International Journal of
Life Sciences
International Peer Reviewed Open Access Refereed Journal

Int. J. of Life Sciences, 2020; 8 (2):327-341
ISSN:2320-7817(p) | 2320-964X(o)

Original Article Open Access

COVID- 19 Apocalypse: Therapeutic and Preventive Measures for its Containment in India

Jiya Verma and Chauhan RS*

Department of Pathology, College of Veterinary and Animal Sciences
G B Pant University of Agri. & Tech.Pantnagar-263145 Uttarakhand
*Corresponding author: profchauhan58@gmail.com

Manuscript details:

Received: 13.05.2020
Accepted: 14.06.2020
Published: 29.06.2020

Cite this article as:
Verma Jiya and Chauhan RS (2020) COVID- 19 Apocalypse: Therapeutic and Preventive Measures for its Containment in India. *Int. J. of. Life Sciences*, Volume 8(2): 327-341.

Available online on http://www.ijlsci.in
ISSN: 2320-964X (Online)
ISSN: 2320-7817 (Print)

ABSTRACT

COVID-19 is a public health emergency of international concern. The outbreak of the disease began as pneumonia of unknown etiology in Wuhan, China. It is a virus induced respiratory illness caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). Close genetic similarity with the bat SARS- like coronavirus RaTG13 and the presence of high degree of similarity between ACE-2 receptors among various animals and humans indicate its likely origin from bats. Person to person contact was also identified. There is no clear evidence of vertical transmission of the virus yet, though its presence is detected in semen of affected individuals. Symptoms appear 2 to 14 days post- exposure and include dyspnoea, coughing, sore throat, fever, repeated shaking with chills, myalgia and anosmia. In some cases, diarrhoea, cutaneous manifestations such as chilblain-like foot lesions have also been reported. Coagulopathy is most probably a consequence of massive inflammatory response and may contribute to the occurrence of thrombosis. The severity of the disease ranges from very mild to severe depending upon the age, immune status and presence of comorbidities. In severe disease, elevated serum levels of proinflammatory cytokines like Interleukin-1, Interleukin-6, Interleukin-12, Interferon-gamma and TGF-beta along with increased level of chemokines are observed. Histopathological examination revealed pulmonary edema along with formation of hyaline membrane and monocytosis. Liver biopsy revealed moderate microvesicular steatosis. Blood examination showed decreased number of CD4 and CD8 cells. Animal trials have shown that ferrets and cats are susceptible to the disease while dogs, ducks, pigs and chickens are not. The results of Thin slice Computed Tomography showed multifocal ground glass opacities. Treatment is not specific. Hydroxychloroquine led to the reduction of viral load. On 1st May, 2020, FDA agreed for Emergency Usage Authorization for the use of Remdesivir as it showed promising results in cell culture, animal models as well as in human trials by decreasing the mortality. Maintenance of hand hygiene and proper cough hygiene is essential. Cowpathy is known to have multiple health restoring properties for boosting immunity and bioenhancer activity, which can also be utilized for prevention and control of coronavirus spread in population. AYUSH ministry of India has reported the beneficial effects of Sanshamani vati,

ayurvedic concoction and homeopathic medicine Arsenicum album and initiated the clinical trial studies on Ashwagandha, Pipali,Yashtimadhu, Guduchi and Ayush-64 combination of herbs. Therefore, preventive and control measures are a must to minimize health losses and decrease the burden on health care system.

Keywords: COVID-19, Pandemic, Therapeutic and Preventive Measures

INTRODUCTION

COVID-19 (Coronavirus Disease-2019) is a viral zoonotic disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) and results in respiratory illness of various degrees in humans and some other mammals. The disease was first reported from Wuhan, China after a cluster of cases of pneumonia of unknown etiology were reported on 31st December, 2019. Symptoms of the disease included respiratory distress, fever and sometimes diarrhoea. These symptoms became more severe with advancing days.COVID-19 is a public health emergency of great international concern. A novel Coronavirus was soon identified as the causative agent. Previous outbreaks caused by coronaviruses include Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012. SARS and MERS have a mortality rate of 11% and 34.4%, respectively (Chan *et al.,* 2003 and WHO, 2004). COVID-19 has a mortality rate of 1% after a more accurate number of infected individuals is included which makes it more life-threatening than seasonal influenza as its mortality rate was about 0.1 percent (Neirderman *et al.*, 2020). However, a retrospective cohort study in China reported the mortality rates of COVID-19 to be as high as 3-4%, as the rates vary widely depending upon the age, morbidity and severity of illness on initial presentation (Zhou *et al.*, 2020).

History of Coronaviruses

Coronaviruses are previously known viruses which cause acute gastroenteritis in neonates of humans, cattle and swine, infectious bronchitis in poultry and severely fatal respiratory diseases in humans. The size of coronaviruses ranges from 60 nm to 140 nm (Richman *et al.*, 2016).The gastroenteric infection occurs via oral route by ingestion of contaminated food and water or by contact with fomites. The virus invades the intestinal villi and crypts resulting in decreased absorptive surface area leading to malabsorption and maldigestion. The patient presents with symptoms such as fever, diarrhoea and dehydration. Post-mortem lesions include congested small and large intestine, presence of muco-hemorrhagic exudate in the intestine along with inflammation of mesenteric lymph nodes (Chauhan, 2018). Histopathology reveals shortening of villi and crypt length, fusion of two adjacent villi, congested mucosa and submucosa along with infiltration of mononuclear cells. There is hyperplasia of goblet cells and hemorrhage from the damaged surface of villi. It is diagnosed on the basis of the above mentioned symptoms along with demonstration of viral antigens or host antibodies using AGPT or ELISA or by using immunoperoxidase technique to demonstrate viral antigen in intestinal tissue. The coronaviruses have also caused respiratory diseases in humans in the past due to crossover of the virus from animals to humans resulting in the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012.

Timeline of COVID-19 as per World Health Organization

On 31st December, 2019, a cluster of cases of pneumonia of unknown etiology were reported by the municipal corporation of Wuhan in China. Soon, a novel coronavirus was pin-pointed as the cause. On 1st January, 2020, WHO set up the IMST (Incident Management Support Team) to deal with the outbreak. On 10thJanuary 2020, WHO gave a panoramic view regarding the technical guidance to detect, test and manage potential cases. Based on the methods of transmission, precautionary measures were advocated. On 12th January, China shared the genetic sequence of the novel coronavirus with public. The first case of the disease outside China was reported in Thailand on 13th January. On 14th January, human to human transmission was suspected. WHO experts from Western Pacific regional office and China conducted a visit to Wuhan on 20th January. On 30th January, the Emergency Committee of WHO advised

the Director General of WHO that the outbreak was a Public Health Emergency of International Concern (PHEIC). By this time, 82 cases were reported from countries outside China. On 11th February, WHO announced the name COVID-19. On 14th February, China reported 1716 cases among health workers along with 6 deaths. On 28th February, WHO raised the global risk of spread from "high "to "very high". On March 1, United Nations released 15 million dollars to UNICEF and WHO to support vulnerable countries. On 11th March, WHO declared the outbreak to be a pandemic due to the intimidating severity and magnitude of spread of the virus. On 18th March, WHO and partners launched an international clinical trial to search for the most effective treatment under the name "Solidarity Trial". On April 2nd, cases of COVID-19 surpassed 1 million. On April 8th, the lockdown was lifted from Wuhan. On 13th April, International Monetary Fund approved immediate debt of 500 million dollars to 25 countries through Catastrophe Containment and Relief Fund. On April 14th, U. S. President announced the cutting of USA's contribution to WHO due to its mismanagement in the outbreak. On April 2nd, the number of cases of COVID-19 surpassed 2 million worldwide. By 27th April, this number increased to 3 million globally. On 1st May, Food and Drugs Administration authorized the use of Remdesivir under Emergency Usage Authorization. The number of cases transcended over 4 million on 9th May. (https://www.devex.com/news/covid-19-a-timeline-of-the-coronavirus-outbreak-96396)

