Global *Journal of Microbiology*
2022; 3(1): 21-38.
ISSN Online: 2766-9513; ISSN Print: 2766-9505
Website: http://naturescholars.com
Email: Glo_J_Mic@126.com
Publisher: Scholars Publishing, LLC

Review

Novel Coronavirus Disease 2019 (COVID-19): Etiology, Pathology, Diagnosis, Treatment and Prevention

Chu-Yun Xing[1,2,#], Hong-Yi Xin[3.4.,#], Qiang Xin[1,5,#], Yan-Hua Xu[2], Hong-Wu Xin[5,6,✉], Xi-He Zhang[3,4, ✉], Xiu-Lan Su[7, ✉], Xiao-Yan Wang [3,4,✉]

1. Graduate School for Medicine, Inner Mongolia Medical University, Hohhot, Inner Mongolian Autonomous Region 010110, China. 2. Department of Oncology, the Second Clinical Medical College of Yangtze University, Jing-Zhou, Hubei 434000, China. 3. The Doctoral Scientific Research Center, People's Hospital of Lianjiang, Guangdong 524400, China. 4. The Doctoral Scientific Research Center, People's Hospital of Lianjiang, Guangdong Medical University, Guangdong 524400, China. 5. Laboratory of Oncology, School of Basic Medicine, Faculty of Medicine, Yangtze University, Jing-Zhou, Hubei 434000, China. 6. Research Centre of Molecular Medicine, School of Basic Medicine, Medical College of Chifeng University, Chifeng, Inner Mongolian Autonomous Region 024000, China. 7. Clinical Medical Research Center, Affiliated Hospital of Inner Mongolia Medical University, Hohhot 010050, China.

#，Authors contributed equally

✉ Correspondence

Xiao-Yan Wang, The Doctoral Scientific Research Center, People's Hospital of Lianjiang, Guangdong Medical University, email: cc11wxy@126.com. Xiu-Lan Su, Clinical Medical Research Center, Affiliated Hospital of Inner Mongolia Medical University, Hohhot 010050, China. slsu@hotmail.com. Xi-He Zhang, The Doctoral Scientific Research Center, People's Hospital of Lianjiang, Guangdong Medical University, email: hljsnjx@163.com. Tel: +86 19126491230. Hong-Wu Xin, Laboratory of Oncology, School of Basic Medicine, Faculty of Medicine, Yangtze University, Jing-Zhou, Hubei 434000, China, hongwu_xin@126.com.

Received: June 24, 2022; Accepted: September 29, 2022; Published online: October 31, 2022.

Cite this paper: Chu-Yun Xing, Hong-Yi Xin, Qiang Xin, Yan-Hua Xu, Hong-Wu Xin, Xi-He Zhang, Xiu-Lan Su, Xiao-Yan Wang (2022). Novel coronavirus disease 2019 (COVID-19): etiology, pathology, diagnosis, treatment and prevention. *Global Journal of Microbiology*, 3(1):21-38. http://naturescholars.com/gjmic.030103. https://doi.org/10.46633/gjmic.030103.

Abstract

Coronavirus disease 2019 (COVID-19) is a pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which has currently become a global concern with low mortality and high morbidity. It poses a huge threat to human health and social economy all over the world. While the current understanding of COVID-19 pathogenesis is significant, a better understanding of the infection and efficacious treatment and prevention strategies for COVID-19 is particularly important. In this paper, we reviewed the literature on the etiology, pathology, diagnosis, treatment and prevention of COVID-19, and collected and summarized the various human invasions of coronaviruses in recent years, including their cellular receptors and accessory receptors for entering human cells. The review offered important insights for the understanding of the coronavirus life cycle to prevent and control coronavirus outbreaks.

Key word: COVID-19, etiology, diagnosis, treatment, prevention and control, vaccines.

Global Journal of Microbiology Vol. 3, No. 1, October 31, 2022

Introduction

Corona Virus Disease 2019 (COVID-19), Which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic(1). The virus was fierce and happened to spread rapidly around the world. Although there is no better way to eradicate the virus, various new vaccines and therapeutic antibodies have been developed to effectively help people resist the virus invasion and treatment. One of the most noteworthy is neutralizing antibodies (nAbs), which provides patients with important specific immune defense against virus infection, enabling rapid development of COVID-19 defense and treatments.

1. The pathogen of COVID-19

SARS-CoV-2 belongs to the β Coronavirus genus, which is composed of a positive-sense single-stranded RNA genome, four structural proteins and sixteen non-structural proteins. The four structural proteins are separately the envelope protein (E), spike glycoprotein (S), membrane protein (M) and nucleocapsid protein (N) and the nonstructural proteins are separately named as nsp1-nsp16. The RNA genome is 27-31kb long, which is the longest nucleic acid chain among RNA viruses. The enveloped SARS-CoV-2 is round or oval particles, usually polymorphic, which diameters ranging from 60 nm to 140 nm. Its genetic characteristics are significantly different from those of SARS-CoV (SARS Coronavirus) and MERS-CoV (MERS associated coronavirus). The current studies showed that it is more than 85% homologous with bat SARS-related (SARS-r) CoV (BAT SL covzc45). SARS-CoV-2 can be isolated and cultured in human respiratory epithelial cells in vitro for 96 hours to be detected, while it will take about 6 days in VroE-6 or Hhuh-7 cell lines for detection.

In recent years, humans have been attacked by coronaviruses for many times. The molecular mechanisms were increasingly revealed. Here the genes, protein secondary structures and extracellular domains of the coronavirus cell receptors and co-receptors in human cells are shown in Tables 1-3. The ligands of the co-receptor ACE2 and CD13 are shown in Table 4. The functions of some co-receptors on cell entry of coronaviruses are listed in Table 5.

2. Pathology of novel coronavirus pneumonia

2.1 Infection and immunity

Infection of SARS-CoV-2 is

Table 1. The Coronavirus receptors and helper receptors in human cells

Seven human-infecting coronaviruses	Cellular receptors for viral entry	Helper receptors for viral entry
COVID-19	ACE2 (angiotensin converting enzyme 2)	CD147 receptor (3) DC-SIGN receptor L-sign receptor DPP4 receptor (not mediated alone) ADAM17 TMPRSS2 (as an activator in early infection)
SARS - CoV	DPP4 (also known as CD26, dipeptidyl peptidase IV)	ADAM17 Protein designed and design related molecules, TMPRSS2 (as activator in early infection)

MERS-CoV	ACE2 (angiotensin converting enzyme 2)	CEACAM5 GRP78 CD9 TMPRSS2 (as an activator in early infection)
HCoV-229E	CD13 (aminopeptidase receptor, APN) (4)	/
HCoV-OC43	Hla-1 (human leukocyte antigen class I) (5)(6)	/
HCoV-NL63	ACE2 (angiotensin converting enzyme 2) (7)	ADAM17
HCoV-HKU1	Hla-1 (human leukocyte antigen class I)	O-acetylated silicic acid (8)

