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THE NOVEL HUMAN CORONAVIRUS: AN OVERVIEW

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ABSTRACT

The coronavirus disease (COVID-19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as the Novel Coronavirus which emerged in Huanan Market, Wuhan, China and spread around the world. Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses, therefore bats could be the possible primary reservoir. In fact, COVID-19 is not the first illness that has made the leap from bats to humans. The viruses that causes SARS, MERS, Ebola, Nipah, Hendra and Marburg can all be traced back to bats, according to the UC Berkley Researchers, although all were spread through intermediate hosts. There is no clinically approved antiviral drug or vaccine available to be used against COVID-19. However, few broad-spectrum antiviral drugs have been evaluated against COVID-19 in clinical trials, resulted in clinical recovery.

KEYWORDS: Morphology, Types, Origin, Transmission, Pathogenicity, Characteristics, Outbreaks, Symptoms, Related-Diseases, Prevention and Treatment.

1. INTRODUCTION

Coronaviruses are a group of related viruses that causes diseases in mammals and birds. Coronaviruses constitute the subfamily Orthocoronavirae in the family Coronaviridae, order Nidovirales, and realm Ribovirae. These are enveloped viruses and the largest amongst known RNA viruses. The name Coronavirus is derived from Latin Corona, meaning "crown" or "halo", which refers to the characteristic appearance of a crown or solar corona around the virions when seen under two-dimensional Transmission Electron Microscopy (TEM), due to the presence of surface covering protein spikes. These are mainly responsible to cause Respiratory Tract Infections. Infections can be mild such as cases seen in Common Cold

predominantly caused by Rhinoviruses and others can be lethal, such as MERS, SARS, COVID-19.

2. Morphology of the coronavirus

Coronaviruses are large pleomorphic spherical particles with bulb like surface projections., with a diameter of about 120nm. The viral envelope consists of a lipid bilayer wherein the membrane, envelope and spike structural proteins are anchored. The Beta Subgroup of the Coronaviruses have a shorter spike like surface protein called "Haemagglutinin Esterase". Inside the envelope lies a "Nucleocapsid" which is formed from multiple copies of the Nucleocapsid protein, which are bound to the positive-sense single stranded RNA genome in a continuous beads-on-a-string type of conformation. The lipid bilayer, membrane proteins and nucleocapsid are the real culprit as they are responsible to protect the virus when it is outside the host cell.

3. Types of coronaviruses

There are seven known types Coronaviruses that affects the humans, says Dr John Swartzberg, Clinical Professor emeritus of infectious diseases and vaccinology at the University of California-Berkley School of Public Health.

Common human coronaviruses include

1.	2299E (ALPHA CORONAVIRUS)
2.	NL63 (ALPHA CORONAVIRUS)
3.	0C43 (BETA CORONAVIRUS)
4.	HKU1(BET CORONAVIRUS)

Other human coronaviruses include

1.	MERS-CoV (The beta coronavirus that causes MERS (Middle East Respiratory Syndrome)
2.	SARS-CoV (The beta coronavirus that causes SARS (Severe Acute Respiratory Syndrome)
3.	SARS-CoV-2 which is the Novel Coronavirus that is COVID-19.

People around the world get commonly infected with Human Coronavirus 229E, NL63, OC43 and HKU1. But sometimes coronaviruses that infect animals can evolve and make people sick and become a new Coronavirus. Three recent examples of this are 2019-CoV, SARS-CoV and MERS-CoV.

