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A Review on Transmission, Prevention, Diagnosis and Treatment of the Novel Corona Virus Syndrome - COVID-19

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ABSTRACT

Since the outbreak of the novel coronavirus in December 2019 in Wuhan China, this novel coronavirus disease (COVID-19) has spread worldwide taking not only epidemic proportions but with its rapid spread World Health Organisation (WHO) was forced to declare it as a pandemic. The Severe Acute Respiratory Syndrome (SARS)-coronavirus (CoV2) is responsible for clusters of severe respiratory illness that simulates acute respiratory syndrome that was what was initially. More experience is getting acquired with changes in treatment approaches to avoid intubation and just ensure oxygen levels maintained. Human to human transmission through droplets, contaminated hands as well as surfaces, has been revealed with an incubation period varying from 2-14 days. Early diagnosis using Reverse Transcription Polymerase Chain Reaction (RT-PCR), quarantine, plasma therapy as well as supportive treatment are necessary for getting a cure. In this review we have tried to analyze the transmission, prevention, diagnosis and treatment of the novel coronavirus syndrome COVID-19.

INTRODUCTION

Coronaviruses are a large family of viruses which may cause illness in animals or humans. Bats have been identified as the natural reservoirs as well as vectors of a lot of coronaviruses; with these viruses having crossed species barriers to infect humans as well as many various types of animals, including avian, rodents and chiropters. In humans, several corona viruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes corona virus disease novel COVID-19. It is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. It has now spread to 200 other countries including India. The World Health Organization (WHO) declared that COVID-19 has assumed pandemic proportions, causing severe Respiratory Tract Infections (RTI) in humans. The aim, therefore, is to collect information and scientific evidence and to provide an overview of the topic that will be continuously updated.

Transmission:

Respiratory infections can be transmitted through droplets of different sizes, when the droplet particles are >5-10 μm in diameter they are referred to as respiratory droplets, and when they are <5μm in diameter, referred to as droplet nuclei.[1] According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes.[2-7] In an analysis of 75,465 COVID-19 cases in China, airborne transmission was not reported.[8]

Droplet transmission occurs when a person is in close contact (within 1 m) with someone who has respiratory symptoms (e.g., coughing or sneezing) and is therefore at risk of having his/her mucosae (mouth and nose) or conjunctiva (eyes) exposed to potentially infective respiratory droplets. Transmission may also occur through fomites in the immediate environment around the infected person.[8] Therefore, transmission of the COVID-19 virus can occur by direct contact with infected people and indirect contact with surfaces in the immediate environment or with objects used on the infected person (e.g., stethoscope or thermometer).

In the context of COVID-19, airborne transmission may be possible in specific circumstances and settings in which procedures or support treatments that generate aerosols are performed; i.e., endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation.

Understanding the modes of transmission of emerging infectious disease is a key factor in protecting healthcare workers and implementing effective public health measures. The lack of 5 evidence on SARS-CoV-2 transmission dynamics has led to shifting isolation guidelines between airborne and droplet isolation precautions by the WHO, U.S. CDC and other public health authorities. Other emerging coronaviruses (e.g. SARS and MERS) have been suggested to have airborne transmission potential [9,10] in addition to more direct contact and droplet transmission. At least one study suggests that MERS-CoV has the possibility of transmission from mildly ill or asymptomatic individuals.[11] Surface samples taken in patient care areas for MERS and SARS have shown positive PCR results[10]; however, experts question the possibility of transmission through contact with surfaces that have been contaminated by an infected person, either by the direct contact of the infected person or the settling of virus-laden particles onto the surface.[12] Nonetheless, coronaviruses have been implicated in nosocomial outbreaks with 15 reports of transmission related to environmental contamination.[13,14] Nosocomial transmission of SARS-CoV-2 has been reported, but the role of aerosol transmission and environmental contamination remains unclear.[15]

There is some evidence that COVID-19 infection may lead to intestinal infection and be present in faeces. However, to date only one study has cultured the COVID-19 virus from a single stool specimen.[16] There have been no reports of faecal–oral transmission of the COVID-19 virus to date.

Epidemiology:

A study of the early transmission dynamics of COVID-19 showed that the mean incubation period was 5.2 days (95% confidence interval [CI], 4.1-7.0) with the 95% percentile of the distribution at 12.5 days.[17] A later study utilizing the travel history and symptom onset of 88 confirmed cases demonstrated a similar mean incubation period of 6.4 days (95% confidence interval [CI], 5.6-7.7).[18] An unusual case was also documented where incubation period was as long as 19 days.[19] The 19 day incubation period is a low probability event and experts point that a 14 days of quarantine is required usually.