Etiology

COVID-19 is a virus induced respiratory illness caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). SARS-CoV-2 is a pneumotropic virus which belongs to the family *Coronaviridae*, sub- family *Orthocoronavirinae* and genus *Betacoronavirus*. It belongs to a separate lineage under the branch *Sarbecovirus* (Paraskevis *et al.*, 2020). SARS-CoV-2 is an enveloped virus which contains RNA as its genetic material.. It employs spike protein (S protein) to enter host cells. When viewed under electron microscope, these club-shaped proteins of coronaviruses project from the surface of the virus giving it the appearance similar to solar corona which is responsible for its name Coronavirus (Almeida *et al.*, 1968). The structural proteins display high degree of conservation while accessory proteins are characteristic to each group of coronaviruses (Fehr *et al.,* 2015). No particular bat CoV has been found to have same proteins as SARS-CoV-2. The SARS-CoV-2 has been observed to be closely related to bat SARS- like coronavirus RaTG13 from which the SARS CoV of 2002 evolved. There was 96.3% genetic similarity between SARS-CoV-2 and RaTG13 (Paraskevis *et al.*, 2020). Coronaviruses are a large group of viruses which have been sorted into different generas on the basis of phylogenetic clustering (Fehr *et al.,* 2015).These viruses belong to the order *Nidovirales.* This order is divided into four families *Arteriviridae, Coronaviridae, Mesoniviridae and Roniviridae* (ICTV). Family *Coronaviridae* comprises of two subfamilies: *Orthocoronavirinae* and *Letovirinae. Orthocoronavirinae* is further sub-divided into 4 genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The comparison of genetic sequence of SARS-CoV-2 revealed 80% alikeness with SARS-CoV and 50% alikeness with MERS-CoV (Lu *et al.*, 2020, Ren *et al.*, 2020). Therefore, SARS-CoV-2 was categorized under the genus Betacoronaviruses (Zhu *et al.*, 2020). The presence of high degree of similarity between Angiotensin Converting Enzyme- 2 (ACE-2) receptors among various animals and humans and the existence of Open Reading Frame on gene 8 evince the likely origin of SARS-CoV-2 from bats (Ren *et al.*, 2020, Wan *et al.*, 2020).

Transmission

The COVID-19 outbreak is suspected to have originated in the wet animal market of Wuhan because of history of exposure of large number of initial patients to the live animal market. Although, the infection is expected to have spread from bats to two species of snakes and then to humans, there is no definite proof for the same. Previous research suggests that only birds and mammals have been known to be the reservoir of coronaviruses (Basseti *et al.*, 2020, Ji *et al.*, 2020). Analysis of SARS-CoV-2 revealed great similarity with two bat-derived SARS-like coronavirus (Lu *et al*, 2020., Wan *et al.*, 2020). The confirmation of spread of viruses not just from animals to humans but also between humans was concluded when cases started coming from people who had no exposure to the wet animal market of Wuhan (Carlos *et al.*, 2020, Wu *et al.*, 2020). Inter-human transmission occurs via direct contact or through respiratory droplets by coughing or sneezing. The virus remains viable for hours in aerosols and for days on other surfaces which is a great concern for community spread from subclinical subjects to healthy humans as well as to the

medical staff (van Doremalen *et al.*, 2020). The increased transmissibility and pandemic risk of COVID-19 is higher than SARS- CoV as the effective reproductive number of the former is 2.9 and for the latter is 1.77 (Liu *et al.*, 2020)

A study was done on 85 COVID-19 positive females for the impact of COVID-19 on pregnancy and parturition. These pregnant women were suffering from dry cough (34%), fever (68%), dyspnea (12%) and diarrhoea (6%) at the time of hospitalization. 92%; of these mothers underwent Caesarean section and delivered babies who were tested negative for SARS-CoV-2 and vaginal delivery accounted for the remaining 8% women. No untoward perinatal effects were seen in neonates in most of the cases (Chen *et al.*, 2020; Li *et al.*, 2020; Wang *et al*, 2020; Chen *et al.*, 2020; Zambrano *et al.*, 2020; Wang *et al.*, Gidlöf *et al.*, 2020; 2020; Yu *et al.*, 2020; Breslin *et al.*, 2020; Iqbal *et al.*, 2020; Zhang *et al.*, 2020 and Liu *et al.*, 2020). In contrast, out of 10 neonates who were observed under another study including 6 premature babies and 8 Caesarean Section delivered babies, 6 needed neonatal ICU care due to shortness of breath along with pyrexia, increased heart rate and pneumothorax. The lab tests of these neonates revealed abnormal Liver Function Test (LFT) values and decrease in number of thrombocytes in blood (Zhu *et al.*, 2020) and one death was reported which may be attributed to premature delivery or CS as well. A case of stillbirth was reported post emergency Caesarean Section where mother suffered from Multiple Organ Dysfunction Syndrome (MODS) along with Acute Respiratory Distress Syndrome (ARDS) (Liu *et al.*, 2020). Another pregnant mother with comorbidities namely diabetes mellitus and intrahepatic cholestasis who tested positive for SARS-CoV-2 underwent successful Caesarean section and was discharged few days later despite massive hemorrhage and bronchopneumonia during CS (Breslin *et al.*, 2020). Another study reported 3 infants delivered by CS to be positive for SARS-CoV-2 (Zhen *et al.*, 2020). Therefore, there is no clear evidence of vertical transmission of virus yet (Zaigham *et al.*, 2020). The presence of virus is seen in semen but it could not confirm the sexual transmission of the disease. However, coronavirus is passed on through contact with droplets from the nose and mouth, including the saliva of an infected person, the chances of which increase with close contact. This means there is a significant risk of passing on COVID-19 through kissing and physical touching if one person has the virus.

Clinical manifestations

COVID-19 is a taxing reality due to its comparatively long asymptomatic period during which the host remains infective and transmits the infection to other healthy subjects thereby contributing to community spread. Symptoms appear 2 to 14 days post- exposure. These include difficulty in breathing, coughing, sore throat, fever, chills, repeated shaking with chills, myalgia and anosmia. The symptoms are milder in children as compared to adults (Centers for Disease Control). In some cases, diarrhoea is also reported (WHO, 2020). Also, recovery is followed by a convalescent period in which the patient recovers from the disease but continues to shed the virus for about 7 to 14 days (Lauer *et al.*, 2020). The severity of the disease ranges from very mild to severe depending upon the age and immune status of the individual. In patients with comorbidities such as hypertension and diabetes mellitus, anemia, acute cardiac injury, acute kidney injury and multiple organ failure have been reported (Chen *et al.*, 2020 and Huang *et al.*, 2020). Though in most cases of COVID-19 positive patients, the above symptoms are seen, a few confirmed cases also suffered from cutaneous manifestations such as red, blue or purple discoloration of toes, hands and trunk (Piccolo *et al.*, 2020 and Recalcati *et al.*, 2020). Some of the critical cases suffered from limb ischemia and gangrene of hands and feet (Zhang *et al.*, 2020). In another case burning sensation and itching was reported by a 16 years old girl which later progressed to excruciating pain and swelling which led to ataxia followed by inability to walk without any other signs of COVID-19 for 24 days after the onset of foot lesions (Nirenberg *et al.*, 2020).

Children have been largely spared from the worst impacts of COVID-19 but now children around the world infected with COVID-19 are developing new symptoms of a rare inflammatory disease. This highlights a new potential risk for children in the pandemic. The symptoms developed are similar to the Kawasaki disease or toxic-shock syndrome. Kawasaki disease is a mysterious illness that primarily affects children up to the age of five. It causes the walls of arteries to become inflamed, resulting in fever and joint pain. A 5-year-old boy in New York has died from this inflammatory illness linked to COVID-19.

Health officials are also investigating 73 similar cases reported across New York. All of these children have exhibited symptoms similar to Kawasaki disease when infected with COVID-19. Some of the symptoms of both the diseases overlap in children but the mysterious illness in COVID-19 patients causes more severe abdominal pain, nausea and vomiting than the Kawasaki disease. The Kawasaki disease also majorly impacts heart blood vessels but in the COVID-19 associated illness, only a few cases describe any vessel inflammation(https://www.wionews.com/world/children-infected-with-covid-19-are-developing- new-symptoms-similar-to-kawasaki-disease-297587).