4. The proximal origin of the virus

The disease has originated from a "Wuhan Seafood Market" where wild animals, including marmots, bats, birds, rabbits and snakes are traded illegally. The virus is known to jump from animals to humans, so its thought that the first people infected with the disease were primarily a group of stallholders from the Seafood Market; who got the virus via contact with the animals. A team of Virologists at the "Wuhan Institute of Virology" released a paper showing that the Novel Coronavirus's genetic makeup is 96% identical to that of a coronavirus found in a bat, while according to an unpublished study argues that genetic sequence of Coronavirus in Pangolins is 99% similar to the human virus. Based on their genomic sequencing analysis, Kristian G Andersen and his collaborators concluded that the most likely origins for SARS-CoV-2 can be based on one of the two possible scenarios:

- In 1stscenario, which is called the "**Natural Selection in an Animal host before Zoonotic Transfer**" the virus evolved to its current pathogenic state through natural selection in a non-human host and then jumped to humans. This is how previous coronavirus outbreak have emerged, with humans getting infected with virus after direct exposure to Civets (SARS) and the camels (MERS). The researchers proposed bats as the most likely reservoir for SARS-CoV-2, but there are no documented cases of direct bat-human transmission, however, suggesting that an intermediate host was likely involved between bats and humans.
- In 2nd scenario, which is termed as "**Natural Selection in Humans following Zoonotic Transfer"** both of the distinctive features of the virus's spike protein that is the RBD (Receptor Binding Portion) that binds to the cells and the cleavage site that opens the virus up would have evolved to their current state before entering to humans.

For instance, some coronaviruses from Pangolins, armadillo-like mammals found in Asia and Africa have a RBD very similar to the novel coronavirus. Study co-author Andrew Rambaut, W. Ian Lipkin, Edward C Holmes and Robert F Garry, cautioned that it is difficult if not impossible to know at this point which of the scenarios is most likely. If the SARS-CoV-2 entered humans in its current pathogenic form from an animal source, it raises the probability of future outbreaks, as the illness-causing strain of the virus could still be circulating in the animal population and might once again jump into humans. The chances are lower of a non-pathogenic coronavirus entering the human population and then evolving properties similar to SARS-CoV-2.

5. Transmission and Transmission routes

The spread of this virus begun from the Huanan Seafood Market, Wuhan and first 41 cases were found to be positive. Two third of the positive cases were directly connected to the market. Initially, reports indicated that person-to-person transmission is limited or non-existent, but now it is quite clear that human-to-human transmission exists and in fact it is must for this epidemic to become "**superspreading".** Novel Coronavirus is thought to be transmitted through respiratory droplets generated via coughing and sneezing, through close contact, through patients in incubation period and via faeco-oral transmission. ACE2, a receptor for virus, is necessary for the viral entry. The ubiquitous expression of ACE2 in various cells, such as lung AT2 cells, upper oesophagus, stratified epithelial cells, and absorptive enterocytes of ileum and colon may contribute to the multi-tissue infection of 2019-nCoV. Therefore, besides respiratory and bodily contact, faecal-oral transmission is a potential route for COVID-19 Infection. In addition, the asymptomatic incubation period for individuals infected with the virus was estimated to range from 1 to 14 days (most likely 3–10 days) which is quite longer than that of SARS-CoV. A very important threshold quantity associated with the viral transmissibility is the basic reproduction number, which is usually denoted by *Ro* (pronounced "R naught"). The epidemiological definition of $R_0$is the average number of people who will catch a disease from one contagious person. It specifically applies to a population of people who were previously free of infection and not vaccinated. Three possibilities exist for the potential spread or decline of a disease, depending on its R_0value:

- If R_0 is less than 1, each existing infection causes less than 1 new infection. In this case, the disease will decline and eventually disappear.
- If R_0 equals 1, the disease will stay alive, but there won't be an epidemic.
- If R_0 is greater than 1, cases could grow exponentially and cause an epidemic or even a pandemic.

From what we currently know, the calculated R_0 value for the novel virus is significantly greater than 1.

