in laboratory culture, one single dose of ivermectin potentially eradicated all viral mRNA within 48 hours and that news made the buzz [12]. However, there is no documented data about its administration routes and dose regimen even as a compassionate drug.

International Journal of Scientific & Engineering Research, Volume 11, Issue 4, April-2020
ISSN 2229-5518

6.3 ACEi/ARB, Decoy ACE2

Angiotensin-Converting Enzyme 2 (ACE2) is a transmembrane protein expressed on the surface of several human tissues including the upper and lower respiratory tracts, the myocardium, and the gastrointestinal tract. The spike (S) glycoprotein of SARS-CoV-2 binds to human receptor ACE2 which then involuntarily serves as the main entry port for the virus into cells. Drugs like angiotensin-converting enzyme inhibitor (ACEi), which acts by preventing the formation of angiotensin II, or Angiotensin II receptor blockers (ARB), which prevent binding of angiotensin II to its receptors on tissues, are usually used for the treatment of heart failure, hypertension or kidney problems. ACEi, ARB or ACEi/ARB combination have been proposed to block SARS-CoV-2 entry into cells. Will the decreasing level of ACE2 receptors in cells help to fight the infection or worsen the infection by receptors upregulation? A study showed that once the virus enters the host cell there is ACE2 expression downregulation causing the enzyme to lose its protective effects in organs [13]. Another study has shown promising results in the hospital where inpatient treatment including ACEi/ARB was associated with a lower risk of all-cause of mortality as compared to ACEi/ARB non-users [14]. Decoy ACE2 receptors (hrsACE2) could be a promising alternative in preventing COVID-19 infection. As its name implies, hrsACE2 acts as a decoy attracting the virus to attach to it rather than infecting human cells and in so doing, it protects the human body from the organ damage due to SARS-CoV-2. However, its availability is yet to reach all countries amidst this pandemic. Patients already on ACEi/ARB should not discontinue the drugs without their physicians' approval while patients starting this ACEi/ARB combination should be monitored for adverse effects in the context of COVID-19 infection.

6.4 Remdesivir

Remdesivir is an adenosine analog that incorporates into virus RNA chains and causes premature termination in viral mRNA chains, a property that makes Remdesivir a promising antiviral drug to prevent the progression of COVID-19. A small investigational treatment group receiving an initial dose of 200mg followed by a daily dose of 100mg over 10 days treatment regimen [15,16] showed some drug efficacy when compared to a placebo group. If this study is reproducible in larger groups then Remdesivir can be approved to be used worldwide to fight COVID infection. Another study proposed that a combination of Remdesivir + HCQ can be highly effective to control SARS-CoV-2 after successful *in vitro* assessment [17]. In wait for approval, some hospitals can offer compassionate use of Remdesivir to critically ill patients.

6.5 BCG/MMR

Scientists are toiling in a race to develop an effective vaccine to fight SARS-CoV-2. Scientists noted at a molecular level that SARS-CoV-2 Spike glycoprotein, membrane fusion protein, shared structural similarities to fusion proteins from both measles and mumps and that the Macro domain of SARS-CoV-2 and rubella shared 29% amino acid sequence identity. At the clinical level, patients who had the childhood MMR vaccines presented with better immunity against COVID-19 than patients who did not have MMR vaccines. These data favoured the use of MMR vaccines to potentially confer some protection against SARS-CoV-2 in a patient at risk and elderlies [18, 19]. Though there is no documented evidence, Dr. Fraustman from Massachusetts General Hospital/ Harvard medical school claimed that Bacillus-Calmet-Guerin (BCG) vaccine can boost the immune system and provides off-target-effect protection [20]. Some countries offering neonates BCG/MMR vaccination campaigns claimed fewer death cases related to COVID-19 albeit the data are not conclusive of BCG efficacy in fighting COVID19. Unfortunately, BCG is not a recommended vaccine for the prevention of COVID-19 by WHO. The use of BCG/MMR is now subjective to each country's health policies.