Pathogenesis

The incubation period of SARS CoV-2 is 2-14 days with an average of 5.2 days. SARS CoV-2 has strong affinity for the lower respiratory tract. The viral glycoproteins present on the surface of virion play an important role in pathogenesis and immunity. Respiratory and gastro-intestinal epithelial cells are primary target cells for coronaviruses (Ahmed *et al.*, 2020). The binding occurs between the receptor-binding domain of virus spikes and Angiotensin Converting Enzyme 2 (ACE2) receptor of humans (Jaimes *et al.,* 2020). The pathological changes associated COVID-19 are likely to be due to elevated levels of serum proinflammatory cytokines and chemokines (Wong *et al.*, 2020). The grave clinical features are a result of combination of virus induced cytopathic effects and host immune response in the form of cytokine storm (Liu *et al.*, 2020). The levels of cytokines like Tumor Necrosis Factor-alpha, Interleukin- 6 and Interleukin-8 were elevated. The patients with severe disease were observed to have elevated serum levels of proinflammatory cytokines like Interleukin-1, Interleukin-6, Interleukin-12, Interferon-gamma and TGF- beta along with increased level of chemokines (Wong *et al.,* 2004; Huang *et al.,* 2005; Chein *et al.,* 2006 and Zhang *et al.,* 2004) The ongoing viral replication along with delayed expression of Interferon Type 1 leads to accumulation of macrophages and monocytes which enhances cytokine levels, increases vascular permeability and leads to extra vascular leakage and diminished T-cell response against the virus (Channappanavar *et al.*, 2016). This is perhaps the reason for aggravation of symptoms following interferon inhalation therapy resulting in pulmonary opacities (Lei *et al.*, 2020). Blood examination from patients showed leucopenia with neutrophilia (70%), increased levels of blood C-reactive protein, increased rate of erythrocyte sedimentation and D dimer level (Lei *et al.*, 2020). COVID-19 associated coagulopathy (CAC) is most probably a consequence of massive inflammatory response (Connors *et al.*, 2020). Analysis of the data from Wuhan hospitals indicates towards the role of host's immune response in development of thrombo-inflammation which may contribute to occurrence of thrombosis (Connors *et al.*, 2020). High level of proinflammatory cytokines in plasma was seen more frequently in ICU patients than non-ICU patients (Huang *et al.*, 2020). The elevated plasma concentrations of proinflammatory cytokines and onset of coagulation may be responsible for higher D dimer levels (Iba *et al.*, 2019; Levi *et al.*, 2018 and Lippi *et al.*, 2014). The injury to endothelial cells leads to decreased number of platelets in circulating blood as well as reduction of natural anticoagulants (Connors *et al.*, 2020). Polyphosphates derived from microorganisms leads to activation of platelets, mast cells and Hageman factor which leads to increased procoagulant effect mediated by internal pathway (Smith *et al.*, 2005). The patients in which disease runs a long course, microvascular thrombosis may be held accountable for multi organ dysfunction syndrome (MODS) (Connors *et al.*, 2020). However, the coagulation defects observed in patients suffering from COVID-19 have not been reported to cause bleeding (Schnittler *et al.*, 2003, Connors *et al.*, 2020).

Microscopic features

Samples were collected from a 50 years old male patient who passed away during treatment after presenting with symptoms namely fever, cough, fatigue and shortness of breath. Lung, liver and heart were examined histopathologically. The reports revealed diffused alveolar damage in both lungs with cellular fibromyxoid exudate. There was pulmonary edema along with formation of hyaline membrane in left lung and there was desquamation of pneumocytes and formation of hyaline membrane in the right lung which indicated Acute Respiratory Distress Syndrome. There was increased infiltration of mononuclear cells predominantly lymphocytosis in both lungs. Viral cytopathic changes such as multi-nucleated syncytial cells with atypical enlarged pneumocytes were observed though no inclusions were identified. Liver biopsy revealed moderate micro-vesicular steatosis and mononuclear infiltrates which may be due to SARS-CoV- 2 or due to drug induced hepatic injury. Blood examination revealed decreased number of CD 4

and CD8 cells. Elevated levels of pro-inflammatory molecules like CCR 6+, Th 17 in the CD4 cells were observed. CD8 cells had higher concentration of cytotoxic granules. The severe immune injury may be ascribed to high cytotoxicity of CD8 cells and increase of Th17 (Zhe *et al.,* 2020). Major cause of death in Covid-19 is disseminated intravascular coagulation (thrombosis) and not pneumonia. Therefore, the way to fight it is with antibiotics, antivirals, anti-inflammatories and anticoagulants. Italian pathologists have discovered that the virus does not only kill pneumocytes, but uses an inflammatory storm to create an endothelial vascular thrombosis. As in disseminated intravascular coagulation, the lung is the most affected because it is the most inflamed, but there is also a heart attack, stroke and many other thromboembolic manifestations. In fact, the protocols left antiviral therapies useless and focused on anti-inflammatory and anti-clotting therapies. These therapies should be done immediately, even at home, in which the treatment of patients responds very well (www.cidrap.umn.edu).

COVID-19 in animals

As the number humans affected with COVID-19 are on the rise, there have been few instances of animals testing positive for the same. British Broadcasting Corporation reported the news of a tiger which tested positive for COVID-19 at Bronx zoo, New York after showing symptoms such as dry cough and loss of appetite which were consistent with the symptoms in humans. The tiger is suspected to have got infected due to contact with an asymptomatic zookeeper. The researchers at State Key Laboratory of Veterinary Biotechnology Institute, Harbin used viruses isolated from an environmental sample from Huanan seafood market and from a human patient to inoculate ferrets. It was revealed that viral replication occurred in upper respiratory tract but viral replication was undetectable in other organs. When rectal swabs were collected from these ferrets, comparatively low copy numbers were observed than those found in nasal washes. Severe lymphoplasmacytic perivasculitis, peribronchitis and vasculitis were observed in two ferrets 13 days post inoculation along with increased numbers of Type II pneumocytes which are important for surfactant production so as to prevent alveolar collapse along with increased number of neutrophils and macrophages in the alveolar septa and alveolar lumen. The experimental inoculation indicated that the SARS-CoV- 2 can replicate in the upper respiratory tract up to 8 days post inoculation without causing critical disease or fatality. Intranasal inoculation of 7 sub adult cats (aged 6 to 9 months) was done. Also, an uninfected cat was kept in the adjacent cage and exposed to inoculated cats to monitor droplet transmission. This uninfected cat got infected with SARS CoV-2 thereby confirming the possibility of droplet transmission and on euthanisation of cats, viral genetic material was detected to be present in its soft palate, turbinate, tonsils and trachea. The presence of viral RNA varied from cat to cat and from organ to organ of such as soft palate, turbinate, tonsils, trachea but not in lungs. Same study was replicated in juvenile cats (aged 70 to 100 days) and the samples from dead and euthanized cats 3 days post-inoculation revealed the development of huge lesions on the mucosal epithelium of nostrils, trachea and lungs. The replication of same experiment in Beagle dogs of 3 months of age, ducks, pigs and chickens showed seronegativity on performing ELISA and infective viral genetic material was not detected in any swab samples (Shi *et al.*, 2020). Studies in China revealed the susceptibility of ferrets to SARS-CoV-2. The ferrets have served as animal models for human pneumotropic viruses (Shi *et al.*, 2017; Stittelaar *et al.*, 2016; Zhang *et al.*, 2013; Imai *et al.*, 2012; Herfst *et al.*, 2012; van den Brand *et al.*, 2008 and Martina *et al.*, 2003). Ferrets and cats have a difference of only two amino acids in the region of Spike protein which attaches to ACE-2 receptors (Shi *et al.*, 2017).World Health Organization epidemiologist refused any role of cats in transmission of the disease to human but said that the cats could get infected by coming in contact with COVID-19 positive patients (https://in.reuters.com/article/health-coronavirus-pets/cats-can-catch-coronavirus-study-finds-prompting-who-investigation-idINKCN21R08V).

Therapeutic approach

Due to considerable similarity between SARS-CoV and SARS-CoV-2 infection regarding clinical presentation, genetic makeup of the virus, its epidemiology and the previously known symptoms, the treatment of SARS was extended for SARS-CoV-2. Majority of the research is focused on restricting the viral entry by counteracting Spike protein mediated entry into the host cell. Many trials are now underway across the scientific community and the invention of a specific drug and effective vaccine is under the pipeline. Due to the novel nature of SARS-CoV-2, there is no specific treatment. The treatments given include nucleoside

analogues and HIV protease inhibitors which have been used for viral attenuation in earlier outbreaks of viral diseases (Lu *et al.*, 2020). The treatment regimen of SARS-CoV-2 consists of administration of 500 milligram Lopinavir, 75 milligrams Oseltamivir, 500 milligram Ritonavir two times a day by oral route and 0.25 gram Ganciclovir for 3 to 14 days intravenously (Chen *et al.*, 2020). Agents which have been used for respiratory viral diseases in the past such as Neuraminidase inhibitors, RNA synthesis inhibitors, Ritonavir are potential agents for treatment. The *in-vivo* and *in-vitro* experiments possess considerable hope to treat SARS-CoV-2 infection with monoclonal antibody targeting spike protein of SARS-CoV and MERS-CoV (Shanmugaraj *et al.*, 2020). A cocktail of different monoclonal antibodies targeting different types of epitopes on viral surface appears to be a promising option but temporal longevity of production along with high cost of manufacturing exceeds clinical application against an emerging pathogen (Shanmugaraj *et al.*, 2020).