6. Pathogenecity of the virus

As mentioned earlier, out of the first infected individuals, all had Viral Pneumonia and one third of the people developed Acute Respiratory Distress Syndrome (ARDS) and they required Intensive care and 6 patients of those (14.6%) died. Since the fatality rate of the early reported case is often high due to bias towards more severe cases, the true mortality rise

can be kept much lower. As of 27th Jan 2020, about 3000 cases have been confirmed in China., and cases were also reported in Japan, South Korea, Thailand, Singapore, the United States, and Australia, all of which were exported from China. The total number of deaths from the Pneumonia related diseases accounts for less than 3%. In Addition, most of those who have died had associated health problems like Hypertension, Diabetes or Cardio-Vascular disease which tends to compromise their immune systems. Although the fatality rate will continue to change until all infected people recover.

7. Characteristics of the coronaviruses

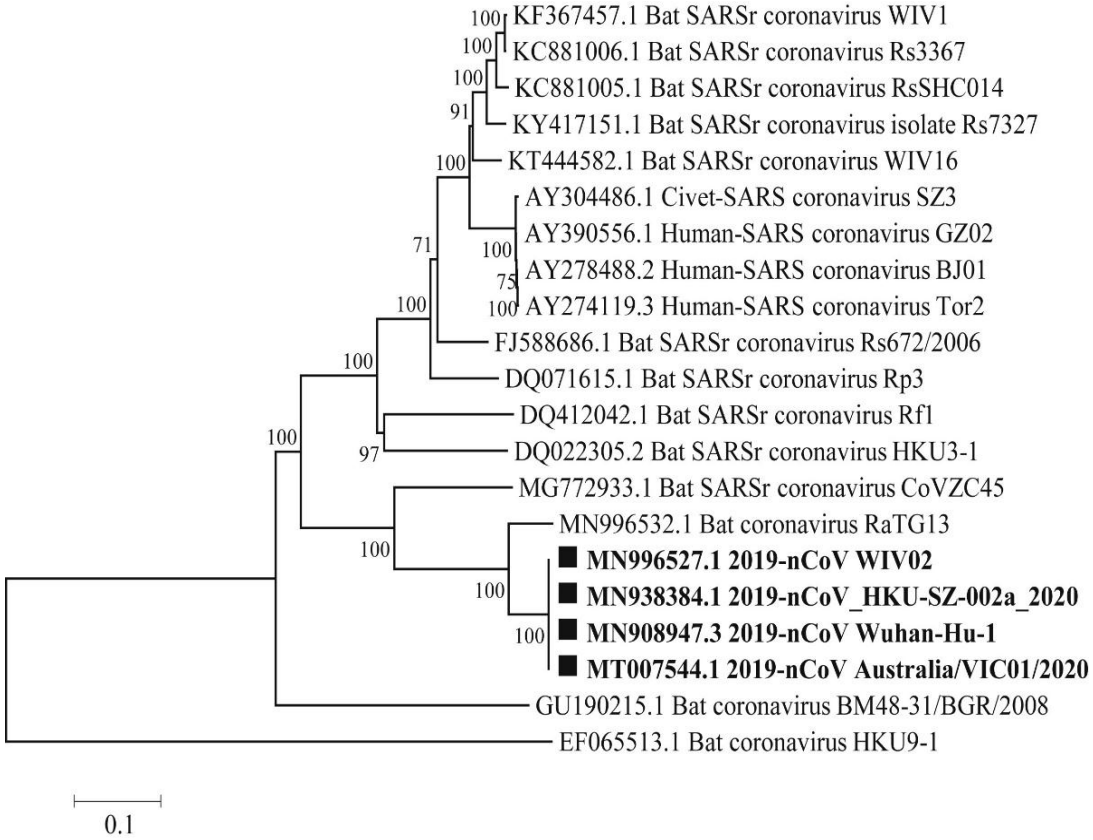
7.1 Epidemiological characteristics

Human Coronaviruses can cause respiratory, gastrointestinal, hepatic and Central Nervous System diseases. Infection could vary from mild, self-limiting disease, to more severe manifestations and death. Out of the seven Human Coronaviruses, two alpha and two beta viruses causes mild-self limiting upper respiratory disease, like common cold in immune-compromised individuals. Exception can be observed for a few cases of severe infections in infants, children and senior. The other three coronaviruses cause fatal respiratory diseases. In 2003, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) emerged in Guangdong province, China, spreading to 37 countries and its subsequent global epidemic was associated with 8096 cases and 774 deaths. Ten years later, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) spread to 27 countries, causing 2494 infected cases and the 858 deaths worldwide. And the recently identified Novel Coronavirus was the third highly pathogenic coronavirus discovered with a Mortality rate of 2% which is much lower than that of SARS-CoV (10%) and MERS-CoV (37%). However, the transmissibility of the novel virus is higher and it has a reproduction number (3.3-5.5) than those of SARS-CoV (2-5) and MERS-CoV (2.7-3.9).

7.2 Genomic characteristics

The coronaviruses possess a genome size ranging from approximately 27 to 34 kilobases being the largest genome amongst known RNA viruses. The genome has a 5’ methylated cap and a 3’ polyadenylated tail. The genome organization of a Coronavirus is 5’-leader-UTR-replicase/transcriptase-spike(S)[envelope(E)-membrane(M)-nucleocapsid(N)-3’UTR-poly(A) tail. The genome codes the replicase/transcriptase polyprotein which self cleaves to form the non-structural proteins. The coronavirus shows the presence of accessory proteins but their function is unique depending on the specific type of the Coronavirus.2019-nCoV shares