6.6 Avastin

Avastin (Bevacizumab) is an anti-VEGF (Vascular Endothelial Growth Factor) drug that is used primarily for treatment of cancer (colon, rectal, lung, and kidney) and for specific eye disease (macular edema). VEGF which is a potent vascular permeability inducer is present in higher concentrations in COVID-19 patients compared to an uninfected person. This increased vascular permeability leads to pulmonary edema (PE), acute lung injury (ALI), and acute respiratory distress syndrome (ARDS), all contributing to the death of critically ill patients. Avastin can be used to reduce vascular permeability, thereby reducing the risk of ALI, PE, and ARDS. Few data show Avastin has been used in some treatment centres with positive results [21]. Hence Avastin may be regarded as a key therapeutic drug in severe cases prone to ALI, PE, and ARDS.

6.7 Low Molecular Weight Heparin

Until recently, Chinese physicians discovered during autopsies that blood clots were not limited to lung but present in heart, kidneys, and liver which concluded that COVID-19 infection is not a simple respiratory infection. SARS-CoV-2 has the ability to cause systemic clotting problems, disseminated intravascular coagulation, making management harsher. Upon admission in a care centre or hospitals, the D-dimer level of patients should be checked. Patients may die of ARDS due to

International Journal of Scientific & Engineering Research, Volume 11, Issue 4, April-2020
ISSN 2229-5518

pulmonary embolism. If the D-dimer results are high at admission or due to sepsis-induced coagulopathy (SIC), patients should be started on low molecular weight heparin anticoagulant therapy [22, 23].

6.8 Convalescent Plasma Exchange

Plasmapheresis is a technic where blood from a person flows through a needle then a catheter to a machine that separates the blood into its major components, cells, and plasma, retaining the required component and returning the rest back to the person's blood circulation. Using this technique, antibodies present in the convalescent plasma of a donor can be transfused to a patient who lacks these protective antibodies, and therefore the latter gains some immunity against the offending organism. This is passive immunity. In the context of SARS-CoV-2, a COVID-19 survivor's blood plasma contains antibodies to SARS-CoV-2 making him a potential donor and a critically ill COVID-19 patient who lacks these protective antibodies is a potential recipient. Once a donor fulfills the donor eligibility protocols, he can donate blood and the separated convalescent plasma collected can be transfused to deserving COVID-19 patients. A small study showed the efficacy of treating critically ill COVID-19 patients with therapeutic plasma exchange [24, 25] albeit plasma exchange does have some drawbacks. This technique has provided satisfying results in hospitals in many countries even though it has a few drawbacks. Amidst this pandemic, the benefit overweighs the risk and medical personals should take the risk.

7 Oxygen Therapy

Majority of patients with COVID-19 show mild to moderate symptoms not requiring oxygen assistance, while some will have respiratory compromise, respiratory failure, or ARDS requiring emergent medical interventions. Oxygen therapy starts with a low flow of 1-2L/min to 5L/min with a nasal cannula, 6-10L/min via venturi mask, and >10L/min via mask with reservoir bag. High Flow Nasal cannula (HFNC) and Non-Invasive Ventilation (NIV) are alternatives in a center where mechanical ventilators are not available for oxygen therapy. However, HFNC and NIV generate aerosol, medium for virus transmission, thus requiring precaution by healthcare workers.

7.1 Endotracheal Intubation

Despite non-invasive oxygen therapy, some patients' general condition deteriorates or develops further complications such as progressive severe pneumonia, Sepsis, ARDS which make them candidates for invasive endotracheal intubation for mechanical oxygen therapy. After pre-oxygenation (100% oxygen for 5min) via continuous positive airway pressure (CPAP), rapid sequence intubation is performed. The operator should use personal protective equipment (PPE) as the risk of airborne viral transmission is highest during this procedure. Mechanical ventilation is set at low tidal volume (4-6ml/kg) and PEEP is high enough to maintain driving pressure. Patients are preferentially in prone position owing to lung anatomical recruitment. Anticoagulant and Avastin are used in some hospitals to prevent embolism and non-cardiac pulmonary edema respectively. Drugs like Remdesivir and/or HCQ+AZI are usually continued depending on hospital protocol. Patients are closely monitored 24/7 for deterioration or improvement.