Table 2.Genes of three important receptors of COVID-19

Recipient	Gene ID and sequence
ACE2	Gene ID: 59272, updated on 27-Dec-2020
DPP4	Gene ID: 1803, updated on 13-Dec-2020
TMPRSS2	Gene ID: 7113, updated on 27-Dec-2020

Table3.Protein secondary structures and extracellular domains of three important novel Coronavirus receptors

Recipient	Protein secondary structure and extracellular domain
ACE2	With α Spiral and irregular curl are dominant
DPP4	/
TMPRSS2	The synthesis of TTSPs initially exists in the form of single chain zymogen. After digestion by arginine or lysine residues, it can be changed into enzyme form and activated. After activation, its catalytic domain is covalently bound with other parts of the molecule and bound to the cell surface with conserved disulfide bond.

initiated by virus binding to the ACE2 cell-surface receptors, followed by fusion of the virus envelope with cell membranes to release the virus genome into the cell (9). At present, the main source of infection is COVID-19 patients and the people with asymptomatic infection. Pathogens stimulate the epithelial cells at the infected site to produce cytokines, which recruit and activate neutrophils and trigger local inflammatory response. C3b combines with virus particles in body fluid, initiating the complement bypass pathway and generating an immune response. Early induced innate immune response occurs at 4-96 hours after infection. Chemokines produced by epithelial cells at the infection site and IL-1, IL-6 and TNF produced by neutrophils-α macrophages and mast cells in surrounding tissues were recruited by proinflammatory factors. Activated macrophages produced, which induces NK cell activation and

enhances the killing effect on target cells. Hepatocytes are stimulated by proinflammatory factors such as IL-1 to produce acute phase proteins, in which mannose-binding lectin （MBL） binds to pathogens and activates complement MBL pathway to produce anti-infective immunity. The adaptive immune response occurs 96 hours after infection: the primitive foreign body stimulates immature dendritic cells, which then migrated to surrounding

Table 4. Ligands entering cellular helper receptors.

Recipient	Normal ligand	function
ACE2 receptor (10)	Targeting Ang2	It shows a protective effect in the cardiovascular system and other organs
	G protein coupled receptor	Block the conversion of Ang1 to Ang2, and then mediate the RAS system
	Binding to amino acid transporters	It plays a key role in the absorption of amino acids in the kidney and intestine
	Ang2 was degraded to heptadeptides angiotensin 1-7 and then bound to MAS receptor and / or degraded to inactive peptide	Negative regulation of the activated renin-angiotensin system
	It acts on the carbon terminal of peptides apelin-13 and apelin-36	Amino acids were cut from them with high catalytic efficiency in vitro
CD13	E-selectin (11)	It plays a key role in the metastasis and development of breast cancer.
	Proinflammatory cytokine 14-3-3ε(in cartilage) (12)	14-3-3εIt binds to the surface of chondrocytes in a CD13 dependent manner, changes cartilage homeostasis and causes osteoarthritis
	CXCL11(13)	It may lead to a decrease in the number of tumor infiltrating lymphocytes and a more angiogenic environment.

immune organs and develops into mature dendritic cells, activating the primary T cells. If the body is infected, the inflammatory factors in body fluid, such as tumor necrosis factor-α, interleukin (IL) - 1, IL-6, IL-12, interferon-γ, monocyte chemoattractant protein-1 and IL-8 will be produced rapidly. Once such inflammatory factors produce in large quantities it will lead to cytokine storm, which is a worthy cause of Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure.

2.2 Respiratory system

SARS-CoV-2 first infects the respiratory epithelial cells in which viral proteins are synthesized. Cellular adaptive immunity against viral infection depends on antigen presentation by the major histocompatibility complex class I and II molecules (MHC-I and II). In particular, CD8+ T cells can recognize viral peptides presented by MHCI molecules and clear the viruses viral infected cells. Activation of T cells by antigen presenting cells (APCs) initiates their proliferation, cytokine

Table5. The functions of some co-receptors that coronaviruses enter cells.

Coronaviruses	The function of co-receptors
SARS - CoV	DPP4 inhibitors are the leading drugs for the treatment of diabetes.GLP-1 is rapidly degraded by dipeptidyl peptidase IV (DPP-IV). DPP-IV inhibitors can prolong the half-life of active GLP-1, so as to promote glucose stimulated insulin secretion and reduce blood glucose.(14)(15)
COVID-19	The related translocation of TMPRSS2 is associated with prostate cancer (16).TMPRSS2's potent antagonists: eight high affinity binding compounds, such as namostat, meloxicam, Ganoderma lucidum mannitol, columbine, myricetin, procyanidin A2, ephedrine and baicalein, may be used as drug treatment of covid-19 (17).
HCoV—OC43/ HCoV—Hku1	Some inhibitory KIRs (killer cell immunoglobulin like receptors) recognize specific HLA class I ligands and play an important role in the prognosis of patients with hematological malignancies after hematopoietic stem cell transplantation (HSCT).(18)

production and killing the infected viruses cells (19).

3. Diagnosis of novel coronavirus pneumonia

3.1 Symptoms and signs of COVID-19

COVID-19 cases have the symptoms such as fever, fatigue, dry cough and dyspnea, with or without upper respiratory symptoms such as nasal congestion and runny nose. In an exclusive interview on January 28, 2020, Zhong Nanshan, an academician of the Chinese Academy of Engineering, pointed out that fever is still a typical symptom of COVID-19 disease despite atypical symptoms.

The main manifestation of the respiratory symptoms is dry cough. And in a few patients, it is accompanied by the symptoms such as nasal congestion, runny nose and sore throat. Severe patients often develop dyspnea and / or hypoxemia one week after onset and even develop rapidly and seriously into respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction and multiple organ failure. In gastrointestinal system the main symptoms are different degrees of diarrhea. Mild diarrhea can be characterized by 2-3times of loose stool, while severe patients can have severe watery diarrhea and collapse. Especially for newborns and children, their gastrointestinal symptoms are more pronounced currently. Children can have nausea, anorexia, vomiting, abdominal pain, diarrhea and other discomfort. Although gastrointestinal symptoms are not seen in all COVID-19 patients, specific and sensitive nucleic acid detection or antibody detection should be performed in the patients with gastrointestinal symptoms, to avoid misdiagnosis and missed diagnosis.

Patients with mild symptoms may have no positive signs. Severe patients may appear shortness of breath, lung dampness, weakened breath sounds, slow percussion, tactile speech tremor increased or decreased symptoms.

3.2 Imaging findings

CT imaging is strongly recommended.

The imaging results vary from patients to patients because of age, immune status, disease stage, underlying basic diseases and drug intervention. The following imaging characteristics of the lesions should be evaluated.

1) Dominant distribution (mainly in the lower layer, along the bronchial vascular bundle).

2) Number (usually more than three lesions, occasionally single or double lesions).

3) Shape (patch, block, nodule, block, honeycomb or grid, linear, etc.).

4) The density (mostly uneven, paving stone like changes are mixed with the ground glass density and the thickening, consolidation and thickening of the bronchial wall.