The most up-to-date source for the epidemiology of this emerging pandemic can be found at the following sources:

- The WHO Novel Coronavirus (COVID-19) Situation Board

- The Johns Hopkins Center for Systems Science and Engineering site for Coronavirus Global Cases COVID-19, which uses openly public sources to track the spread of the epidemic.

Prevention:

Based on current evidence, the COVID-19 virus is transmitted between people through close contact and droplets. Airborne transmission may occur during aerosol-generating procedures and support treatments (e.g. tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy) [20]; thus, WHO recommends airborne precautions for these procedures.

For all, the most effective preventive measures include:

• maintaining physical distance (a minimum of 1 metre) from other individuals;

• performing hand hygiene frequently with an alcohol-based hand rub if available and if your hands are not visibly dirty or with soap and water if hands are dirty;

• avoiding touching your eyes, nose, and mouth;

• practicing respiratory hygiene by coughing or sneezing into a bent elbow or tissue and then immediately disposing of the tissue;

• wearing a medical mask if you have respiratory symptoms and performing hand hygiene after disposing of the mask;

• routine cleaning and disinfection of environmental and other frequently touched surfaces.

In health care settings, the main Infection Prevention and Control (IPC) strategies to prevent or limit COVID-19 transmission include the following: [21]

1. Ensuring triage, early recognition, and source control (isolating suspected and confirmed COVID-19 patients);

2. Applying standard precautions [22] for all patients and including diligent hand hygiene;

3. Implementing empiric additional precautions (droplet and contact and, wherever applicable for aerosol-generating procedures and support treatments, airborne precautions) for suspected and confirmed cases of COVID-19;

4. Implementing administrative controls;

5. Using environmental and engineering controls. [23]

Standard precautions are meant to reduce the risk of transmission of blood borne and other pathogens from both recognized and unrecognized sources. They are the basic level of infection control precautions to be used, as a minimum, in the care of all patients.

Additional transmission-based precautions are required by health care workers to protect themselves and prevent transmission in the health care setting. Contact and droplets precautions should be implemented by health workers caring for patients with COVID-19 at all times. Airborne precautions should be applied for aerosol-generating procedures and support treatments.

Although use of PPE is the most visible control used to prevent the spread of infection, it is only one of the IPC measures and should not be relied on as a primary prevention strategy. In the absence of effective administrative and engineering controls, PPE has limited benefit, as described in WHO's infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care. These controls are summarized here.

Administrative controls include ensuring resources for infection prevention and control (IPC measures, such as appropriate infrastructure, the development of clear IPC policies, facilitated access to laboratory testing, appropriate triage and placement of patients, including separate waiting areas/rooms dedicated to patients with respiratory symptoms, and adequate staff-to-patient ratios, and training of staff. In the case of COVID-19, consideration should be given, wherever possible, to establish differentiated care pathways that minimize mixing of known or suspected COVID-19 patients with other patients (e.g. through separate health facilities, wards, waiting, and triage areas).

Environmental and engineering controls aim at reducing the spread of pathogens and the contamination of surfaces and inanimate objects. They include providing adequate space to allow social distance of at least 1 m to be maintained between patients and health care workers and ensuring the availability of well-ventilated isolation rooms for patients with suspected or confirmed COVID-19, as well as adequate environmental cleaning and disinfection.[23]

Coveralls, double gloves, or head covers (hood) that cover the head and neck used in the context of filovirus disease outbreaks (e.g. Ebola virus) are not required when managing COVID-19 patients. WHO has recently summarized reports of transmission of the COVID-19 virus and provided a brief overview of current evidence on transmission from symptomatic, pre-symptomatic, and asymptomatica people infected with COVID-19 (full details are provided in WHO COVID-19 Situation report 73).[24]

Current evidence suggests that most disease is transmitted by symptomatic laboratory confirmed cases. The incubation period for COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days. During this period, also known as the "pre-symptomatic" period, some infected persons can be contagious and therefore transmit the virus to others.[25-30] In a small number of reports, pre-symptomatic transmission has been documented through contact tracing efforts and enhanced investigation of clusters of confirmed cases.[25-30] This is supported by data suggesting that some people can test positive for COVID-19 from 1-3 days before they develop symptoms.[31,32]

Thus, it is possible that people infected with COVID-19 could transmit the virus before symptoms develop. It is important to recognize that pre-symptomatic transmission still requires the virus to be spread via infectious droplets or through touching contaminated surfaces. WHO regularly monitors all emerging evidence about this critical topic and will provide updates as more information becomes available.

