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DIAGNOSIS AND MANAGEMENT OF NOVEL CORONAVIRUS 2019: A RAPIDLY EVOLVING GLOBAL HEALTH THREAT

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ABSTRACT
The outbreak of Coronavirus Disease 2019 (COVID-19) has drastically impacted the lives of people globally so far. A new cluster of infections of *COVID*-19 have been reported from the pandemic's first epicenter Wuhan, China, and has a rapid progression to other countries. The clinical symptoms of COVID-19 patients include fever, dry cough, dyspnoea, chest pain fatigue and myalgia with a small population of patients complaining of headache, dizziness, abdominal pain, diarrhoea, nausea and vomiting. The elderly population with age above 70 yrs with comorbidities like diabetes, chronic obstructive pulmonary disease (COPD), hypertension, obesity and cancer are vulnerable to serious outcomes like acute respiratory distress syndrome (ARDS) and cytokine storm. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS- CoV) are two highly transmissible and pathogenic viruses that have emerged in humans at the beginning of the 21st century. These viruses are also most likely thought to be originated from bats. At present, there are very few antiviral medications, but several potent candidates of antivirals and repurposed drugs are under serious investigation. This paper summarizes the current knowledge on coronaviruses, their pathogenesis, clinical manifestations, and finally treatment strategies to combat this pandemic of COVID-19.

KEYWORDS:
Coronavirus, COVID-19, pathogenesis, pandemic, antiviral

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1. INTRODUCTION

On 31st December 2019, the cluster of cases of pneumonia of unknown etiology was identified in Wuhan City, Hubei province in China. These patients most notably had clinical symptoms of dry cough, dyspnoea, fever, and bilateral lung infiltrates on imaging. Cases were all associated with Wuhan's Seafood Wholesale Market, which trades in live animal species including poultry, bats, marmots, and snakes (1) . The causative agent was identified from throat swab samples and subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Indeed, coronaviruses are recognized to cause respiratory and intestinal infections in animals and humans. They were not considered as highly pathogenic to humans until the outbreak of severe acute respiratory syndrome (SARS) in 2002 and 2003 in Guangdong province, China. The most recent outbreak of corona virus disease 2019 (currently known as COVID -19), which lead to severe respiratory disease in humans, has been a potential threat to human health attracting worldwide attention after SARS, another highly pathogenic coronavirus, Middle East Respiratory Syndrome Coronavirus (MERS- CoV) emerged in Middle Eastern countries in 2012. SARS coronavirus (SARS- CoV) uses angiotensin- converting enzyme 2 (ACE2) as a receptor and primarily infects ciliated bronchial epithelial cells and type II pneumocytes whereas MERS- CoV uses dipeptidyl peptidase 4 (DPP4; also known as CD26) as a receptor and infects unciliated bronchial epithelial cells and type II pneumocytes SARS- CoV and MERS- CoV were transmitted directly to humans from market civets and dromedary camels, respectively, and both viruses are thought to have originated in bats (2). In current times, the World Health Organization (WHO) has declared the coronavirus infectious disease (coronavirus Infectious disease 2019, termed COVID19) as a pandemic caused by a newly discovered coronavirus strain named 'severe acute respiratory syndrome coronavirus 2 or SARS-Cov-2 (3). Although all the coronaviruses have the ability to infect humans and develop severe respiratory syndrome, the novel virus has been considered as superior than other coronaviruses, i.e., SARS, MERS, and influenza. The number of confirmed cases of COVID -19 are higher than the total number of suspected SARS cases. They cause several diseases involving respiratory, enteric, hepatic, and neurological systems with varying severity among humans and animals. In addition, it was found that SARS-CoV-2 has a higher binding affinity to ACE2 receptors. Therefore soluble ACE2 may be a potential candidate for the treatment of COVID-19(4).