5) Accompanied by physical changes (air Broncho gram, rare pleural effusion and intimal lymph node enlargement, etc.).

The following typical CT / X-ray imaging are included.

1) Multiple, fragmented, segmented, or segmented ground glass density shadows of both lungs. They are classified as "paving stone" changes by fine grid or honeycomb like septum thickening. The thinner the CT scan layer, the clearer the ground glass opacity and the thicker the septum. High resolution computed tomography (HRCT) The resolution of X-ray is worse than that of CT, which shows the opacity of ground glass with fuzzy edges.

2) Multiple, plaques or large plaques of the two lungs have a little grid or honeycomb septum thickening, especial lying the middle and lower lobe, which is more common in elderly or severe patients.

The typical CT / X-ray imaging findings are listed as following.

1) Monomer, or multi-layer or extensive lower layer grid or honeycomb thickened interstitial diaphragm, bronchial wall thickening, twists and turns and thick chain opacity. Some piecemeal mergers can be seen, occasionally with a small amount of pleural infusion or enlarged intimal lymph nodes. This is seen in the elderly.

2) Single or multiple solid nodules or nodules are located in the center of the nodules and surrounded by ground glass opacity (20).

3.3 Physicochemical and etiological diagnosis

Studies on the physicochemical properties of SARS-CoV and MERS-CoV showed the coronaviruses are sensitive to ultraviolet irradiation and heating, and can be effectively inactivated with ethyl ether, 75% ethanol, chlorine disinfectant, per acetic acid and chloroform inactivated 56℃ 30 minutes.

At present, etiological diagnosis is widely used, by nucleic acid detection of respiratory secretions such as nasal swabs and pharyngeal swabs of infected persons, or by detecting specific antibodies from venous blood. Nucleic acid detection is currently the "gold standard" for SARS-CoV-2 detection, which has the characteristics of early diagnosis, high sensitivity and specificity; and the antibody detection is convenient and rapid, which can be used as a supplementary means of nucleic acid diagnosis. However, due to the limitations of "false positive" and "false negative" antibody detection, they are not suitable for the screening of general population such as returning to work, childbirth and school, or for epidemiological investigation in low epidemic areas.

3.4 Diagnostic criteria

There exist two diagnostic criteria in China. First, in the provinces outside Hubei the suspected cases can be identified by the following epidemiological history combined with clinical manifestations.

Epidemiological history: 1) within 14 days before onset, there were travel history or residential history of the community in Wuhan and the surrounding areas, or other places with reported cases; 2) there was a history of contact with SARS-CoV-2 infected persons (positive for nucleic acid detection) within 14 days before onset; 3) during the 14 days before onset, patients came from Wuhan and surrounding areas, or had fever or respiratory symptoms from communities with reported cases; 4) onset of cluster.

Clinical manifestations: 1) fever and / or respiratory symptoms; 2) having the above imaging

features of pneumonia; 3) normal or decreased total leukocyte count or decreased lymphocyte count in the early stage of onset.

Have a history of either type of epidemiology that corresponds to either of the clinical manifestations. Having no clear epidemiological history but conforming to three of the clinical manifestations.

Confirmed cases: suspected cases with one of the following etiological evidence:

1) Respiratory tract specimens or blood samples were tested by real-time fluorescence RT-PCR as SARS-CoV-2 nucleic acid positive.

2) Respiratory tract specimens or blood samples tested for viral gene sequencing and were highly homologous with known SARS-CoV-2.

Second, in the province Hubei the diagnostic criteria of the suspected cases are listed as following.

Epidemiological history: the epidemiological history of other provinces was not significantly different from that of Wuhan province.

Clinical manifestations: 1) fever and / or respiratory symptoms; 2) normal or decreased total leukocyte count or decreased lymphocyte count in the early stage of onset.

Anyone with epidemiological history, no epidemiological history, and in line with 2 clinical manifestations at the same time.

Clinically diagnosed cases: suspected cases with imaging features of pneumonia.

Confirmed cases: clinically diagnosed cases or suspected cases have one of the following etiological evidence: 1) real-time fluorescence RT-PCR detection of respiratory tract specimens or blood samples for New Coronavirus nucleic acid positive; 2) respiratory tract specimens or blood samples of viral gene sequencing, highly homologous with known New Coronavirus.

Clinical classification: 1) mild: mild clinical symptoms, no pneumonia in imaging; 2) ordinary: fever, respiratory tract and other symptoms, with pneumonia in imaging; 3) severe: any of the following: A. Respiratory distress, RR > 30 times / min; B. oxygen saturation ≤ 93% at rest; C. arterial partial pressure of oxygen (pa02) / oxygen uptake concentration (fi02) ≤ 300 MMHG (1 mmhg = 0.133 kpa). 4) critical: those who meet one of the following conditions: A. respiratory failure and need mechanical ventilation; B. shock; C. ICU monitoring and treatment combined with other organ failure .

Differential diagnosis: with other known viral pneumonia such as influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, and SARS coronavirus. It should also be distinguished from Mycoplasma pneumoniae, Chlamydia pneumoniae and bacterial pneumonia. Besides, it should be distinguished from non-infectious diseases, such as vasculitis, dermatomyositis and organic pneumonia.

4. Treatment of COVID-19

4.1 General Treatment

General treatment include rest in bed, strengthened supportive treatment and ensuring sufficient nutrients, keeping the balance of water and electrolyte to maintain the stability of internal environment, accompanied by closely monitoring vital signs, finger oxygen saturation, blood routine, urine routine, CRP and biochemical indexes according to the condition (liver enzyme, myocardial enzyme, renal function, etc.), coagulation function, arterial blood gas analysis, chest imaging, etc. The cytokines can be tested if possible. Effective oxygen therapy measures can be given in time, including nasal catheter, mask oxygen and trans-nasal high flow oxygen therapy.

4.2 Antiviral therapy

During the COVID-19 outbreak, the following small molecule antiviral drugs have been reported to be used. However, the existing chemical small molecule targeted drugs have limited efficacy and large side-effects against COVID-19.

Chloroquine has been widely used as an antimalarial and immunomodulatory drug. Recent cell experiments have shown that chloroquine is highly effective in controlling COVID-19 infection in vitro; in VeroE6 cells, it plays a role in the onset and post-onset stages of SARS-CoV-2 infection. Chloroquine phosphate was tested in clinical research in more than 10 hospitals in Beijing, Guangdong and Hunan. Preliminary clinical results showed that chloroquine phosphate is effective in the treatment of COVID-19-associated pneumonia. In February 2020, after the demonstration by Academician Zhong Nanshan and other experts, it was included in the seventh edition of the diagnosis and treatment protocol. Subsequently, the Chinese National Health Commission issued the Notice on Adjusting the Usage and Dosage of Chloroquine phosphate in the treatment of COVID-19. In March 2020, FDA urgently approved hospitals to use hydroxychloroquine sulfate and chloroquine phosphate to treat hospitalized adolescents and adult COVID-19 patients (21)(22).