79.5% identity with SARS-CoV and 96% identity with bat-CoV-RaTG13. The genetic characteristics of 2019-nCoV are significantly different from SARS-CoV and SARS-CoV, which are closely related only to the specific bat SARS-like coronaviruses, bat-CoV-RaTG13 and bat-SL-CoVZC45, with 96% and 86.9% nucleotide sequence identities, respectively. Therefore 2019-nCoV is considered as a SARS related coronavirus (SARS-CoV) by pairwise protein sequence analysis shown in figure.



8. Outbreak

This contagious virus has quickly spread globally, the outbreak was declared by WHO a Public Health Emergency of international concern (PHEIC) as it had spread to several countries with many countries reporting human to human transmission.

Various strategies and studies are made in order to control the outbreak:

1. Containment- aims to trace and isolate those infected as well as other measures of infection control and vaccination to stop the disease from spreading to rest of the population
2. Mitigation -when containment is not sufficient to stop the disease spread, efforts then move to mitigation stage ,which shows the spread and mitigate its effect on health care system and society

3. Suppression- suppression requires more extreme measures so as to reverse the pandemic by reducing the basic reproduction number to less than 1.

9. Symptoms

Symptoms of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. It takes 2-14 days after exposure, for symptoms to develop. The symptoms are usually mild and begin gradually. Some people become infected but don't develop any symptoms and don't feel unwell. Typical signs and symptoms include: fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%), chills (11.4%), nausea or vomiting (5.0%), nasal congestion (4.8%), diarrhea (3.7%), and hemoptysis (0.9%), and conjunctival congestion (0.8%). People with COVID-19 generally develop signs and symptoms, including mild respiratory symptoms and fever, on an average of 5-6 days after infection (mean incubation period 5-6 days, range 1-14 days).

Most people (about 80%) recover from disease without needing special treatment. Around 1 out of every 6 people who gets COVID-19, becomes seriously ill and develops difficulty in breathing. Older people and those with underlying medical problems or diabetes, are more likely to develop serious illness. Those with weakened immune system may develop more serious symptoms, like pneumonia or bronchitis. A minority of patients would get worse instead of better. This usually happens after 5-7 days of illness and these patients will have more shortness of breath and worsening cough. For those who suffer from allergies or chronic sinus problems in general, how do it is best identified the differences between seasonal symptoms and COVID-19 symptoms? A stuffy and runny nose aren't common symptoms of new corona virus.