The administration of Lopinavir and Ritonavir to 199 patients in China in a randomized trial showed no beneficial effect compared to placebo (Cao *et al.*, 2020). The anti-malarial drug Hydroxychloroquine led to the reduction of viral load and its combination with Azithromycin augmented its effect (Gautret *et al.*, 2020). The effect of Chloroquine was studied on vero E6 cell lines infected with SARS-CoV-2 and it was observed to greatly reduce viral replication (Wang *et al.*, 2020). This effect is attributed to increased endosomal pH and interference with glycosylation of cellular receptors of SARS-CoV-2 (Wang *et al.*, 2020). Patients experiencing ARDS should be administered conservative fluid therapy and pragmatic antibiotic therapy to prevent secondary bacterial infection. Patients with hypoxemia are provided oxygen therapy. Acute Kidney Injury (AKI) patients are advised renal replacement therapy (Wang *et al.*, 2020). Patients with severe immune reactions may be treated with glucocorticoids (WHO, 2020). Antibiotics and antifungals should be administered rationally if sepsis or co-infection is suspected.

On 1st May, 2020, Food and Drugs Administration (FDA) gave a nod to Emergency Usage Authorization but did not approve the use of the RNA polymerase inhibitor drug Remdesivir as it showed promising results in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. The FDA authorized the use of this drug only for treatment of adults and children with suspected or laboratory confirmed COVID-19 and for those suffering from severe disease. An analysis was started with 61 patients within the age range of 23 to 82 years comprising 75% males from various countries who tested positive for COVID-19. Data from 8 of these patients couldn't be analyzed due to various reasons. Out of remaining 53 patients, 34 (64%) were receiving invasive ventilation, 30 (57%) were receiving mechanical ventilation while 4 (8%) were undergoing extra corporeal membrane oxygenation. These patients were incorporated in a trial to determine the efficacy and safety of Remdesivir as it has been reported to show good efficacy against the Filovirus which caused the Ebola outbreak and the coronaviruses which caused SARS and MERS (de Wit *et al.*, 2020; Sheahan *et al.*, 2017; Sheahan *et al.*, 2020 and Wang *et al.*, 2020). In *in-vitro* trials, Remdesivir has been shown to have remarkable activity (Mulangu *et al.*, 2019 and European Medicines Agency, 2020). Therefore, a 10 day course of Remdesivir was started in this small cohort with the initial loading dose on day 1 as 200 mg followed by 100 mg intravenously for the next 9 days. 4 patients discontinued the treatment due to worsening of pre- existing conditions. 40 (75%) patients under the study received a complete 10 days course of Remdesivir, 10 (19%) got the treatment for 5 to 9 days while 3 (6%) got less than 5 days of treatment. It was concluded that the improvement in clinical symptoms was more in patients receiving non-invasive ventilation than those receiving invasive ventilation and less in patients of 70 years of age or more. No association was discovered between the clinical improvement and their country of treatment, gender, co-existing conditions and days elapsed since the onset of symptoms before administration of 1st dose of Remdesivir (Grein *et al.*, 2020). Regarding the safety of the drug, 32 patients (60%) reported conditions such as diarrhoea, hypotension, renal impairment and increased hepatic enzymes. Most of these effects were seen in those subjects who were receiving invasive ventilation. Severe adverse effects such as AKI, MODS, hypotension and septic shock were reported in 12 (23%) patients who were receiving invasive ventilation. No clear evidence of nephrotoxicity was seen in these patients on Remdesivir administration, though non- clinical studies have reported renal abnormalities. Liver dysfunction was observed but whether the hepatotoxicity was due to the drug or the underlying disease is unclear. The overall mortality in the

Remdesivir treated group was 13 % which is much lower compared to 22% in a randomized control trial in which patients were treated with Lopinavir-Ritonavir wherein only 1 out of 199 patients was undergoing invasive ventilation prior to the initiation of the treatment (Cao *et al.*, 2020).

Passive immunization by administration of convalescent plasma has been shown to greatly reduce the viral load and amplified the amount of neutralizing antibody formation (Duan *et al.*, 2020; Shen *et al.*, 2020; Zhang *et al.*, 2020; Ahn *et al.*, 2020 and Ye *et al.*, 2020). An increase in the level of IgG up to 145800 and the IgM titers up to 145800 was observed (Shen *et al.*, 2020). Improvement was noticed in all the patients with regards to their body temperature, lung lesions, respiratory distress, being able to breathe without ventilation within 1 to 35 days post transfusion (Duan *et al.*, 2020; Shen *et al.*, 2020; Zhang *et al.*, 2020; Ahn *et al.*, 2020 and Ye *et al.*, 2020). No mortality was reported post- CPT but the simultaneous administration of antiviral drugs etc may also be responsible for this (Rajendran *et al.*, 2020). Though in almost all the cases no adverse effects were observed but in one case, the patient presented with evanescent red spot on the face (Duan *et al.*, 2020). The convalescent plasma therapy is no "magic bullet" to deal with coronavirus, and only large-scale controlled trials can ascertain its efficacy as part of the treatment strategy (India Today, 4th May 2020). The therapy involves taking antibodies from the blood of a person who has recovered from Covid-19 and transfusing those antibodies into an active coronavirus patient to help kickstart the immune system to fight the infection. The Health Ministry of India last week warned against its use, saying that the plasma therapy for treatment of coronavirus patients is at an experimental stage and has the potential to cause life-threatening complications. However, some state governments, including Rajasthan, Punjab, Maharashtra and Delhi have shown keenness for plasma therapy treatment, and the Centre has permitted few states to perform plasma therapy on a limited number of Covid-19 patients (India Today, May4,2020).

Prognosis

As of date 13th May 2020, the date of preparation of this paper, a total 74,281 people have been affected in India; of which 24,386 (32.82%) have recovered, 41,480 are active and 2,415 (3.25%) have deceased, according to the news update of Government of India (India TV News at 5.0 pm on 13-05-2020). Therefore, the mortality rate for COVID-19 is 3.25 % compared to 11% for SARS-CoV and 34.4% for MERS-CoV. The total number of cases of COVID-19 in the world were 43,63,997 with 16,13,429 (36.97%) recoveries and 2,93,560 (6.72%) mortality (https://www.worldmeters.info). The prognosis is favorable for patients with good immune status and not suffering from any comorbidities. The patients aged above 70 years are at high risk of death due to poor immune status. The contributing factors for increased death include senility, hypertension, diabetes and low body temperature (Neiderman *et al.*, 2020). Patients with comorbidities such as diabetes mellitus and hypertension suffer from Acute Kidney Injury (AKI) and Acute Respiratory Distress Syndrome (ARDS) (Chen *et a.l*, 2020, Huang *et al.*, 2020).

Diagnosis

It is done on the basis of symptoms such a dry cough, fever, gastroenteritis and myalgia. Lab results include elevated C-Reactive Protein, increased level of LDH, creatinine, increased Erythrocyte Sedimentation Rate and prolonged prothrombin time (Wang *et al.*, 2020). Nasal and throat swabs are used for detection of viral genetic material using rRT-PCR for confirmation (Nandi and Chauhan, 2006). The results of Thin slice Computed Tomography vary among different patients and according to the stage of the disease. Multifocal ground glass opacities with or without patchy consolidation and predilection of posterior part or lobe are seen (Zu *et al.*, 2020). These are considered cardinal hallmarks (Wang *et al.*, 2020 and Chung *et al.*, 2020). Though rRT-PCR is the reference standard but due to false negative results, chest CT scan becomes a necessary tool which has a sensitivity of 98% (Fang *et al.*, 2020). For the detection of sero-conversion of infectious agents generally immunodiagnostic tests including ELISA, Dot immunobinding assay etc are carried out on serum samples of the infected individuals (Chauhan, 1995 and Chauhan, 2003). Laboratory tests that detect antibodies to SARS-CoV-2 in people, including rapid immunodiagnostic tests, need further validation to determine their accuracy and reliability. Inaccurate immunodiagnostic tests may falsely categorize people in two ways. The first is that they may falsely label people who have been infected as negative, and the second is that people who have not been infected are falsely labeled as positive. Both errors have serious consequences and will affect

control efforts. These tests also need to accurately distinguish between past infections from SARS-CoV-2 and those caused by the known set of six human coronaviruses. Four of these viruses cause the common cold and circulate widely. The remaining two are the viruses that cause Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome. People infected by any one of these viruses may produce antibodies that cross-react with antibodies produced in response to infection with SARS-CoV-2. Many countries are now testing for SARS-CoV-2 antibodies at the population level or in specific groups, such as health workers, close contacts of known cases, or within households. WHO supports these studies, as they are critical for understanding the extent of – and risk factors associated with – infection. These studies will provide data on the percentage of people with detectable COVID-19 antibodies, but most are not designed to determine whether those people are immune to secondary infections (www.who.int).