Remdesivir is a drug used to treat Ebola virus. It is an adenosine analogue with broad spectrum antiviral activity(23). It can inhibit bat coronavirus, circulating virus, SARS coronavirus, MERS coronavirus and filamentous virus and so on. Clinical trials have shown that it has a certain effect on COVID-19, and further clinical verification is required (24).

Abidol is used to treat human influenza A and B infections and influenza complications. At the same time, it can also treat other respiratory virus infections. The mechanism is not by blocking specific protein conformation, but by reducing the speed of fusion reaction. It has broad-spectrum antiviral potential(25). Abidol can effectively inhibit coronaviruses in vitro, and some COVID-19 patients treated with Abidol is improved. The drug has been included in the new coronavirus pneumonia treatment protocols.

Ribavirin is a hypoxanthine nucleoside analogue which is metabolized to ribavirin triphosphate by cellular kinases(26). It has inhibitory effects on RNA and DNA viruses and has broad-spectrum antiviral properties. It has been approved to treat hepatitis C virus (HCV) and respiratory syncytial virus (RSV). The combination of ribavirin and interferon can enhance the anti-MERS-CoV activity of interferon in vitro (27). Clinical studies have found that the clinical efficacy of ribavirin on SARS-CoV-2 is lower than that of abidol and interferon.

Favipiravir (T705, also known as Favipiravir) is a nucleotide drug and an RdRp inhibitor. It has a good therapeutic effect on severe and drug-resistant influenza patients. It is classified as a broad-spectrum antiviral drug. It can inhibit many RNA viruses such as Ebola virus and Bunia virus. The preliminary results from Raisa et al in vitro research and ongoing clinical trials indicated that favipiravir has a certain efficacy on SARS-CoV-2 (28).

In addition, anti-HIV drugs such as Griffixin, Darunavir, Lopinavir/Ritonavir, and α-interferon and other drugs have a certain effect on the treatment of SARS-CoV-2(29), Remdesivir, Ribavirin and Favipiravir are effective in inhibiting RdRP (30)(31) of the viruses.

4.3 Specific antibody therapy research

New Coronavirus (SARS-CoV-2) has become a global pandemic, which has caused serious burdens on public health, and social economy. There is an urgent need for effective control measures. Antibodies have a good precedent in the prevention and treatment of outbreak of infectious diseases. With the rapid development of human biomedicine, many new effective antiviral therapies with fewer side effects are increasingly developed. One of the most intensive studies focuses on inducing neutralizing antibodies (nAbs) to the virus.

Neutralizing antibody is a kind of antibody produced by B lymphocytes when pathogenic microorganisms invade the human body. When viruses, bacteria and other pathogenic

microorganisms invade the human body, they will activate the immune system and the stimulated B cells can produce a variety of antibodies. However, only part of the antibodies can quickly recognize pathogenic microorganisms and bind to their surface antigens, preventing them from binding to target cell surface receptors. This process is called neutralization, and the antibodies that work are called neutralizing antibodies.

4.3.1 Antiviral mechanism of sars-cov-2 neutralizing antibody

Covid-19 pathogen SARS-CoV-2 is infused with the receptor ACE-2 on human cells through the spike protein (S protein), so that the virus enters the cell, replicates, matures and infects other part of the human body through endocytosis. Neutralizing antibody responses against SARS-CoV-2 S proteins often target the receptor-binding domain (RBD; also called the S1B domain). This is an important way for neutralizing antibodies to play an antiviral role in controlling human infection.

4.3.2 Research and development progress of SARS-CoV-2 neutralizing antibody

4.3.2.1 Etesevimab (JS016/LY-CoV016) 1 Bamlanivimab (LY-CoV555)

On January 27, 2021, Jun reported the double antibody therapy with the antibodies Etesevimab and Lilly Bamlanivimab in a phase III clinical research for the primary end point that significantly reduced hospitalizations and deaths among severely at-risk COVID-19 patients (32).

4.3.2.2 REGN-COV2

Regn-cov2 is a combination of two monoclonal antibodies (regn10933 and regn10987) specifically designed to block the infectivity of SARS-CoV-2. In September 2020, yuan announced the first batch of data for the descriptive analysis of SARS-CoV-2 antibody cocktail therapy phase REGN-COV2-1/2/3 clinical trial(32). The data show that the drug reduces the viral load, reduces the symptoms of non-hospitalized covid patients, and show a positive trend in reducing medical treatment.

4.3.2.3 VIR-7831

Vir-7831 is a monoclonal antibody with dual action mechanism. In preclinical trials, the antibody displayed the ability to neutralize SARS-CoV-2 by binding a epitope on SARS-CoV-2 shared with SARS-COV-1(32).This epitope is highly conserved, which may make it more difficult to produce escape mutants. Moreover, the modification of the FC end of the antibody can not only block the virus from entering healthy cells, but also activate the immune system, which has the potential to eliminate infected cells.

At present, a total of 12 neutralizing antibody projects in the world have entered clinical research, and the above are neutralizing antibodies with rapid R & D progress. Because neutralizing antibody has the dual functions of prevention and treatment, better specificity and safety, and can be prepared on a large scale, it is expected to become a new crown "specific drug" and a powerful weapon for the prevention and control of infectious diseases. Vaccine prevention combined with antibody drug therapy is the end of hope for COVID-19.

Neutralizing antibodies play a key role in clearing the virus in patients with COVID-19. In recent months, many nAbs of SARS-CoV-2 have been reported, which promotes the application of nAbs based immunotherapy in the treatment of COVID-19. Studies have shown that nAbs titer in patients with COVID-19 is closely related to the concentration of immunoglobulin IgG targeting spike glycoprotein receptor binding region (RBD), suggesting that RBD on spike glycoprotein may contain major neutralizing epitopes. For the RBD targeted antibodies that have been reported and the complex structure has been published in protein data bank, the authors put forward unique insights on

how these nAbs specifically recognize the RBD of SARS-CoV-2 or cross reactivity with other coronaviruses.

nAbs can be used as an effective treatment for covid-19 because of its excellent neutralization efficiency and mature industrial production process. For example, CB6 antibody shows strong virus inhibition in vivo in the administration of non-human primates; Regenerant cocktail antibody regn10987 + regn10933 can neutralize all identified virus mutants. At present, the challenges faced by nAbs in treating COVID-19 include the aggravation of viral infection caused by ADE and the high mutation rate of single strand RNA virus, which may lead to viral infection and increase of antibody resistance. These risks and challenges may be addressed by optimizing animal models and using cocktail therapy.

Studies have calculated the relationship between six air pollutant DEDS and plasma nAb titer through multivariable corrected regression model. The analysis shows that there is a significant correlation between air pollutant DEDS and plasma nAb titer, which means that the higher the daily exposure of air pollutants, the lower the plasma nAb titer. In conclusion, this study first reported the relationship between air pollutant exposure and plasma nAb titer after COVID-19 inactivated vaccine, suggesting that long-term exposure to air pollutants may inhibit the expression of plasma nAb by inducing chronic inflammation.