2. PHYLOGENETIC TREE OF CORONAVIRUS

Coronavirus belongs to the family of *Coronavirinae*, order *Nidovirales* based on the crown or halo-like appearance given by the glycoprotein-studded envelope on electron microscopy.They are large, pleomorphic RNA viruses characteristically containing crown-shape peplomers with 80-160 nm in size and 27-32 kb positive polarity. Coronaviruses include four genera — *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and

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Deltacoronavirus. The *alphacoronaviruses* and *betacoronaviruses* were found to infect only mammals. Infact, bats and rodents are thought to be the reservoir for alphaCoV and betaCoV. In addition, gamma coronaviruses and deltacoronaviruses were found to infect birds, but some of them can also infect mammals. (5) Alphacoronaviruses and betacoronaviruses usually cause respiratory illness in humans and gastroenteritis in animals(6). Only six human coronaviruses (HCoVs) were known till 2019, which could be held responsible for respiratory diseases. Out of these, four (HCoV–229E, OC43, NL63, and HKU1) are endemic globally and cause upper respiratory infections in immunocompetent hosts, although some of them can cause severe infections in infants, young children and elderly individuals. The other two, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are known to cause severe lower respiratory tract. On the basis of current sequence databases, all human coronaviruses were found to have animal origin. SARS- CoV, MERS- CoV, HCoV- NL63 and HCoV-229E are considered to have originated in bats; HCoV- OC43 and HKU1 likely originated from rodents(7). Moreover, domestic animals also act as intermediate hosts facilitate virus transmission from natural hosts to humans. Domestic animals themselves can suffer disease caused by bat- borne or closely related coronaviruses: genomic sequences highly similar to PEDV were detected in bats, and Swine acute diarrhoea syndrome coronavirus SADS- CoV is a recent spill over from the faeces of horseshoe bats to pigs. (8)

3. CHARACTERISTICS OF COVID 19

3.1` Incubation Period

It is the time from infection to onset of illness. The incubation period for COVID-19 is considered as 14 days following exposure, with most cases occurring approximately four to five days after exposure. The clinical manifestations of COVID-19 range from asymptomatic/mild symptoms to severe illness leading to mortality. Common symptoms include fever, cough, and shortness of breath. In a study of 1099 patients from China with laboratory-confirmed symptomatic COVID-19, the median incubation period was four days (interquartile range, 2 to 7). Another study including 181 confirmed cases reported a mean incubation period of approximately 5 days, and those symptoms would develop in 97.5% of infected individuals within 12 days. Based on the incubation period of SARS-CoV and MERS-CoV, as well as observational data, the United States CDC (Centres for disease control & prevention) has estimated that symptoms of COVID-19 usually develop within 2-14 days after exposure. Hence, fourteen days has been accepted globally as time for restricting the movement of infected individuals (quarantine period).(9)

3.2 Modes of Transmission

SARS-CoV-2 virus is a *zoonotic coronavirus*, which evolved after SARS-CoV and MERS-CoV, but appears *to be* the only one with pandemic potential. It spreads from human to human due to close contact with an infected

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person, exposed to coughing, sneezing, respiratory or aerosol droplets. These aerosols droplets can penetrate the human body (lungs) via inhalation through the nose or mouth.(10) Droplet particles having size >5-10 µm in diameter are referred to as respiratory droplets, and when less than 5µm in diameter, they are referred to as droplet nuclei. Transmission of the COVID-19 virus can also occur by indirect contact with surfaces in the immediate environment or with objects used on the infected person (e.g., stethoscope or thermometer) and subsequently touching his/her mouth, nose, or eyes (11). Additionally, it has been shown experimentally that the virus can remain viable in aerosols for at least 3 hours, and can be transmitted in closed environments if inhaled into the lungs. Therefore, airborne transmission is a possibility during aerosol-generating procedures, e.g., endotracheal intubation, bronchoscopy, non-invasive positive-pressure ventilation, tracheostomy, cardiopulmonary resuscitation, etc.