10. Related disease

Most people infected with COVID-19 virus have mild disease and recover. Approximately 80% have had mild to moderate disease, which includes non-pneumonia and pneumonia cases, 13.8% have severe disease (dyspnea, respiratory frequency≥30/minute, blood oxygen saturation≤93%, PaO2/FiO2 ratio<300, and lung infiltrates>50% of the lung field within 24-48 hours) and 6.1% are critical (respiratory failure, septic shock and multiple organ dysfunction/ failure).

Individuals at highest risk for severe disease and death include people aged over 60 years and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cancer, smokers, patients with low immune systems or who take medicines to suppress their immune systems because they have some sort of autoimmune condition or cancer. Disease in children appears to be relatively rare and mild amongst individuals aged under 19 years. A very small proportion of those aged under 19 years have developed severe (2.5%) or critical disease (0.2%).

11. Prevention

In infection control, there is a line between things that are transmitted by traveling in air briefly in respiratory droplets and things that are actually aerosolized and float around for a while. Small bits of fluid that can be felt and see when someone sneezes. When someone sneezes or cough, these droplets get on surfaces and then one can touch them and get them on hands or can fly right into mouth or nose or eyes. So, one should prevent entry of this droplets into mucous membrane sites like mouth, nose and eyes, by taking preventive measures like covering mouth while coughing, with a tissue or coughing into upper sleeve or elbow and avoiding coughing into hands, washing hands often with soap and water for at least 20 seconds, especially after going to the bathroom, before eating and after blowing nose, coughing or sneezing. If soap and water are not readily available, use an alcohol- based hand sanitizer with at least 60% alcohol. Avoid touching your mouth, nose or eyes.

- Human-to-human transmission have been described with incubation times between 2-10days, facilitating its spread via droplets, contaminated hands or surfaces, as described earlier. Therefore, literature study has been carried out about the persistence of human and veterinary coronaviruses on inanimate surfaces as well as inactivation with biocidal agents used for chemical disinfection, as in healthcare facilities.

➢ Analysis of 22 studies reveals that human coronaviruses such as SARS coronavirus, MERS coronavirus or Human Coronavirus can persist on inanimate surfaces like metal, glass or plastic for up to 9 days. But can be efficiently inactivated by surface disinfection procedures with 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute. Ethanol (78-95%), Propan-2-ol (70-100%), the combination of 45% 2-Propanol with 30% 1-Proapanol, Glutardialdehyde (0.5-2.5%), formaldehyde (0.7-1%) and povidone iodine (0.23-7.5%) readily inactivated coronavirus infectivity. So, WHO recommends “to ensure that environmental cleaning and disinfection procedures are followed consistently and correctly to prevent viral transmission through surfaces due to

frequent touch. A concentration of 70% ethanol is also recommended by WHO for disinfecting small surfaces. WHO also recommends to preferably apply alcohol-based hand rubs for decontamination of hands. Two WHO recommended formulations (80% ethanol or 75% 2-propanol) have been evaluated in suspension tests against SARS-CoV and MERS-CoV and described to be very effective. Transmission in healthcare settings can be successfully prevented.

- Prevention of coronavirus infection also includes isolation of infected patients. Quarantine may be imposed on asymptomatic exposed persons.

➢ For general public, social distancing should be used as much as possible.

➢ For patients managed at home, patients are encouraged to self- isolate to single area of house, to practice good hand and cough hygiene and to wear face mask during any contact with household members. Household members should wear face masks, gown, gloves when caring for patient, remove and discard when leaving the room (do not reuse). Wash hands for at least 20 seconds, alcohol- based sanitizer is acceptable, if soap and water are not available.

- In healthcare settings

➢ Provide patients with face mask and place the patient in closed room (with safeguard against air-borne transmission and frequent air exchange). Persons entering the room should follow standard, contact and airborne precautions: Gloves, gowns, eye protection and respirator (N95) with adherence to hospital donning and doffing protocols. Equipment used for patient care should be of single use (disposable) or should be disinfected between patients; as earlier said, WHO suggests using 70% ethanol.