7.2 Extracorporeal Membrane Oxygenation

Extracorporeal Membrane Oxygenation (ECMO) is a method used to pump blood from a patient's blood circulation to a machine that artificially oxygenates the blood before returning it to the patient's blood circulation, thereby bypassing the patient's lungs function. ECMO requires enormous interdisciplinary teamwork and highly trained medical personals round the clock to run the machine and to monitor the patient's condition. Therefore potential candidates for ECMO are patients who are no longer supportable with mechanical ventilation and have a high risk of mortality, for example, a patient with $PaO2/FiO2 < 100$ despite optimal care. The physician must be objective and selective when starting a candidate on ECMO stressing on patient's age and any associated comorbidities. Few studies favour the use of ECMO on critically ill COVID-19 patients as there has been much improvement in certain patients' overall condition while some patients died due to other comorbidities [26]. Another study deduced no significant difference in mortality between ECMO and conventional therapy [27]. ECMO does save lives and as to 24 April 2020, 50/116 (43%) COVID-19 patients worldwide on ECMO were discharged alive based on the ELSO registry [28]. It should be stressed that ECMO is not a therapy to be rushed to the frontline and should be cautiously recommended for COVID-19 patients.

8 Conclusion

Owing to a dearth of time and knowledge about SARS-CoV-2, we are clueless standing with unloaded arms against a rapidly outspreading foe. Sanitary preventions alone might buy us just enough time before an undesirable future reunion with SARS-CoV-2. Unless we have a silver bullet vaccine soon, active immunity backed by HCQ+AZI and/or above-mentioned compassionate drugs and passive immunity con-

International Journal of Scientific & Engineering Research, Volume 11, Issue 4, April-2020
ISSN 2229-5518

ferred through plasma exchange are the rays of hope to fight COVID-19. Invasive intervention and treatment strategies are here for critically ill patients. In a fateful wait for an effective vaccine and/or drug, let us hope this time the CARPATHIA comes quicker.

CONFLICT OF INTEREST

The author has no conflict of interest.

REFERENCES

[1]. Kristian G. Andersen AR, W. Ian Lipkin, Edward C. Holmes & Robert F. Garry Nature Medicine 2020; 26, :450–2;doi.org/10.1038/s41591-020-0820-9

[2]. Liu J LX, Qian S et al. Community transmission of severe acute respiratory syndrome coronavirus 2, Shenzhen, China. Emerg Infect Dis 2020. doi.org/10.3201/eid2606.200239

[3]. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention 2020; https://www.cdc.gov/ access24.04.2020

[4]. MIT Develops Cheaper And Faster COVID-19 Diagnostic Test. Thailand Medical News mar 13 2020:https://www.thailandmedical.news:access24.04.2020

[5]. COVID-19 MENARINI DIAGNOSTICS: KIT FOR DIAGNOSIS IN 20 MINUTES. 02 apr 2020:https://www.menarini.com/ access 24.04.2020

[6]. Alvarez J. New CRISPR-Based COVID-19 Test Kit Can Diagnose Infection in Less Than an Hour. University of California San Francisco 16 apr 2020; https://www.ucsf.edu/news/2020/04/417181/new-crispr-based-covid-19-test-kit-can-diagnose-infection-less-hour access 24.04.2020

[7]. Kai-Cai Liua PX, Wei-Fu Lvc et al. CT manifestations of coronavirus disease-2019: A retrospective analysis of 73 cases by disease severity. European Journal of Radiology 2020; 126 https://doi.org/10.1016/j.ejrad.2020.108941

[8]. Guillaume Hache P, Jean Marc Rolain et al. Combination of hydroxychloroquine plus azithromycin as potential treatment for COVID 19 patients: pharmacology, safety profile, drug interactions and management of toxicity. https://wwwmediterranee-infectioncom/wp-content/uploads/2020/04/azithroquine_manuscript-soumispdf access 23042020 2020;