Table1 respiratory routes of transmission (12)

Route of transmission	Particles involved	Characteristics
Contact. • Direct	• From an infected person	• direct transfer of virus from an infected person to a susceptible individual (via contaminated hands)
• Indirect	• Deposited on objects	• Virus transfer through contaminated objects
Airborne • Droplet	• Large respiratory Droplets (>5 µm). Remain suspended in air for few minutes • Travel only short distances (>1m)	• Short range transmission. • Direct inoculation of person through coughing/sneezing/ breathing of infected person. • Deposition mainly on mucous membranes and upper respiratory tract.
• Aerosol	• Aerosols, droplet nuclei (< 5 µm). • Remain in air for an almost infinite amount of time. • Travel over long distances (>1 m)	• Long range transmission. • Inhalation of aerosols in respirable size range. • Deposition along the respiratory tract, including the lower airways.

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3.3 Severity of Infection

It is still not clear, that how long an individual with COVID-19 remains infectious. The duration of infection is often measured indirectly by detection of viral RNA in respiratory specimens. Higher viral loads have been detected soon after symptom onset, suggesting that transmission may be more likely to occur in the earlier stages of infection. The viral shedding duration seems to vary according to disease severity. It has been found that around 90% of patients with milder symptoms had a negative viral RNA test on nasopharyngeal swabs by day 10 post-onset, while the test remained positive for a long time in all severe cases. On the other hand, it has been reported that the viral load detected in asymptomatic patients was similar to that in symptomatic subjects. Nevertheless, the extent to which this occurs remains to be determined. The magnitude of immune response diminishes, which increases the probability of re-infection within a year from initial exposure[13].

4. MOLECULAR STRUCTURE AND MECHANISM OF INVASION OF SARS-COV-2

SARS COV-2 has four structural proteins: S (Spike), E (Envelope), M (Membrane) and N (nucleocapsid) protein as shown in figure 1. The Nucleocapsid protein holds the RNA genome and Spike, Envelope and Membrane protein together creates a viral envelope. Coronaviruses mainly recognize their corresponding receptors on target cells through S proteins on their surface. M protein is the central organizer of coronavirus assembly and is most abundant on viral surface and defines the shape of the viral envelope. Envelope protein is the smallest of all major structural proteins on viral membrane. It releases viruses from the host cell and during viral replication, it is localized specifically at the endoplasmic reticulum and Golgi apparatus. Indeed, the nucleocapsid is present underneath the capsid where this protein is bound to viral single-stranded RNA. It inhibits host cell defence mechanism and assist viral RNA application(13).

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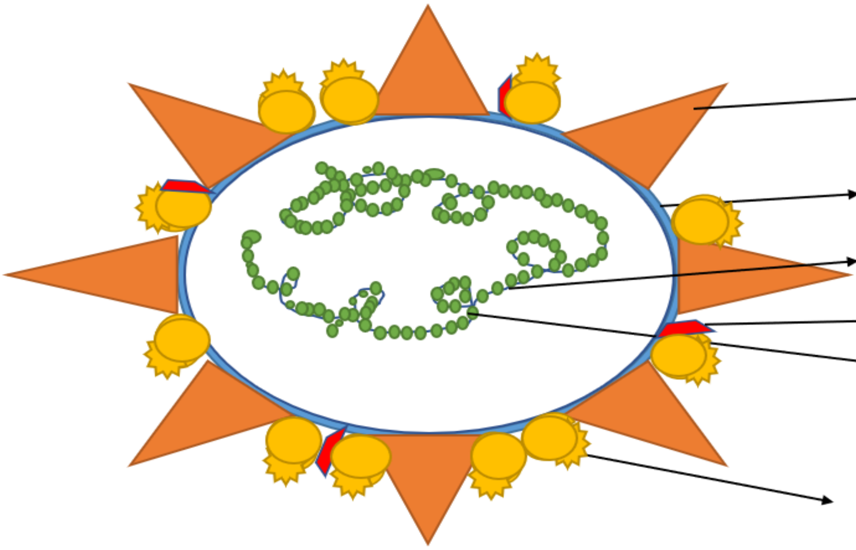

Figure1: Genetic structure of coronavirus

Mechanism:

It is assumed that human coronaviruses invade the cells, predominantly, by specific receptors. After the virus enters the host cell and uncoats, the genome is transcribed and then translated. A unique feature of replication is that all the mRNAs form a “nested set” with common 3′ ends; only the unique portions of the 5′ ends are translated. There are 7 mRNAs produced. The shortest mRNA codes for the nucleoprotein, and the others each direct the synthesis of a further segment of the genome. The proteins are assembled at the cell membrane and genomic RNA is incorporated as the mature particle forms by budding from internal cell membranes(7).