Neutralizing antibodies (nAbs) provide patients with important specific immune defense against viral infection. In recent years, many antiviral nAbs have been developed, and some are currently under clinical development. The role and importance of nabs in the prevention of SARS-CoV-2 infection have been comprehensively reviewed elsewhere. SARS-CoV-2 enters the host cell through binding of S protein to ACE-2 receptor. S protein is the main inducer of nAbs. RBD in S1 unit is the most critical target of SARS-CoV-2 nAbs. These nAbs can interrupt the interaction between RBD and its receptor ACE2. Most nAbs are identified as targeting RBD regions.

4.3.3 Side effects of neutralizing antibody

After primary SARS-CoV-2 infection, the serum of patients with SARS-CoV-2 had IgG, IgM and IgA responses. IgGs played a key role in neutralizing SARS-CoV-2. Serum IgGs reached the peak in the recovery period and decreased after recovery. Memory B cells still have a long-term protective effect in cellular immune response. Although anti-S protein neutralizing IgGs can significantly reduce virus replication, immune responses can lead to fatal acute lung injury by promoting the production of IL-8/MCP-1 and the accumulation of inflammatory macrophages. These studies are of great significance to observe the IgG response of sars-cov-2 patients. On January 16, 2021, the Indian website reported that 4319 medical and nursing personnel and front-line staff were Vaccinated with COVID-19 vaccine in the Indian capital on the same day, and 51 adverse reactions were reported after vaccination. After vaccination, one person had a serious adverse reaction. He first felt headache, dyspnea and tachycardia. After injected with hydrocortisone and other drugs, he still did not improve. Then he was sent to the intensive care unit of in Indian Academy of Medical Sciences. Some doctors said that his symptoms worsened after the first stable half hour. Indian media said his vital signs are stable at present.

On June 16, 2021, "Russia" (RT) reported that at least 13 Israelis had "facial paralysis" after receiving the new vaccine developed by Pfizer Pharmaceutical Co, Ltd. The report also said that the U.S. Food and Drug Administration (FDA) reported a similar situation a month ago, but they denied that the situation was related to the vaccine.

The monoclonal antibody named 4a8 showed high efficiency and ability against both true and false SARS-CoV-2 but did not bind to virus RBD. The epitope of 4a8 was defined as the N-terminal domain (NTD) of S protein. The structure of its complex with S protein was determined by freeze electron microscope (34). The total resolution of 4a8-NTD interface was 3.1 angstrom and the local resolution was 3.3 Angstrom. This indicates that NTD is a promising target for COVID-19.

SARS-CoV-2 specific human monoclonal antibody cr3022 can effectively bind to COVID-19 RBD (KD is 6.3 nm) (35). The epitope of cr3022 does not overlap with the ACE2 binding site in COVID-19 RBD. These results suggest that cr3022 may have the potential to be developed as a candidate therapy, alone or in combination with other neutralizing antibodies, for the prevention and treatment of COVID-19.

ACE2 receptor therapy: apn01 (soluble form of recombinant human ACE2 (rhACE2)), can not only prevent virus entry, but also protect the lungs from damage (36). Antibody against cytokine storm: after SARS-CoV-2 infects human body, it rapidly activates inflammatory T cells, but also macrophages, and many cytokines in body fluids such as TNF-α, IL-1, IL-6, IFN-α, IFN-β, IFN-γ, MCP-1 and IL-8 are produced rapidly and in large quantities, forming an inflammatory storm, leading to serious lung immune injury. Besides focusing on the severe condition of pneumonia, SARS-CoV-2 may attack many important organs and cause multiple organ failure with cytokine storm (41). The serine protease TMPRSS2 mesylates SARS-CoV-2 and activates S protein, while Kamostat, an inhibitor of TMPRSS2, can prevent SARS-CoV-2 from infecting lung cells (43). Through interaction with ACE2 receptor, the initial spike protein activation of membrane protease serine 2 (TMPRSS2) is very important for the entry of sars-cov-2 and virus transmission (44).TMPRSS2 is the key protease to help COVID-19 enter target cells.

Table 6.Neutralizing antibody treatment of S protein.

Neutralizing antibody to S protein	Function
Pan coronavirus fusion inhibitor peptide EK1 targeting the HR1 domain of HCoV s protein	To prevent sars-cov-2 protein mediated membrane fusion and pseudovirus infection, IC50 were 1.3 and 15.8 nm, respectively. This inhibition is 241 and 149 times stronger than the original EK1 peptide, respectively (37).
Single domain antibody VHHs of Alpaca	Immunization with stable coronavirus s protein can neutralize sars-cov-2 s pseudovirus(38).
Cross neutralizing antibody s309	By activating s RBD, it can effectively neutralize sars-cov-2, SARS COVID pseudovirus and real sars-cov-2 (39).
Human monoclonal antibody McAb 47d11	It is most likely to target the conserved core structure of S1b RBD and neutralize sars-cov-2 in cell culture.

4.4 TCM Prevention and treatment

Traditional Chinese Medicine (TCM) plays a key

role in the treatment of COVID-19. Novel Coronavirus disease falls into the category of "epidemic" diseases in Traditional Chinese medicine. Practice has proved that TCM plays a key role in alleviating fever symptoms and complications, reducing the dosage of hormones and controlling the progress of the disease. With obvious effects, the seventh edition of the diagnosis and treatment plan recommends "three prescriptions and three drugs ", such as Jinhua Qinggan granule, Lianhua Qingwen capsule, Qingfei Paidu decoction, Huashi Baidu formula Xuanfei Baidu formula, and Xue-Bi-Jing injection. Qingfei Paidu decoction is listed as the first choice of clinical treatment of traditional Chinese medicine. Traditional Chinese medicine can effectively alleviate symptoms, reduce the development from mild and ordinary type to severe type, improve the cure rate, reduce the disease death rate, and promote people's recovery in the recovery period. Jinhua qinggan granule among the three drugs is a proprietary Chinese medicine developed during influenza A in 2009. It has the functions of dispersing wind, dispersing lung, clearing heat and detoxifying. It is suitable for the symptoms of mild and ordinary COVID-19 patients. Lianhua Qingwen capsule / granule is a classic prescription. It originates from Maxing Shigan Decoction and YinQiao powder. It can also clear distemper and detoxify, clear lung and relieve fever. It is suitable for mild and common 2019-ncov patients. Xuebijing injection is a Chinese patent medicine listed for SARS in 2003. In the treatment of severe and critical patients, it is suitable for systemic inflammatory response syndrome induced by infection and can also cooperate with the treatment of multiple organ dysfunction syndrome. It can remove blood stasis, detoxify and treat sepsis. Qingfei Paidu Decoction comes from four classic prescriptions of Maxing Shigan decoction, Wuling powder, Xiaochaihu Decoction and Shegan Mahuang Decoction in Zhong-Jing Zhang treatise on typhoid and miscellaneous diseases. In February 2020, the office of the State Administration of Traditional Chinese Medicine issued a notice on the recommendation of "Qingfei detoxification Decoction" recommended in the treatment of COVID-19 infection with integrated traditional Chinese and Western medicine. The notice points out that Qingfei detoxification decoction has an effective rate of over 90% in relieving symptoms and curing. Huashi Baidu prescription Baidu Formula is the core prescription recommended by the national TCM medical team according to the national early diagnosis and treatment plan. It is suitable for mild, ordinary and severe patients. It can fight the virus, eliminate inflammation and improve immunity. It has played a positive role in the treatment of COVID-19 patients in Wuhan. Xuan-Fei Paidu recipe is suitable for patients with mild and ordinary diseases. It can promote lung dampness, clear away heat and evil purge lung and detoxify.