[9]. Matthieu Mahévas V-TT, Mathilde Roumier et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. medrxiv 12 apr 2020; https://doi.org/10.1101/2020.04.10.20060699

[10]. Therapeutic Options for COVID-19 Currently Under Investigation. COVID-19 Treatment Guidelines 2020; https://covid19treatmentguidelines.nih.gov/ access24.04.2020

[11]. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combiniationof Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Molina et al. Medicine et Maladies Infectieuses 2002; in press. Doi: https://doi.org/10.10.16/j.medmal.2020.03.006

[12]. Ivermectin can kill COVID-19 within 48 hours', Monash University study finds. https://wwwthepharmalettercom/article/ivermectin-can-kill-covid-19-within-48-hours-monash-university-study-finds access24042020 2020;

[13]. Muthiah Vaduganathan MD, M.P.H., Orly Vardeny, Pharm.D., Thomas Michel, M.D., Ph.D.,et al. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med April 23, 2020 382:1653-1659:DOI: 1610.1056/NEJMsr2005760

[14]. Peng Zhang LZJCea. Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. ahajournals 2020; DOI: 10.1161/CIRCRESAHA.120.317134

[15]. NIH clinical trial of remdesivir to treat COVID-19 begins. National Institute of Health 25 Feb 2020; https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins access 22.04.2020

[16]. Jonathan Grein MD, Norio Ohmagari, M.D., Ph.D., Daniel Shin, M.D.,et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med April 10, 2020; DOI: 10.1056/NEJMoa2007016

[17]. Wang, M., Cao, R., Zhang, L. *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* **30,** 269–271 (2020). https://doi.org/10.1038/s41422-020-0282-0

[18]. Adam Young BN, Rocio Fernandez Mendez et al. Homologous protein domains in SARS-CoV-2 and measles, mumps and rubella viruses: preliminary evidence that MMR vaccine might provide protection against COVID-19. medrxiv 10 apr 2020; i: https://doi.org/10.1101/2020.04.10.20053207

[19]. KAIDAN M. Scientists find MMR vaccine could help fight COVID-19 in major breakthrough. express 2020; https://www.express.co.uk/lifetyle/health/1272112/Coronavirus-breakthrough-MMR-Covid-19-cure-cambridge-latest-measles-mumps access23.04.2020

[20]. Yu G. How a 100-year-old vaccine for tuberculosis could help fight the novel coronavirus. CNN Health April 10, 2020; https://edition.cnn.com/2020/04/09/health/tuberculosis-bcg-vaccine-coronavirus/index.html access24.04.2020

[21]. Bevacizumab in Severe or Critical Patients With COVID-19 Pneumonia (BEST-CP). clinicalTrialsgov apr 19, 2020; https://clinicaltrials.gov/ct2/show/NCT04275414 access 24.04.2020

[22]. Tang N LD, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020 Apr;18; (4):844-847. doi: 10.1111/jth.14768

International Journal of Scientific & Engineering Research, Volume 11, Issue 4, April-2020
ISSN 2229-5518

[23]. CHEN SHI CW, HANXIANG WANG et al. The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective clinical study. medrxiv 15 apr 2020; doi: https://doi.org/10.1101/2020.03.28.20046144

[24]. Shen C WZ, Zhao F et al,. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA 2020 Mar 27.; doi: 10.1001/jama.2020.4783.

[25]. Keith, P., Day, M., Perkins, L. *et al.* A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Crit Care***24,**128 (2020).https://doi.org/10.1186/s13054-020-2836-4

[26]. Zeng, Y., Cai, Z., Xianyu, Y. *et al.* Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: a retrospective case series. *Crit Care* **24,** 148 (2020). https://doi.org/10.1186/s13054-020-2840-8

[27]. Cortegiani A IG, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020 Mar 10. ; S0883-9441(20)30390-7. doi: 10.1016/j.jcrc.2020.03.005

[28]. ECMO in COVID-19. Extracorporeal Life Support Organization ECMO and ECLS > COVID-19 2020; https://www.elso.org/COVID19.aspx access 24.04.2020