Steps include:

1. Binding of SARS COV-2 to host cells with viral spike engaging the cell surface protein Angiotensin-Converting Enzyme 2 or ACE-2.
2. The spike protein is cleaved by host protease to activate membrane fusion by TMPRSS2, which resides on the cell surface. After spike activation and membrane fusion, the single positive strand of viral RNA is released into host cystosol.
3. It is translated by the host ribosome into large polyproteins. They are immediately proteolyzed into smaller pieces by activity of proteases. And then the pieces then assemble to form RNA dependent RNA polymerase or replicase.

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4. The replicate creates full-length negative-strand genome as a template and full-length positive strand genome for packaging. The replicase also transcribes subgenomic RNA that encodes nucleocapsid protein and the transmembrane spike matrix and envelope protein.
   The nucleocapsid protein wraps up the new full length RNA genome, while transmembrane proteins are translated at Endoplasmic reticulum for transport into Golgi and exocytic vesicles.

5.Transmembrane proteins assemble around nuclear capsids to pinch them off into new variants within the exocytic vesicle. These are then released from cells upon exocytosis.

5. FACTORS CONTRIBUTING TO SPREAD PREVALENCE OF SARS COVID 19

The prevalence of COVID-19 is high; the population is generally susceptible to SARS-CoV-2. Immediate measures are clearly needed to control the spread of the disease. Using the Susceptible-Exposed-Infectious-Recovered (SEIR) model, Wu et al. estimated the R0 (Basic Reproduction number) of SARS-CoV-2 to be 2.47–2.86 (14) . The estimated R0 values of other β-coronaviruses, such as SARS-CoV, are 2.2–3.6. Although, in commonly used infection models, when $R_0 > 1$ the infection will be able to start spreading in a population, but not if $R_0 < 1$. Generally, the larger the value of R_0, the harder it is to control the epidemic (15). Therefore, these results indicate that SARS-CoV-2 has relatively high transmissibility.

6. CLINICAL INVESTIGATIONS

COVID-19 is found to target lower airway and leads to upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat. The clinical features of COVID-19 are varied, ranging from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction. The common clinical features include fever, cough, chill, sore throat, headache, fatigue, and breathlessness, dyspnoea, loss of taste or smell and lymphopenia. Additionally, patients infected with COVID-19 developed intestinal symptoms like diarrhoea on the other side only a low percentage of MERS-CoV or SARS-CoV patients exhibited diarrhoea. In a subset of patients, by the end of the first week, the disease can progress to pneumonia, respiratory failure and death. This progression is associated with an extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα (9). The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients>70-years old compared with those under the age of 70. In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs that likely induced both systemic and localized immune response that led to increase inflammation (16). The elderly people and those with underlying diseases (i.e., hypertension, chronic obstructive diabetes, cardiovascular disease,

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pulmonary disease,), are susceptible to coronavirus and develop rapidly acute respiratory distress syndrome, septic shock, metabolic acidosis and can lead to death.

7. DIAGNOSIS

Real time polymerase chain reaction (RT-PCR) is routinely used to detect causative viruses from respiratory secretions. During COVID-19 transmission events, RT-PCR has served as the primary clinical laboratory diagnostic test(17). There are various laboratory tests for coronavirus

Detection:

a. Chest imaging

Computerized tomography (CT) scans of the chest of symptomatic patients are useful before symptoms arise. Indeed, Chest radiography reveals patchy or diffuse asymmetric airspace cloudiness, similar to other causes of coronavirus pneumonia in symptomatic patients(18).

b. Nucleic acid amplification tests (NAAT)