Prevention

A quote by Benjamin Franklin, "By failing to prepare, you are preparing to fail" is of utmost relevance in this scenario. The intercontinental ramification of the viral disease is exacerbating. Due to the extremely contagious nature of the SARS CoV-2, a multi-faceted approach is required. Imposition of cordon sanitaire is indispensable. One should avoid travel to hotspot areas at all costs and avoid consumption of raw or undercooked meat from COVID-19 affected areas. As the virus is enveloped, therefore it is sensitive to lipid solvents such as soap, alcoholic hand rubs, sanitizers etc. Maintenance of hand hygiene by following 20 seconds hand wash procedure helps in killing the virus and prevents its further spread. Correct use of face marks i.e. by washing hands before its application is essential, the mask should cover the nose as well as mouth in such a way that there is no gap between these and the mask. After use, the mask should be removed by holding it from the edges and discarded or washed with soap or detergent and dried in sun. The virus remains viable for hours in aerosols and for days on other surfaces which is a great concern for community spread from subclinical subjects to healthy humans as well as to the medical staff (van Doremalen, 2020). This gruelling situation requires early detection, active surveillance and proper measures of isolation. Surveillance should also be considered in domestic felines. Social distancing from humans and domestic felines should be strictly followed to limit the spread of the virus. The World Health Organization recommends testing of suspected patients and isolation and supportive treatment for confirmed patients. Lockdown has been imposed in all affected areas so as to restrict movement in order to flatten the curve of incidence over time.

AYUSH ministry of India has advocated the use of an ayurvedic concoction. The concoction was administered to 6,210 volunteers at 179 quarantine centers out of which only 11 tested positive and these people received the concoction only for 3 days though the ideal duration is 7 days. The ayurvedic tablet Sanshamani vati is also helpful in boosting the immunity. The homeopathic medicine Arsenicum album of 30 potency is also known to increase body's resistance against various affections. Other proposed measures include drinking warm water, doing yoga and meditation, intake of milk containing turmeric and incorporation of spices such as Lahsun (Garlic), Haldi (Turmeric), Dhaniya (Coriander) and Jeera (Cumin) in food (Singh *et al*., 2001). Application of sesame or coconut oil in the nostrils or swishing the oil in the mouth followed by washing with warm water is also beneficial. Steam inhalation with fresh Pudina (Mint) leaves or Ajwain (Caraway) seeds is effective in curing dry cough and sore throat. The clinical trials of Ayurvedic medicines to fight COVID-19 has begun in the country. Today clinical trials of AYUSH medicines like Ashwagandha, Yashtimadhu, Guduchi Pippali, Ayush-64 on health workers and those working on the frontline in high risk areas have begun. The ministry of AYUSH, the ministry of health and the Ministry of science and technology through the Council of Scientific and Industrial Research (CSIR) jointly with technical support of the Indian Council of Medical Research (ICMR) are carrying out the trial (https://economictimes. indiatimes.com/ news/ politics-and-nation/ayush-pushes-traditional-cure-med-council-backs-modern-drugs/articleshow/74680699.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst).

Cowpathy is the use of milk, ghee, curd, urine and dung together known as Panchgavya to treat various diseases. These products have been shown to have multiple health restoring properties. There is a great body of evidence to indicate that the use of cow urine potentiates immunity (Joshi *et al*., 2012). When administered in mice as a distillate, there was a

significant increase in humoral and cellular immunity by 45% and 58% respectively. The production of Interleukin 1 and Interleukin 2 from peripheral blood leucocytes of mice was enhanced by 16% and 21% respectively. A tremendous increase of 104 % was observed in the phagocytic activity of macrophages. Its antioxidant property leads to protection and repair of DNA and reduction of oxidative stress. The prophylactic effects of urine of cows indigenous to India are more compared to buffaloes, exotic cows, crossbred cows, hill cows and goats. These effects are further reinforced by the results of HPLC analysis which revealed the presence of "Rasayan" in the urine of Indian indigenous cows. Therefore, it can be used as immune- enhancer by formulation of the product in such a way that it has a more pleasant taste thereby expanding the range of its acceptability. Cow urine has antioxidant properties and thus it neutralizes the oxidative stress produced in body through action on free radicals. It has been found to repair the damaged DNA and thus is effective even in the cancer therapy. Cow urine enhances the immunocompetence and improves general health of an individual. It has vital potential to enhance the activity of macrophages and lymphocytes (both T and B cells), and has been reported to increase the humoral and cellular mediated immunity (Banga *et al*., 2005; Chauhan, 2013; Chauhan *et al*., 2001; Dhama *et al*., 2005 and Dhama *et al*., 2014). Increased immunocompetence of an individual is a very essential parameter to prevent the occurrence of new diseases and development of cancers by several mechanisms; of which the upregulation of lymphocyte proliferation and stimulation activity, increased macrophage activity, higher antibody production and increased synthesis and secretion of cytokines (IL-1, Il-2) plays significant role. The use of ancient Ayurvedic knowledge and wisdom for immunity boosting and making the people refractory to the new and opportunistic pathogens in order to minimize the losses in terms of medical costs including morbidity and mortality in population is an important measure (Chauhan,2017 and Chauhan,2020)). Further, on completion of the AYUSH clinical trials, the focus of medical fraternity may shift on prevention of COVID-19 through indigenously developed natural therapeutic and preventive preparations at a comfortable cost instead of using high profile modern therapy.

Conflict of Interest

The author declares that there is no conflict of interest.

REFERENCES

Ahmad T, Khan M, Haroon, *et al*. COVID-19: Zoonotic aspects [published online ahead of print, 2020 Feb 27]. Travel Med Infect Dis. 2020;101607. doi:10.1016/j.tmaid.2020.101607

Ahn, J. Y., Sohn, Y., Lee, S. H., Cho, Y., Hyun, J. H., Baek, Y. J., Jeong, S. J., Kim, J. H., Ku, N. S., Yeom, J. S., Roh, J., Ahn, M. Y., Chin, B. S., Kim, Y. S., Lee, H., Yong, D., Kim, H. O., Kim, S., & Choi, J. Y. (2020). Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea. *Journal of Korean medical science*, ***35*****(14),** e149. https://doi.org/10.3346/jkms.2020.35.e149

Almeida, J. D., Berry, D. M., Cunningham, C. H., Hamre, D., Hofstad, M. S., Mallucci, L., and Tyrrell, D. A. J. (1968). Coronaviruses. Nature, **220 (**650**),** 2. doi:10.1038/220650b0.

Banga RK, Singhal LK and Chauhan RS. 2005. Cow urine and immunomodulation: An update on cowpathy. *International Journal of Cow Science*, **1**(2): 26-29.

Bassetti, M., Vena, A., & Giacobbe, D. R. (2020). The novel Chinese coronavirus (2019-nCoV) infections: Challenges for fighting the storm. European journal of clinical investigation, 50(3), e13209. https://doi.org/10.1111/eci.13209.

Breslin, N., Baptiste, C., Miller, R., Fuchs, K., Goffman, D., Gyamfi-Bannerman, C., & D'Alton, M. (2020). COVID-19 in pregnancy: early lessons. *American Journal of Obstetrics & Gynecology MFM*, 100111.