12. Treatment

According to the World Health Organization (WHO), the Centre for Disease Control & Prevention (CDC) and the US Food & Drug Administration (FDA), there are no specific therapies approved for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 COVID-19. Multiple agents are under investigation based on in vitro activity (against SARS-CoV-2 or related viruses) and on limited clinical experience. Efficacy has not been established for any drug therapy.

Goals: Ensure adequate oxygenation and hemodynamic support during acute phase of illness. For direct antiviral treatment of SARS-CoV-2, China International Exchange and Promotive Association for Medical Healthcare (CPAM) recommends use of lopinavir; ritonavir [2

capsule (dose undefined) by mouth twice daily] in combination with nebulized alfa-interferon (5 million units in Sterile Water for Injection inhaled twice daily). In addition to CPAM, a group of Korean physicians with experience in treating SARS-CoV-2 infected patients have developed recommendations for the treatment of COVID-19. According to these physicians, antiviral medications are not recommended for use in young, healthy patients with mild symptoms and no underlying comorbid conditions.

However, treatment with lopinavir 400 mg; ritonavir 100 mg (2 tablets by mouth twice daily) or chloroquine (500 mg by mouth twice daily) should be considered for use in older patients or patients with underlying conditions and serious symptoms. If chloroquine is unavailable, they recommend considering use of hydroxychloroquine (400 mg by mouth once daily).

- **Antimicrobials with potential activity against SARS-CoV-2**

1. **Remdesivir –** Investigational antiviral available under an FDA Emergency Use Authorization (EUA); data from several large clinical trials suggest clinical benefit.
2. **Chloroquine –** In vitro and limited early clinical data suggested potential benefit; FDA EUA revoked due to lack of data to support efficacy.
3. **Hydroxychloroquine –** In vitro and limited early clinical data suggest potential benefit; FDA EUA revoked due to lack of data to support efficacy.
4. **Lopinavir; Ritonavir –** Preclinical data suggested potential benefit; however, more recent data failed to confirm.
5. **Ivermectin –** In vitro data suggest activity; however, clinical data are limited and potential doses may far exceed those approved in humans.
6. **Favipiravir –** Broad spectrum investigational antiviral; licensed in other countries for treatment of influenza.

- Potential treatment options include:

➢ Remdesivir (GS-5734) is an investigational nucleotide analogue, which is broad spectrum antiviral, initially developed to treat Ebola, but it is a nucleotide analogue that mimics adenosine, one of the building blocks of any RNA virus's genome. Remdesivir interfere with the RNA dependent RNA POLYMERASE, the enzyme that viruses use to copy their genomes, so, the virus cannot replicate anymore, so it's a very logical target to begin with. Remdesivir exerts effects on the MERS-COV polymerase via delayed RNA chain termination. This means that when viral polymerase incorporates analogue instead of the natural nucleotide, it adds three more nucleotides and then stops. When it can't copy it's

genome, the virus can't reproduce and make it's host sick. It is hypothesized that the extra three nucleotides may protect the drug from being removed by the coronavirus's exonuclease enzyme.

In preclinical trials, Remdesivir has demonstrated significant activity against coronavirus and a high genetic barrier to resistance. Remdesivir has shown prophylactic and therapeutic efficacy against 2002 SARS-COV in a mouse model. Resistance mutations have not been identified.

The NIH COVID-19 treatment guidelines recommend the following regarding use of remdesivir:

- There is insufficient evidence to recommend for or against treating patients with mild to moderate COVID-19 (i.e., non-hospitalized patients or hospitalized patients that do not require supplemental oxygen).
- For hospitalized patients who require supplemental oxygen BUT NOT high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, remdesivir either alone or in combination with a corticosteroid is recommended.
- For patients who initially started on remdesivir monotherapy and then progressed to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, the NIH add a corticosteroid and continue remdesivir until the treatment course is completed.
- Remdesivir therapy may be stopped early if patient is discharged from hospital or may be extended up to 10 days if no improvement is observed at day 5.