4.5 Psychological counseling

As COVID-19 is a new acute infectious disease, its ferocity and infectivity were fierce. . The medical profession still needs to deepen its understanding. Patients in such a sudden event will have some psychological barriers, such as social cognitive bias, panic tension, loneliness and helplessness, anxious anxiety, depression and desperation (45).

Health education: patiently and easily explain the basic situation of the disease to the patients and their families, so that the patients and their families can correctly understand the occurrence, development and prognosis of the disease, correctly understand the necessity and importance of isolation treatment and isolation medical observation, actively cooperate with isolation and treatment.

Fear alleviation: treat every patient and family member with enthusiasm, introduce the basic information and medical facilities of the ward,

strengthen the confidence of the patients to overcome the disease and help the family members correctly understand the positive significance of isolation treatment.

Relieve loneliness: medical staff needs to care for the pain of patients and their families, with appropriate language, friendly attitude, inquire about the cold and warm and taking care of everything. Medical staff tries do their best to take shifts every day and spend time to accompany and communicate with patients and their families, so as to gradually eliminate or alleviate the loneliness of patients and their families.

Alleviate anxiety and impatience: medical staff can encourage patients keep positive attitude, encourage patients to contact and greet their family members or friends through video phone, or take the initiative to ask under medical observation family member's physical condition, such as abnormal, should be timely symptomatic treatment, gradually eliminate or relieve the patients and their families, anxiety and impatience.

Alleviating depression and hopelessness: medical staff correctly interpret patients' conditions according to their different conditions, eliminate their ideological concerns, and enable them to treat the disease positively and optimistically and actively cooperate with Hospital & APOS, treat and care to gradually go out of the shadows of illness and despair, to regain the light.

6. Prevention and control of COVID-19

6.1 Ways and means of infection

Airborne droplet transmission refers to the infection caused by airborne droplets and infects human nasopharyngeal mucosa, and the exhaled gas is inhaled directly at a close distance. Contact transmission: refers to the droplet deposited on the surface of the article, and then contacted with the mucous membranes of the mouth, nose and eyes after contacting the contaminated hand, resulting in infection. Aerosol transmission: refers to the mixing of droplets in the air to form aerosol, which leads to infection after inhalation. At present, the most important way of the three known transmission routes is air droplet transmission and contact transmission.

6.2 Elimination / isolation of infectious sources

At present, the main source of infection of COVID-19 is SARS-CoV-2 infected patients, asymptomatic infection can also become a source of infection. Suspected cases clinically diagnosed cases (Hubei Province only) and confirmed cases should be isolated and treated in designated hospitals with effective isolation and protection conditions. Suspected cases and clinically diagnosed cases (Hubei Province only) should be isolated and treated separately in a single room. Asymptomatic infected persons should be isolated for 14 days, or if the nucleic acid test is negative after 7 days, the isolation can be lifted. Clean and disinfect medical devices, contaminated items, surfaces and floors; disinfect the air.

6.3 Cut off the route of transmission

Pay attention to hand hygiene. Wash your hands in seven steps when you get home; wear a mask properly when going out to prevent the virus from entering the mouth and nose; care should be taken to clean and disinfect homes and public places: it is recommended to choose effective disinfectants for hands and skin, such as iodophil, chlorine containing disinfectant and hydrogen peroxide disinfectant, or quick drying hand disinfectant for wiping and disinfection. Indoor air can be disinfected with per acetic acid, chlorine dioxide, hydrogen peroxide and other disinfectants. The surface of environmental objects can be wiped, sprayed or soaked with disinfectants such as chlorine disinfectant and chlorine dioxide.

6.4 Protection of vulnerable groups

Vaccinations are available; try not to go to crowded places; low temperature makes people less resistant. Pay attention to cross infection; eat right and get enough sleep; check in regularly.

6.5 COVID-19 vaccine

Inactivated vaccines belong to the first generation of vaccines, which is one of the most widely used effective vaccines in the world. It refers to a vaccine made by inactivating viruses with chemical agents(46). However, protection from inactivated vaccines may be low in high-risk populations such as children, the elderly and those with chronic diseases. The preparation and identification of virus strains suitable for vaccine production and vaccine production process are complex and the cycle is long; The protective effect of vaccine is limited by the matching degree of surface antigen between vaccine strain and epidemic strain. In addition, the safety of inactivated vaccine is high.

Genetically engineered vaccines are known as the second generation vaccines which refers to the vaccines prepared by cloning the virus gene fragment (or epitope sequence) into a suitable expression vector by the technologies of molecular biology. The virus antigen are expressed in vitro and then purified for vaccines, or the vaccines can be made by using the live recombinant vectors that can express the virus antigen itself(47). Common genetically engineered vaccines include recombinant subunit vaccine, virus like particle vaccine, live virus vector vaccine and so on.

The mRNA vaccine refers to the vaccine form that introduces the mRNA expressing antigen target into the body through a specific delivery system, expresses protein in the body and stimulates the body to produce specific immune response, to obtain immune protection. After COVID-19 pneumonia outbreak in late 2019, the mRNA vaccines have once again demonstrated its immense potential as a platform for rapid development of technology. Studies have shown that both self-amplified and non-replicating mRNA vaccines have good application prospects and can provide immune protection against a variety of pathogens with pandemic potential.

In less than half a year after the outbreak of the epidemic, 14 mRNA vaccines have launched clinical trials, of which mRNA-1273, jointly developed by the National Institute of Allergy and Infectious Diseases (NIAID) and biotechnology company Moderna, is the fastest developed mRNA vaccine. The phase I clinical study of the vaccine was launched in March 2020, The safety and immunogenicity of three doses (250μg, 100μg, 25μg) were evaluated by two doses of primary immunization on day 0 and booster immunization on day 28. The safety and immunogenicity of three doses of vaccine were preliminarily evaluated. The results of the first stage showed that neutralizing antibodies were detected in 8 initial subjects inoculated with medium and low doses 15 days after the initial immunization, and the immune intensity was dose-dependent. After 2 weeks of booster immunization, the antibody level of subjects in low-dose group and high-dose group reached or exceeded the level after the recovery of patients with COVID-19. Then, the vaccine has entered the stage of phase III clinical research. The latest report also showed that several vaccines, including in China, have entered the phase III clinical trial stage, rising hopes for people all over the world. According to a peer-reviewed paper in the latest issue of the medical journal Lancet Infectious Diseases, all four Chinese vaccines can trigger a rapid immune response, and the vaccines developed by China Kexing Company are more suitable for vaccination in the third world countries than the COVID-19 vaccines of American pharmaceutical manufacturers Pfizer and Modern.