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., Yuan, Y., ... Wang, C. (2020). A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *The New England journal of medicine*, ***382*****(19),** 1787–1799. https://doi.org/10.1056/NEJMoa2001282

Carlos, W. G., Dela Cruz, C. S., Cao, B., Pasnick, S., & Jamil, S. (2020). Novel Wuhan (2019-nCoV) Coronavirus. *American journal of respiratory and critical care medicine*, ***201*****(4),** 7–8. https://doi.org/10.1164/rccm.2014P7

Chan-Yeung, M., & Xu, R. H. (2003). SARS: epidemiology. *Respirology (Carlton, Vic.)*, ***8 Suppl*** **(Suppl 1)**, S9–S14. https://doi.org/10.1046/j.1440-1843.2003.00518.x

Channappanavar, R., Fehr, A. R., Vijay, R., Mack, M., Zhao, J., Meyerholz, D. K., & Perlman, S. (2016). Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell host & microbe*, ***19*****(2)**, 181–193. https://doi.org/10.1016/j.chom.2016.01.007

Chauhan RS, Singh BP and Singhal LK. 2001. Immunomodulation with Kamdhenu ark in mice. *Journal of Immunology and Immunopathology*, **3**: 74-77.

Chauhan RS, Singh BP, Singhal LK, Agrawal DK and Singh AK. 2001. Enhancement of phagocytic activity of leucocytes in mice with Kamdhenu ark. *In:XVI Annual Convention of IAVA and National Symposium on Animal Structural*

Dynamics to Improve Health and Production, Pantnagar. November 8-10, 2001.

Chauhan RS. 1995. Veterinary Clinical and Laboratory Diagnosis. 1st Edn. Jay Pee Brothers Medical Publishers (Pvt.) Ltd. New Delhi. pp 326.

Chauhan RS. 2003. Veterinary Laboratory Diagnosis. IBDC, Lucknow. pp 411.

Chauhan RS. 2013. Indigenous cow urine and Immunomodulation. *Journal of Immunology & Immunopathology*. **15:**19-22.

Chauhan RS. 2018. Illustrated Textbook of Veterinary Pathology. Brillion Publishing, New Delhi. pp 868.

Chauhan RS.2017. Cowpathy : A new version of ancient science. *ICAR NEWS,* **23** (4): 4-5.

Chauhan, RS . 2020. Research on Panchgavya- Current status and future directions. In: National Seminar on Panchgavya for Health Care – A Potetial area for Pharmaceutical Research, held on 8-9 Feb 2020 at Anurag College of Pharmacy, Nagpur.

Chen, H., Guo, J., Wang, C., Luo, F., Yu, X., Zhang, W., Li, J., Zhao, D., Xu, D., Gong, Q., Liao, J., Yang, H., Hou, W., & Zhang, Y. (2020). Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet (London, England)*, ***395*(10226)**, 809–815. https://doi.org/10.1016/S0140-6736(20)30360-3

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)*, ***395*(10223),** 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Chen, S., Liao, E., Cao, D., Gao, Y., Sun, G., & Shao, Y. (2020). Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia. *Journal of medical virology*, 10.1002/jmv.25789. Advance online publication. https://doi.org/10.1002/jmv.25789

Chien, J. Y., Hsueh, P. R., Cheng, W. C., Yu, C. J., & Yang, P. C. (2006). Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. *Respirology (Carlton, Vic.)*, ***11*(6),** 715–722. https://doi.org/10.1111/j.1440-1843.2006.00942.x

Chung, M., Bernheim, A., Mei, X., Zhang, N., Huang, M., Zeng, X., Cui, J., Xu, W., Yang, Y., Fayad, Z. A., Jacobi, A., Li, K., Li, S., & Shan, H. (2020). CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology*, ***295*(1),** 202–207. https://doi.org/10.1148/radiol.2020200230

Connors, J. M., & Levy, J. H. (2020). COVID-19 and its implications for thrombosis and anticoagulation. Blood, blood.2020006000. Advance online publication. https://doi.org/10.1182/blood.2020006000

de Wit E, Feldmann F, Cronin J, *et al.* (2020): Prophylactic and therapeutic Remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A; **117**: 6771-6.

Dhama K, Chauhan RS and Singhal Lokesh. 2005. Anti-cancer activity of cow urine: Current status and future directions. *International Journal of Cow Science,* **1**(2): 1-25.

Dhama K, Khurana SK, Karthik K, Tiwari R, Malik YPS and Chauhan RS. 2014. Panchgavya: Immune-enhancing and Therapeutic Perspectives. *Journal of Immunology and Immunopathology,* **16**: 1-11.

Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., Zhou, M., Chen, L., Meng, S., Hu, Y., Peng, C., Yuan, M., Huang, J., Wang, Z., Yu, J., Gao, X., Wang, D., Yu, X., Li, L., Zhang, J., … Yang, X. (2020). Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proceedings of the National Academy of Sciences of the United States of America*, ***117*(17),** 9490–9496. https://doi.org/10.1073/pnas.2004168117

European Medicines Agency. Summary on compassionate use: Remdesivir Gilead. April 3, 2020 (https://www .ema.europa .eu/ en/ documents/ other/ summary-compassionate-use-remdesivir-gilead_en.pdf).

Fang, Y., Zhang, H., Xie, J., Lin, M., Ying, L., Pang, P., & Ji, W. (2020). Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology*, 200432. Advance online publication. https://doi.org/10.1148/radiol.2020200432

Fehr, AR, & Perlman S. (2015). Coronaviruses: an overview of their replication and pathogenesis. *Methods in molecular biology (Clifton, N.J.)*, ***1282,*** 1–23. https://doi.org/10.1007/978-1-4939-2438-7_1

Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Dupont, H. T., Honoré, S., Colson, P., Chabrière, E., La Scola, B., Rolain, J. M., Brouqui, P., & Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International journal of antimicrobial agents*, 105949. Advance online publication. https://doi.org/10.1016/j.ijantimicag.2020.105949

General Office of National Health Committee. Office of state administration of traditional Chinese medicine. Notice on the issuance of a programme for the diagnosis and treatment of novel coronavirus (2019-nCoV) infected pneumonia (trial fifth edition) (2020-02-26)[EB/OL]. http://bgs.satcm.gov.cn/zhengcewenjian/2020-02-06/12847.html Google Scholar

General Office of National Health Committee. Office of State Administration of Traditional Chinese Medicine. Notice on the issuance of a program for the diagnosis and treatment of novel coronavirus (2019-nCoV) infected pneumonia (trial sixth edition) (2020-02-19) [EB/OL]. http://yzs.satcm.gov.cn/zhengcewenjian/2020-02-19/13221.html] Google Scholar

Gidlöf, S., Savchenko, J., Brune, T., & Josefsson, H. (2020). COVID-19 in pregnancy with comorbidities: More liberal testing strategy is needed. *Acta obstetricia et gynecologica Scandinavica*, 10.1111/aogs.13862. Advance online publication. https://doi.org/10.1111/aogs.13862.

Grein J, Ohmagari N, Shin D, *et al*. (2020) :Compassionate Use of Remdesivir for Patients with Severe Covid-19 [published online ahead of print, 2020 Apr 10]. N Engl J Med. ;NEJMoa2007016. doi:10.1056/NEJMoa2007016

Herfst, S., Schrauwen, E. J., Linster, M., Chutinimitkul, S., de Wit, E., Munster, V. J., Sorrell, E. M., Bestebroer, T. M., Burke, D. F., Smith, D. J., Rimmelzwaan, G. F., Osterhaus, A. D., & Fouchier, R. A. (2012). Airborne transmission of influenza A/H5N1 virus between ferrets. *Science (New York, N.Y.)*, ***336*****(**6088**),** 1534–1541. https://doi.org/10.1126/science.1213362

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*, ***395*****(10223),** 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Huang, K. J., Su, I. J., Theron, M., Wu, Y. C., Lai, S. K., Liu, C. C., & Lei, H. Y. (2005). An interferon-gamma-related cytokine storm in SARS patients. *Journal of medical virology*, ***75*****(2),** 185–194. https://doi.org/10.1002/jmv.20255

Iba, T., Levy, J. H., Wada, H., Thachil, J., Warkentin, T. E., Levi, M., & Subcommittee on Disseminated Intravascular Coagulation (2019). Differential diagnoses for sepsis-induced disseminated intravascular coagulation: communication from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH*, ***17*****(2)**, 415–419. https://doi.org/10.1111/jth.14354

Imai, M., Watanabe, T., Hatta, M., Das, S. C., Ozawa, M., Shinya, K., Zhong, G., Hanson, A., Katsura, H., Watanabe, S., Li, C., Kawakami, E., Yamada, S., Kiso, M., Suzuki, Y., Maher, E. A., Neumann, G., & Kawaoka, Y. (2012). Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature*, ***486***(7403)**,** 420–428. https://doi.org/10.1038/nature10831

Iqbal, S. N., Overcash, R., Mokhtari, N., Saeed, H., Gold, S., Auguste, T., Mirza, M. U., Ruiz, M. E., Chahine, J. J., Waga, M., & Wortmann, G. (2020). An Uncomplicated Delivery in a Patient with Covid-19 in the United States. *The New England journal of medicine*, ***382*****(16),** e34. https://doi.org/10.1056/NEJMc2007605

Jaimes, J. A., Millet, J. K., Stout, A. E., André, N. M., & Whittaker, G. R. (2020). A Tale of Two Viruses: The Distinct Spike Glycoproteins of Feline Coronaviruses. *Viruses*, ***12*****(1),** 83. https://doi.org/10.3390/v12010083

Ji, W., Wang, W., Zhao, X., Zai, J., & Li, X. (2020). Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. *J. Med. Virol*. **92 (4)** 433–440, https://doi.org/10.1002/jmv.25682.