➢ Corticosteroids : The World Health Organization (WHO) strongly recommends use of systemic corticosteroids (for 7 to 10 days) to treat patients with severe or critical COVID-19; but suggests against use of corticosteroids in patients with non-severe COVID-19.

➢ COVID-19 Convalescent Plasma:

- Plasma collected from persons who have recovered from COVID-19 that may contain antibodies to SARS-CoV-2.
- Administration of plasma from persons who have recovered from COVID-19 provides antibodies to the recipient, which may neutralize the virus and reduce disease progression.

- Potential benefits include improvement in symptoms, reduced need for supplemental oxygen or mechanical ventilation, and reduced mortality. COVID-19 convalescent plasma is not intended for prevention of the infection.
- Nondrug and supportive care includes oxygenation, ventilation and fluid management guided by WHO:

❖ Oxygenation and Ventilation: Nasal Cannula at 5L/minute, SpO2 of 90% or higher in non-pregnant adults and children, SpO2 of 92% or higher in pregnant patients, SpO2 of 94% or higher in children who require urgent resuscitation. Mechanical ventilation may be necessary for patients in whom oxygenation targets cannot be met with less invasive measures or who cannot maintain the work of breathing; recommended settings are tidal volume of 4 to 8 ml/kg and inspiratory pressures less than 30 cm water.

❖ Fluid management: Over hydration should be avoided, because it may precipitate or exacerbate acute respiratory distress syndrome. In patients with shock; administration of crystalloids (saline or lactated Ringer solution) is recommended, to maintain arterial pressure.

13. CONCLUSION

The novel coronavirus originated from China and rapidly spread up to 188 countries. This proves that the pandemic has led to global socio-economic disruption. Until now, no promising clinical treatments or prevention strategies have been developed against human coronaviruses. However, the researchers are working to develop efficient therapeutic strategies to cope with the novel coronaviruses. Various broad-spectrum antivirals previously used against influenza, SARS and MERS coronaviruses have been evaluated either alone or in combinations to treat COVID-19 patients, mice models, and clinical isolates. Remdesivir, Lopinavir, Ritonavir, and Oseltamivir significantly blocked the COVID-19 infection in infected patients. It can be concluded that the homologous recombination event at the S protein of RBD region enhanced the transmission ability of the virus. While the decision of bring back the nationals from infected area by various countries and poor screening of passengers, become the leading cause of spreading virus in others countries. Most importantly, human coronaviruses targeting vaccines and antiviral drugs should be designed that could be used against the current as well as future epidemics. There are many companies working for the development of effective SARS-CoV-2 vaccines, such as Moderna Therapeutics, Inovio Pharmaceuticals, Novavax, Vir Biotechnology, Stermirna Therapeutics, Johnson & Johnson, VIDO-InterVac, GeoVax-BravoVax, Clover Biopharmaceuticals,

CureVac, and Codagenix. But there is a need for rapid human and animal-based trails as these vaccines still require 3 to 10 months for commercialization. There must be a complete ban on utilizing wild animals and birds as a source of food. Beside the development of most efficient drug, a strategy to rapidly diagnose SARS-CoV-2 in suspected patient is also required. The signs and symptoms of SARS-CoV-2 induced COVID-19 are a bit similar to influenza and seasonal allergies (pollen allergies). Person suffering from influenza or seasonal allergy may also exhibit temperature which can be detected by thermo-scanners, hence the person will become suspected. Therefore, an accurate and rapid diagnostic kit or meter for detection of SARS-CoV-2 in suspected patients is required, as the PCR based testing is expensive and time consuming. Chinese doctors have efficiently controlled the outbreak in china and limited the mortality rate to less than 3% only. The therapeutic strategies used by Chinese, should also be followed by other countries.

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