Routine confirmation of cases of COVID -19 is based on the nucleic acid amplification tests (NAAT) by detecting unique sequences of viral RNA . This test can be performed by real -time reverse transcription polymerase chain reaction (RT -PCR) technique. Real -time RT -PCR is a popular technique in molecular biology for monitoring the amplification of a targeted DNA molecule in real time. Whereas RT -PCR combines reverse transcription of RNA into DNA and PCR amplification of the DNA followed by readout using fluorescence(19). The test is done by collecting respiratory or blood samples. The respiratory samples are obtained by a nasopharyngeal swab. The test results are generally available within a few hours to two days. Blood samples can be collected two times in two weeks apart and the results have little immediate value (CDC, 2020j). NAATs can be broadly divided into 4 roles:

- qualitative or quantitative parasite detection
- measurement of the multiplicity of infection,
- genotyping to differentiate recrudescence from reinfection, and
- identification of drug resistance mutations.

c. Serological testing

Cases that have a strong epidemiological connection to COVID -19 infection with consideration of past events or conditions and NAAT assays are found to be negative but, serological surveys can be used for testing for investigation of the ongoing outbreak (WHO, 2020g) . For this purpose, paired serum samples could support diagnosis once validated serology tests are available. (20)

8. TREATMENT AND PREVENTION

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. Though, a randomized multicentre controlled clinical trial is currently undergoing to assess the efficacy and safety of abidole in patients with COVID-19(21) . First-line treatment for fevers include antipyretic therapy such as paracetamol, whilst expectorants such as guaifenesin may be used for a non-productive cough. Isolation and supportive care including oxygen therapy, fluid management, and antibiotics treatment for secondary bacterial infections is recommended. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock. (22).

In a recent phase II clinical trial by the researchers, it was found that a combination of 3 drugs— interferon beta-1b, lopinavir-ritonavir, and ribavirin plus standard care is successful in treating mild-to-moderate cases of covid-19. It also shortens the duration of viral shedding — that is, the period during which the virus is detectable in a person’s body and transmissible to others (23). Remdesivir was the first drug reported to treat the first US case of COVID-19 successfully. Although, Chloroquine drug because of its immunomodulator effects, suppressing the production/release of TNF-α and IL-6, interferes with viral infection and replication and has a potent effect on SARS-CoV infection and spread. It was also believed to have great potential to treat COVID-19. Several studies have revealed that chloroquine interfered with the glycosylation of cellular receptors of SARS-CoV. On March 28, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the anti-malaria drugs hydroxychloroquine and chloroquine for the treatment of severe COVID-19 symptoms. However, the FDA released a statement on April 24, 2020, cautioning that both medications carry the risk of “serious and potentially life- threatening heart rhythm problems.”

On May 1, 2020, the FDA granted another EUA for the investigational antiviral drug remdesivir. A combination of chloroquine and remdesivir was proven to efficiently inhibit the recently emerged SARS-CoV-2 in vitro. Scientists previously confirmed that the protease inhibitors lopinavir and ritonavir, used to treat the infection with human immunodeficiency virus (HIV) , could improve the outcome of MERS-CoV and SARSCoV patients. It has reported that lopinavir/ritonavir dug decreased the β-coronavirus viral loads of a COVID-19 patient in Korea after treatment. Additionally, clinicians combined Chinese and Western medicine treatment including lopinavir/ritonavir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine) and gained significant improvement in pneumonia associated symptoms in Shanghai Public Health Clinical Center, China. The other antiviral drugs include nitazoxanide, favipiravir, nafamostat, and so on (Table

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1) (24). Indeed, The U.S. Department of Health and Human Services (DHHS) predicts that a COVID-19 vaccine will be available for emergency use in the U.S. by 2021.

WHO released a document summarizing WHO guidelines and scientific evidence derived from the treatment of previous epidemics from HCoVs on January 28, 2020. This document addresses measures for recognizing and sorting patients with severe acute respiratory disease; strategies for infection prevention and control; early supportive therapy and monitoring; a guideline for diagnosis; management of respiratory failure, septic shock, treatments, and considerations for pregnant patients.

Among these recommendations, strategies for addressing respiratory failure, including protective mechanical ventilation and high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) includes:

a) Intubation and protective mechanical ventilation

Special precautions are necessary during incubation. The procedure should be executed by an expert operator who uses personal protective equipment (PPE) such as FFP3 or N95 mask, protective goggles, disposable gown long sleeve raincoat, disposable double socks, and gloves. If possible, rapid sequence intubation (RSI) should be performed.