Joshi A**,** Bankoti K, Bisht T and Chauhan RS(2012)**.** Immunomodulatory effect of Gir cow urine distillate in Rabbits. *Journal of Immunology and Immunopathology.***14**(1): 57-61.

Lauer, S. A., Grantz, K. H., Bi, Q., Jones, F. K., Zheng, Q., Meredith, H. R., Azman, A. S., Reich, N. G., & Lessler, J. (2020). The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Annals of internal medicine*, **M20**-0504. Advance online publication. https://doi.org/10.7326/M20-0504

Lei, J., Li, J., Li, X., & Qi, X. (2020). CT Imaging of the 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology*, ***295*****(1),** 18. https://doi.org/10.1148/radiol.2020200236.

Levi, M., & Scully, M. (2018). How I treat disseminated intravascular coagulation. *Blood*, ***131*****(8),** 845–854. https://doi.org/10.1182/blood-2017-10-804096

Li, Y., Zhao, R., Zheng, S., Chen, X., Wang, J., Sheng, X., Zhou, J., Cai, H., Fang, Q., Yu, F., Fan, J., Xu, K., Chen, Y., & Sheng, J. (2020). Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. *Emerging infectious diseases*, ***26*****(6),** 10.3201/eid2606.200287. Advance online publication. https://doi.org/10.3201/eid2606.200287

Lippi, G., Bonfanti, L., Saccenti, C., & Cervellin, G. (2014). Causes of elevated D-dimer in patients admitted to a large urban emergency department. *European journal of internal medicine*, ***25*****(1),** 45–48. https://doi.org/10.1016/j.ejim.2013.07.012

Liu T, Hu J, Kang M, Lin L, Zhong H, Xiao J, et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). 2020; doi: 10.1101/2020.01.25.919787.

Liu, D., Li, L., Wu, X., Zheng, D., Wang, J., Yang, L., & Zheng, C. (2020). Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. *AJR. American journal of roentgenology*, 1–6. Advance online publication. https://doi.org/10.2214/AJR.20.23072

Liu, J., Zheng, X., Tong, Q., Li, W., Wang, B., Sutter, K., Trilling, M., Lu, M., Dittmer, U., & Yang, D. (2020). Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. *Journal of medical virology*, ***92*****(5)**, 491–494. https://doi.org/10.1002/jmv.25709

Lu H (2020), Drug treatment options for the 2019-new coronavirus (2019-nCoV), Biosci.Trends **14(1),** 69-71 https://doi.org/10.5582/bst.2020.01020

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Chen, J., … Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England)*, ***395*****(**10224**),** 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

Martina, B. E., Haagmans, B. L., Kuiken, T., Fouchier, R. A., Rimmelzwaan, G. F., Van Amerongen, G., Peiris, J. S., Lim, W., & Osterhaus, A. D. (2003). Virology: SARS virus infection of cats and ferrets. *Nature*, ***425*****(**6961**),** 915. https://doi.org/10.1038/425915a

Middle East Respiratory Syndrome Coronavirus. Available at: https://www.who.int/emergencies/mers-cov/en/. Accessed 16 Feb 2020.

Mulangu S, Dodd LE, Davey RT Jr, et al. (2020): A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med; **381**: 2293-303.

Nandi S and Chauhan RS. 2006. Manual of Viral Disease Investigation. IVRI, Izatnagar. pp 116.

Niederman, M. S., Richeldi, L., Chotirmall, S. H., & Bai, C. (2020). Rising to the Challenge of the Novel SARS-coronavirus-2 (SARS-CoV-2): Advice for Pulmonary and Critical Care and an Agenda for Research. *American Journal of Respiratory and Critical Care Medicine*, (ja), **201 (**9**),** 1019-1038

Nirenberg, M. S., & Del Mar Ruiz Herrera, M. (2020). Foot Manifestations in a COVID-19 Positive Patient: A Case Study. Journal of the American Podiatric Medical Association, 10.7547/20-088. Advance online publication. https://doi.org/10.7547/20-088

Paraskevis, D., Kostaki, E. G., Magiorkinis, G., Panayiotakopoulos, G., Sourvinos, G., & Tsiodras, S. (2020). Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases*, ***79***, 104212. https://doi.org/10.1016/j.meegid.2020.104212

Piccolo V, Neri I, Filippeschi C, Oranges T, Argenziano G, Battarra VC, Berti S, Manunza F, Belloni Fortina A, Di Lernia V, Boccaletti V. (2020): Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. Journal of the European Academy of Dermatology and Venereology.

Rajendran, K., Narayanasamy, K., Rangarajan, J., Rathinam, J., Natarajan, M., & Ramachandran, A. (2020). Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. *Journal of Medical Virology*.

Recalcati S. (2020). Cutaneous manifestations in COVID-19: a first perspective. *Journal of the European Academy of Dermatology and Venereology : JEADV*, 10.1111/jdv.16387. Advance online publication. https://doi.org/10.1111/jdv.16387

Ren, L. L., Wang, Y. M., Wu, Z. Q., Xiang, Z. C., Guo, L., Xu, T., Jiang, Y. Z., Xiong, Y., Li, Y. J., Li, X. W., Li, H., Fan, G. H., Gu, X. Y., Xiao, Y., Gao, H., Xu, J. Y., Yang, F., Wang, X. M., Wu, C., Chen, L., … Wang, J. W. (2020). Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chinese medical journal*, ***133*****(9),** 1015–1024. https://doi.org/10.1097/CM9.0000000000000722

Richman, D. D., Whitley, R. J., & Hayden, F. G. (Eds.). (2016). *Clinical virology*. John Wiley & Sons.

Schnittler, H. J., & Feldmann, H. (2003). Viral hemorrhagic fever--a vascular disease?. *Thrombosis and haemostasis*, ***89*****(6),** 967–972.

Shanmugaraj, B., Siriwattananon, K., Wangkanont, K., & Phoolcharoen, W. (2020). Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). *Asian Pac J Allergy Immunol*, *38*(1), 10-18. Shanmugaraj, B., Siriwattananon, K., Wangkanont, K., & Phoolcharoen, W. (2020). Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). *Asian Pac J Allergy Immunol*, ***38*****(1),** 10-18.

Sheahan, T. P., Sims, A. C., Graham, R. L., Menachery, V. D., Gralinski, L. E., Case, J. B., Leist, S. R., Pyrc, K., Feng, J. Y., Trantcheva, I., Bannister, R., Park, Y., Babusis, D., Clarke, M. O., Mackman, R. L., Spahn, J. E., Palmiotti, C. A., Siegel, D., Ray, A. S., Cihlar, T., … Baric, R. S. (2017). Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Science translational medicine*, ***9*****(396),** eaal3653. https://doi.org/10.1126/scitranslmed.aal3653

Sheahan, T. P., Sims, A. C., Leist, S. R., Schäfer, A., Won, J., Brown, A. J., Montgomery, S. A., Hogg, A., Babusis, D., Clarke, M. O., Spahn, J. E., Bauer, L., Sellers, S., Porter, D., Feng, J. Y., Cihlar, T., Jordan, R., Denison, M. R., & Baric, R. S. (2020). Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature communications*, ***11*****(1)**, 222. https://doi.org/10.1038/s41467-019-13940-6

Shen, C., Wang, Z., Zhao, F., Yang, Y., Li, J., Yuan, J., Wang, F., Li, D., Yang, M., Xing, L., Wei, J., Xiao, H., Yang, Y., Qu, J., Qing, L., Chen, L., Xu, Z., Peng, L., Li, Y., Zheng, H., … Liu, L. (2020). Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*, ***323*****(16),** 1582–1589. Advance online publication. https://doi.org/10.1001/jama.2020.4783