Declarations

1) ***Consent to publication***

We declare that all authors agreed to publish the manuscript at this journal based on the signed

Copyright Transfer Agreement and followed publication ethics.

2) Ethical approval and consent to participants

Not applicable.

3) *Disclosure of conflict of interests*

We declare that no conflict of interest exists.

4) Funding

None

5) Availability of data and material

We declare that the data supporting the results reported in the article are available in the published article.

6) Authors' Contributions

Authors contributed to this paper with the design (HWX), literature search (CYX), drafting (CYX), revision (CYX and HYX, QX, YHX HWX, XHZ, XLS, XYW), editing (CYX and HYX, QX, YHX XHZ, HWX, XYW) and final approval (HWX, XHZ, XLS, XYW).

7) *Acknowledgement*

None

8) Authors' biography

None

References

1. Asselah, T.; Durantel, D.; Pasmant, E.; Lau, G.; Schinazi, R. F. J. J. o. H. COVID-19: Discovery, diagnostics and drug development. **2020**, *74*. DOI: 10.1016/j.jhep.2020.09.031.

2. Cai, G.; Cui, X.; Zhu, X.; Zhou, J. A Hint on the COVID-19 Risk: Population Disparities in Gene Expression of Three Receptors of SARS-CoV. **2020**. DOI: 10.20944/preprints202002.0408.v1.

3. My, A.; Hn, B.; Xue, D. A.; Ms, C.; Ow, B.; Kn, D.; Ys, E.; F , H. M.; Mi, G.; Tk, H. J. R. I. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. **2020**, *58*, 155-168. DOI: 10.1016/j.resinv.2019.12.005.

4. Zeng, J. T.; Li, Q.; Zhou, L. L.; Dong, S. S.; Zheng, J. Epitopes of spinogenic proteins of SARS-COV-2, HCOV-OC43 and HCOV-HKU1. *Laboratory medicine* **2020**. DOI: 10.3969/j.issn.1673-8640.2020.09.018.

5. Szczepanski, A.; Owczarek, K.; Bzowska, M.; Gula, K.; Drebot, I.; Ochman, M.; Maksym, B.; Rajfur, Z.; Mitchell, J.; Pyrc, K. J. V. Canine Respiratory Coronavirus, Bovine Coronavirus, and Human Coronavirus OC43: Receptors and Attachment Factors. **2019**, *11*. DOI: 10.3390/v11040328.

6. Xing, J. F.; Qian, Y. HcoV-NL63 -- a newly discovered pathogen of respiratory tract infection virus. *International Journal of Virology*. **2007**, *14*, 5. DOI: 10.3760/cma.j.issn.1673-4092.2007.03.004.

7. Li, Y.; Zhang, Z.; Yang, L.; Lian, X.; Xie, Y.; Li, S.; Xin, S.; Cao, P.; Lu, J. J. S. S. E. P. The MERS-CoV Receptor DPP4 as a Candidate Binding Target of the SARS-CoV-2 Spike - ScienceDirect. **2020**. DOI: 10.1016/j.isci.2020.101160.

8. Benton, D. J.; Wrobel, A. G.; Xu, P.; Roustan, C.; Gamblin, S. J. J. N. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. **2020**. DOI: 10.1038/s41586-020-2772-0.

9. Kuba, K.; Imai, Y.; Ohto-Nakanishi, T.; Penninger, J. M. J. P.; Therapeutics. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. **2010**, *128*, 119-128. DOI: 10.1016/j.pharmthera.2010.06.003.

10. Carrascal, M. A.; Silva, M.; Ferreira, J. A.; Azevedo, R.; Ferreira, D.; Silva, A. M. N.; Ligeiro, D.; Santos, L. L.; Sackstein, R.; Videira, P. A. J. B. e. B. A.-G. S. A functional glycoproteomics approach identifies CD13 as a novel E-selectin ligand in breast cancer. **2018**, S0304416518301454. DOI: 10.1016/j.bbagen.2018.05.013.

11. Meriam; Nefla; Laure; Sudre; Guillaume; Denat; Sabrina; Priam; Gwena?lle; Science, A.-L. J. J. o. C. The pro-inflammatory cytokine 14-3-3ε is a ligand of CD13 in cartilage. **2015**. DOI: 10.1242/jcs.169573.

12. Proost, P.; Mortier, A.; Loos, T.; Vandercappellen, J.; Gouwy, M.; Ronsse, I.; Schutyser, E.; Put, W.; Parmentier, M.; Struyf, S. J. B. Proteolytic processing of CXCL11 by CD13/aminopeptidase N impairs CXCR3 and CXCR7 binding and signaling and reduces lymphocyte and endothelial cell migration. **2007**, *110*, 37-44. DOI: 10.1182/blood-2006-10-049072.

13. Li, G.; Meng, B.; Yuan, B.; Yi, H.; Huang, H. J. E. J. o. M. C. The optimization of xanthine derivatives leading to HBK001 hydrochloride as a potent dual ligand targeting DPP-IV and GPR119. **2019**, *188*, 112017. DOI:

14. Jae-Hwi; Jang; Florian; Janker; Ingrid; De; Meester; Stephan; Arni; Carcinogenesis, N. J. The CD26/DPP4-inhibitor vildagliptin suppresses lung cancer growth via macrophage-mediated NK cell activity. **2019**. DOI: 10.1093/carcin/bgz009.

15. A Craig Mackinnon, B. C. Y., Loren J Joseph, Hikmat A Al-Ahmadie %J Archives of Pathology; Medicine, L. Molecular biology underlying the clinical heterogeneity of prostate cancer: an update. **2009**, *133*, 1033-1040. DOI: 10.1043/1543-2165-133.7.1033.

16. Hema, D. K.; Reddy, G. J.; Pooja, M.; Dodoalaa, S.; Kogantia, B. J. E. J. o. P. Unravelling high-affinity binding compounds towards transmembrane protease serine 2 enzyme in treating SARS-CoV-2 infection using molecular modelling and docking studies. **2020**. DOI: 10.1016/j.ejphar.2020.173688.

17. Symons, H. J.; Leffell, M. S.; Rossiter, N. D.; Zahurak, M.; Jones, R. J.; Fuchs, E. J. J. B. o. B.; Blood, M. T. J. o. t. A. S. f.; Transplantation, M. Improved survival with inhibitory killer immunoglobulin receptor (KIR) gene mismatches and KIR haplotype B donors after nonmyeloablative, HLA-haploidentical bone marrow transplantation. **2010**, *16*, 533-542. DOI: 10.1016/j.bbmt.2009.11.022.