Mechanical ventilation should be with lower tidal volumes (4 to 6 ml/kg predicted body weight, PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H2O. PEEP must be as high as possible to maintain the driving pressure (Pplat-PEEP) as low as possible (< 14 cmH2O). Moreover, disconnections from the ventilator must be avoided for preventing loss of PEEP and atelectasis.

b) Non-invasive ventilation

Concerning HFNO or non-invasive ventilation (NIV), the experts' panel, points out that these approaches performed by systems with good interface fitting do not create widespread dispersion of exhaled air, and their use can be considered at low risk of airborne transmission. Essentially, non-invasive techniques can be used in non-severe forms of respiratory failure. However, if the scenario does not improve or even worsen within a short period of time (1–2 hours,) the mechanical ventilation must be preferred.

Table 1: Common antiviral drugs used for treatment

Drugs	Target diseases	Mechanism
Chloroquine	Malaria, autoimmune disease	Inhibits HCoV-OC43 replication in HRT-18 cell(25)
Ivermectin	HIV, SARS	Inhibit IMPα/β1-mediated nuclear import of viral proteins(26)
Lopinavir/ Ritonavir	HIV/AIDS, SARS, MERS	Inhibiting HIV-1 protease, resulting in non-infectious, immature viral particles(27)
Ribavirin	HCV, SARS, MERS	Interfering with the synthesis of viral mRNA (a broad-spectrum activity against several RNA and DNA viruses)
Ganciclovir	AIDS-associated cytomegalovirus infections	Potent inhibitor of the Herpesvirus family including cytomegalovirus(28)
Remdesivir	Ebola, SARS, MERS	Interfering with virus post-entry(29)
Nitazoxanide	MERS coronavirus	Inhibits the replication of a broad range of influenza A and B strains including influenza A subtypes H1N1, H3N2, H3N2v, H3N8, H5N9, H7N1 and oseltamivir- and amantadine-resistant strains .(30)

Prevention and control strategies and methods are reported at three levels: national level, case-related population level, and general population level. At the national level, medical institutes can adopt isolation treatment and observation protocols to prevent and control the spread of the COVID-19. On 22 January 2020, the National Health Commission published national guidelines for the prevention and control of COVID-19 for medical institutes to prevent nosocomial infection. National-level strategies have also been issued with targeted measures for rural areas (issued on 28 January 2020) and the elderly population (issued on 31 January 2020)(31).Preventive strategies are focused on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an

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infected patient. For instance, droplet, contact, and airborne precautions should be adopted during specimen collection, and sputum induction should be avoided(32).

The WHO and other organizations have issued the following general recommendations:

- Wash hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- Avoid close contact with subjects suffering from acute respiratory infections.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Maintain hygienic measures for the prevention and control of infections.
- Individuals with weak immunity should avoid public gatherings.

The most important strategy for the populous to undertake is to frequently wash their hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment.

Healthcare workers caring for infected individuals should utilize the contact and airborne precautions to include PPE such as N95 or FFP3 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.

Indeed, the guideline also suggests eliminating, panic among the general population and handle the problem.

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10. CONCLUSION AND FUTURE PROSPECTS

The recent COVID-19 outbreak has been deemed a global health emergency. Internationally, the number of confirmed reports has continued to rise. Evidently, the pandemic potential of COVID-19 demands rigorous surveillance and on-going monitoring to accurately track and potentially predict its future host adaptation, evolution, transmissibility, and pathogenicity.

At the moment, there is no vaccine and no specific treatment for COVID-19. Since COVID-19 is very comparable to SARS-CoV. Therefore, some important features of SARS epidemic are guiding the predictions on the current pandemic. It is perhaps clear that quarantine alone may not be sufficient to prevent the spread of COVID-19, and the global impact of this viral infection is one of heightening concern. The likelihood of transmission can be reduced by practicing hygienic measures and social distancing. Indeed, rapid diagnosis with quarantine and integrated interventions will have a prodigious effect on upcoming trends of the outbreak.

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