Shi, J., Deng, G., Kong, H., Gu, C., Ma, S., Yin, X., Zeng, X., Cui, P., Chen, Y., Yang, H., Wan, X., Wang, X., Liu, L., Chen, P., Jiang, Y., Liu, J., Guan, Y., Suzuki, Y., Li, M., Qu, Z., … Chen, H. (2017). H7N9 virulent mutants detected in chickens in China pose an increased threat to humans. *Cell research*, ***27*****(12),** 1409–1421. https://doi.org/10.1038/cr.2017.129

Shi, J., Wen, Z., Zhong, G., Yang, H., Wang, C., Huang, B., Liu, R., He, X., Shuai, L., Sun, Z., Zhao, Y., Liu, P., Liang, L., Cui, P., Wang, J., Zhang, X., Guan, Y., Tan, W., Wu, G., Chen, H., … Bu, Z. (2020). Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. *Science (New York, N.Y.)*, eabb7015. Advance online publication. https://doi.org/10.1126/science.abb7015

Singh Harpal, Sharma VK and Chauhan RS. 2001. Herbal preparations and biostimulators in tissue repair. Monograph. College of Veterinary Sciences. G.B. Pant Univ. Pantnagar 48.pp

Smith, S. A., Mutch, N. J., Baskar, D., Rohloff, P., Docampo, R., & Morrissey, J. H. (2006). Polyphosphate modulates blood coagulation and fibrinolysis. *Proceedings of the National Academy of Sciences of the United States of America*, ***103*****(4),** 903–908. https://doi.org/10.1073/pnas.0507195103

Stittelaar, K. J., de Waal, L., van Amerongen, G., Veldhuis Kroeze, E. J., Fraaij, P. L., van Baalen, C. A., van Kampen, J. J., van der Vries, E., Osterhaus, A. D., & de Swart, R. L. (2016). Ferrets as a Novel Animal Model for Studying Human Respiratory Syncytial Virus Infections in Immunocompetent and Immunocompromised Hosts. *Viruses*, ***8*****(6),** 168. https://doi.org/10.3390/v8060168

van den Brand, J. M., Haagmans, B. L., Leijten, L., van Riel, D., Martina, B. E., Osterhaus, A. D., & Kuiken, T. (2008). Pathology of experimental SARS coronavirus infection in cats and ferrets. *Veterinary pathology*, ***45*(4),** 551–562. https://doi.org/10.1354/vp.45-4-551

Virus Taxonomy: 2018 Release. International Committee on Taxonomy of Viruses (ICTV). October 2018. Retrieved 24 January 2019

Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *Journal of virology*, ***94*(7),** e00127-20. https://doi.org/10.1128/JVI.00127-20

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, ***323*(11),** 1061–1069. Advance online publication. https://doi.org/10.1001/jama.2020.1585

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research*, ***30*(3),** 269–271. https://doi.org/10.1038/s41422-020-0282-0

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research*, ***30*(3),** 269–271. https://doi.org/10.1038/s41422-020-0282-0

Wang, S., Guo, L., Chen, L., Liu, W., Cao, Y., Zhang, J., & Feng, L. (2020). A case report of neonatal COVID-19 infection in China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciaa225. Advance online publication. https://doi.org/10.1093/cid/ciaa225

Wang, X., Zhou, Z., Zhang, J., Zhu, F., Tang, Y., & Shen, X. (2020). A case of 2019 Novel Coronavirus in a pregnant woman with preterm delivery. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciaa200. Advance online publication. https://doi.org/10.1093/cid/ciaa200

WHO (2020). https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19

WHO. (2004). WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS) at https://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1.pdf?ua=1. Published January, 2004. Updated October,2004. Google Scholar

WHO.(2017) Middle East respiratory syndrome case definition for reporting to WHO. 2017. https://www.who.int/csr/disease/coronavirus_infections/mers-interim–case-definition.pdf?ua=1. Google Scholar

WHO.(2019) Coronavirus Disease 2019(COVID-19): situation report-28. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200217-sitrep-28-covid-19.pdf?sfvrsn=a19cf2ad_2. Published February 18, 2020. Accessed February 20, 2020 Google Scholar

WHO.(2020) Home care for patients with suspected novel coronavirus (nCoV) infection presenting with mild symptoms and management of contacts [EB/OL]. https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts. Published January 20, 2020. Accessed February 11, 2020 Google Scholar

Wong, C. K., Lam, C. W., Wu, A. K., Ip, W. K., Lee, N. L., Chan, I. H., Lit, L. C., Hui, D. S., Chan, M. H., Chung, S. S., & Sung, J. J. (2004). Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clinical and experimental immunology*, ***136*(1),** 95–103. https://doi.org/10.1111/j.1365-2249.2004.02415.x

Wu, P., Hao, X., Lau, E., Wong, J. Y., Leung, K., Wu, J. T., Cowling, B. J., & Leung, G. M. (2020). Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, ***25*(3),** 2000044. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000044

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F. S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet. Respiratory medicine*, ***8*(4),** 420–422. https://doi.org/10.1016/S2213-2600(20)30076-X

Ye, M., Fu, D., Ren, Y., Wang, F., Wang, D., Zhang, F., ... & Lv, T. (2020). Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *Journal of Medical Virology*.

Yu, N., Li, W., Kang, Q., Xiong, Z., Wang, S., Lin, X., Liu, Y., Xiao, J., Liu, H., Deng, D., Chen, S., Zeng, W., Feng, L., & Wu, J. (2020). Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. *The Lancet. Infectious diseases*, ***20*(5),** 559–564. https://doi.org/10.1016/S1473-3099(20)30176-6

Zaigham, M., & Andersson, O. (2020). Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta obstetricia et gynecologica Scandinavica*, 10.1111/aogs.13867. Advance online publication. https://doi.org/10.1111/aogs.13867

Zambrano, L. I., Fuentes-Barahona, I. C., Bejarano-Torres, D. A., Bustillo, C., Gonzales, G., Vallecillo-Chinchilla, G., Sanchez-Martínez, F. E., Valle-Reconco, J. A., Sierra, M., Bonilla-Aldana, D. K., Cardona-Ospina, J. A., & Rodríguez-Morales, A. J. (2020). A pregnant woman with COVID-19 in Central America. *Travel medicine and infectious disease*, 101639. Advance online publication. https://doi.org/10.1016/j.tmaid.2020.101639

Zhang, B., Liu, S., Tan, T., Huang, W., Dong, Y., Chen, L., Chen, Q., Zhang, L., Zhong, Q., Zhang, X., Zou, Y., & Zhang, S. (2020). Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection. *Chest*, S0012-**3692(20)**30571-7. Advance online publication. https://doi.org/10.1016/j.chest.2020.03.039

Zhang, L., Jiang, Y., Wei, M., Cheng, B. H., Zhou, X. C., Li, J., Tian, J. H., Dong, L., & Hu, R. H. (2020). Analysis of the Pregnancy Outcomes in Pregnant Women With COVID-19 in Hubei Province]***55*(0),** E009. Advance online publication. https://doi.org/10.3760/cma.j.cn112141-20200218-00111

Zhang, Q., Shi, J., Deng, G., Guo, J., Zeng, X., He, X., Kong, H., Gu, C., Li, X., Liu, J., Wang, G., Chen, Y., Liu, L., Liang, L., Li, Y., Fan, J., Wang, J., Li, W., Guan, L., Li, Q., … Chen, H. (2013). H7N9 influenza viruses are transmissible in ferrets by respiratory droplet. *Science (New York, N.Y.)*, ***341*(6144),** 410–414. https://doi.org/10.1126/science.1240532

Zhang, Y., Cao, W., Xiao, M., Li, Y. J., Yang, Y., Zhao, J., ... & Li, T. S. (2020). Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. Zhonghua xue ye xue za zhi= Zhonghua xueyexue zazhi, **41**, E006-E006.

Zhang, Y., Li, J., Zhan, Y., Wu, L., Yu, X., Zhang, W., Ye, L., Xu, S., Sun, R., Wang, Y., & Lou, J. (2004). Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infection and immunity*, ***72*(8),** 4410–4415. https://doi.org/10.1128/IAI.72.8.4410-4415.2004

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)*, ***395*(10229),** 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., Tan, W., & China Novel Coronavirus Investigating and Research Team (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine*, ***382*(8),** 727–733. https://doi.org/10.1056/NEJMoa2001017

Zu, Z. Y., Jiang, M. D., Xu, P. P., Chen, W., Ni, Q. Q., Lu, G. M., & Zhang, L. J. (2020). Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology*, 200490. Advance online publication. https://doi.org/10.1148/radiol.2020200490.