18. Majedi, F. S.; Hasani-Sadrabadi, M. M.; Thauland, T. J.; Li, S.; Butte, M. J. J. N. L. Augmentation of T-Cell Activation by Oscillatory Forces and Engineered Antigen-Presenting Cells. **2019**, *19*. DOI: 10.1021/acs.nanolett.9b02252.

19. Jin, Y. H.; Cai, L.; Cheng, Z. S.; Cheng, H.; Research, X. W. J. M. M. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). **2020**, *7*. DOI: 10.1186/s40779-020-0233-6.

20. Chorin, E.; Dai, M.; Shulman, E.; Wadhwani, L.; Bar-Cohen, R.; Barbhaiya, C.; Aizer, A.; Holmes, D.; Bernstein, S.; Spinelli, M. J. N. M. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. DOI: 10.1038/s41591-020-0888-2.

21. Gautret, P.; Lagier, J. C.; Parola, P.; Hoang, V. T.; Raoult, D. J. I. J. o. A. A. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. **2020**, 105949. DOI: 10.1016/j.ijantimicag.2020.105949.

22. Maria, L.; Agostini; Erica, L.; Andres; Amy, C.; Sims; Rachel, L.; Graham; Timothy, P.; mBio, S. J. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. **2018**. DOI: 10.1128/mBio.00221-18.

23. Holshue, M. L.; Debolt, C.; Lindquist, S.; Lofy, K. H.; Pillai, S. K. J. N. E. J. o. M. First Case of 2019 Novel Coronavirus in the United States. **2020**, *382*, 929-936. DOI: 10.1056/NEJMoa2001191.

24. Wang, Z.; Chen, X.; Lu, Y.; Chen, F.; Zhang, W. J. B. t. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. **2020**, *14*. DOI: 10.5582/bst.2020.01030.

25. Aljabr, W.; Touzelet, O.; Pollakis, G.; Wu, W.; Munday, D. C.; Hughes, M.; Hertz-Fowler, C.; Kenny, J.; Fearns, R.; Barr, J. N. J. J. o. V. Investigating the Influence of Ribavirin on Human Respiratory Syncytial Virus RNA Synthesis by Using a High-Resolution Transcriptome Sequencing Approach. **2016**, *90*, 4876-4888. DOI: 10.1128/JVI.02349-15.

26. Crotty, S.; Cameron, C.; Andino, R. J. J. o. M. M. Ribavirin's antiviral mechanism of action: Lethal mutagenesis? **2002**, *80*, 86-95. DOI: 10.1097/00001432-200112000-00015.

27. Sangawa, H.; Komeno, T.; Nishikawa, H.; Yoshida, A.; Takahashi, K.; Nomura, N.; Furuta, Y. J. A. A.; Chemotherapy. Mechanism of action of T-705 ribosyl triphosphate against influenza virus RNA polymerase. **2013**, *57*, 5202-5208. DOI: 10.1128/AAC.00649-13.

28. Kabir, M. T.; Uddin, M. S.; Hossain, M. F.; Abdulhakim, J. A.; Aleya, L. J. F. i. C.; Biology, D. nCOVID-19 Pandemic: From Molecular Pathogenesis to Potential Investigational Therapeutics. **2020**, *8*, 616. DOI: 10.3389/fcell.2020.00616.

29. Akta, A.; Tüzün, B.; Aslan, R.; Sayin, K.; Ataseven, H. J. J. o. b. S.; Dynamics. New Anti-Viral drugs for the treatment of COVD-19 instead of favipiravir. **2020**. DOI: 10.1080/07391102.2020.1806112.

30. Eastman, R. T.; Roth, J. S.; Brimacombe, K. R.; Simeonov, A.; Science, M. H. J. A. C. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. **2020**, *6*, 672-683. DOI: 10.1021/acscentsci.0c00489.

31. Tuccori, M.; Ferraro, S.; Convertino, I.; Cappello, E.; Focosi, D. J. m. Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. **2020**, *12*, 1854149. DOI: 10.1080/19420862.2020.1854149.

32. Huang, Y.; Sun, H.; Yu, H.; Li, S.; Zheng, Q.; Xia, N. J. A. T. Neutralizing antibodies against SARS-CoV-2: current understanding, challenge and perspective. **2020**, 4. DOI: 10.1093/abt/tbaa028.

33. Tian, X.; Li, C.; Huang, A.; Xia, S.; Lu, S.; Shi, Z.; Lu, L.; Jiang, S.; Yang, Z.; Wu, Y. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. DOI: 10.1101/2020.01.28.923011.

34. Hong, P. J.; Look, D. C.; Ping, T.; Lei, S.; Hickey, M.; Gakhar, L.; Chappell, M. C.; Wohlfordlenane, C.; Mccray, P. B. J. A. J. o. P.-L. C.; Physiology, M. Ectodomain shedding of angiotensin converting enzyme 2 in human airway epithelia. **2009**, *297*. DOI: 10.1152/ajplung.00071.2009.

35. Xia, S.; Zhu, Y.; Liu, M.; Lan, Q.; Xu, W.; Wu, Y.; Ying, T.; Liu, S.; Shi, Z.; Jiang, S. J. C.; Immunology, M. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. DOI: 10.1038/s41423-020-0374-2.

36. Wrapp, D.; Vlieger, D. D.; Corbett, K. S.; Torres, G. M.; Mclellan, J. S. J. C. Structural Basis for Potent Neutralization of Betacoronaviruses by Single-Domain Camelid Antibodies. **2020**, *181*, 1436-1441. DOI:

37. Pinto, D.; Park, Y. J.; Beltramello, M.; Walls, A. C.; Tortorici, M. A.; Bianchi, S.; Jaconi, S.; Culap, K.; Zatta, F.; Marco, A. D. J. N. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. DOI: 10.1038/s41586-020-2349-y.

38. Wang, C.; Li, W.; Drabek, D.; Okba, N.; Bosch, B. J. J. N. C. A human monoclonal antibody blocking SARS-CoV-2 infection. **2020**, *11*. DOI:

39. Deng, Q.; Hu, B.; Zhang, Y.; Wang, H.; Zhou, Q. J. I. J. o. C. Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. **2020**, *311*. DOI: 10.1016/j.ijcard.2020.03.087.

40. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Phlmann, S. J. C. SARS-CoV-2

Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. **2020**, *181*. DOI: 10.1016/j.cell.2020.02.052.

41. Zhang, H.; Penninger, J.; Li, Y.; Zhong, N.; Slutsky, A. S. J. I. C. M. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. **2020**, *46*, 586-590. DOI: 10.1007/s00134-020-05985-9.

42. Chen, Z. Thoughts on novel Coronavirus vaccine development. *Life science research* **2020**. DOI: 10.16605/j.cnki.1007-7847.2020.04.001.

43. Yang, H. Q.; Liu, L. J.; Ge, Y. H. Emerging infectious diseases and new vaccine technologies. *Chinese Journal of New Drugs.* **2020**, *29*, 9. DOI: 10.3969/j.issn.1003-3734.2020.21.009.