In this document medical masks are defined as surgical or procedure masks that are flat or pleated (some are shaped like cups); they are affixed to the head with straps. They are tested according to a set of standardized test methods (ASTM F2100, EN 14683, or equivalent) that aim to balance high filtration, adequate breathability and optionally, fluid penetration resistance. This document does not focus on respirators; for guidance on use of respirators see IPC guidance during health care when COVID-19 infection is suspected.[33]

Wearing a medical mask is one of the prevention measures that can limit the spread of certain respiratory viral diseases, including COVID-19. However, the use of a mask alone is insufficient to provide an adequate level of protection, and other measures should also be adopted. Whether or not masks are used, maximum compliance with hand hygiene and other IPC measures is critical to prevent human-to-human transmission of COVID-19. WHO has developed guidance on IPC strategies for home care [34] and health care settings[33] for use when COVID-19 is suspected.

Diagnosis:

The identification COVID-19 cases due to community transmission are one of the most importance focuses of the laboratory diagnosis of infection. Following analytical methods are performed for diagnosis and screening of the patients with COVID-19 infections.

1. Pre-Analytical Issues

Within 5 – 6 days of the onset of symptoms, patients with COVID-19 infections have demonstrated high viral loads in their upper and lower respiratory tract.[35-38] A nasopharyngeal (NP) swab and/or an oropharyngeal (OP) swab are often recommended for screening or diagnosis early infection.[36,39,40] Ideally, sputum or bronchoalveolar lavage should be used for collecting lower respiratory tract specimens as they yielded highest viral loads for the diagnosis of COVID-19.[41,42]

Processing of respiratory specimen should be done in a class II biological safety cabinet.[39,43,44] Ideally, some would argue that biosafety level three (BSL3) work procedures should be used and that the safety cabinet should be in a negative pressure room within the laboratory such as done for mycobacterial cultures. For nucleic acid extraction before real-time RT-PCR is performed, the specimen should be transferred to lysis buffer under this BSL-2 cabinet. This lysis buffer should contain a guanidinium-based inactivating agent as well as a non-denaturing detergent. Indeed, the buffers included in common commercial extraction platforms, such as the bioMerieux easy MAG or QIAGEN EZ1, do contain guanidium/detergents and are able to inactivate any viable coronavirus.[45-47] Because this test is a reverse transcription method, the saliva/swabs used to collect the clinical specimens should be quickly added to lysis buffer to disinfect the specimen as well as to stop degradation of the coronavirus RNA cabinet.[39,43,44] The clinical specimens/swabs should not be heated to 56°C for 30 minutes as evidence suggests that this process may also degrade the coronavirus RNA, even as it inactivates viable coronavirus.[39,48]

2. Analytical Issues

Immunoassays have been developed for rapidly detection of SARS-CoV-2 antigens or antibodies. These rapid point-of-care immunoassays are generally lateral flow assays. Such lateral flow assays have been developed for detecting antigens such as the SARS162 CoV-2 virus or for detecting antibodies (IgM and IgG] against COVID-19 infections.

Rapid antigen lateral flow assays would theoretically provide the advantage of fast time to results and low-cost detection of SARS-CoV-2 but are likely to suffer from poor sensitivity based on the experience with this method for influenza (Flu) viruses.[49-53] Monoclonal antibodies specifically against SARS-CoV-2 have been under preparation, and several rapid antigen assays are being developed. There is concern that given the variability of viral loads in COVID-19 patients, antigen detection may miss cases due to low infectious burden or sampling variability. Serology measures the host response to infection and is an indirect measure of infection that is best utilized retrospectively. Serological methods are rapidly being developed and have proven to be useful in confirming COVID-19 infection.[54] Serology previously has had an important role in the epidemiology of SARS [55] and other coronavirus outbreaks.[56]

Random-amplification deep sequencing methods played a major role in the initial identification of SARS-CoV-2. [57-61] Deep sequencing molecular methods such as next generation sequencing and metagenomic next generation sequencing will continue to be needed to determine future mutations of SARS CoV-2 but are currently impractical for diagnosing COVID-19 infections. Most of the molecular diagnostics being developed for the diagnosis of COVID-19 infections involve real-time RT-PCR assays including those from the US Centers for Disease Control and Prevention.[62] Other molecular methods are being developed and evaluated worldwide and include loop-mediated isothermal amplification, multiplex isothermal amplification followed by microarray detection, and clustered regularly interspaced short palindromic repeats.[63]

A real-time RT-PCR method is recommended for molecular testing.[39,43,44] A major advantage of real-time RT-PCR assays is that amplification and analysis are done simultaneously in a closed system to minimize false-positive results associated with amplification product contamination. There are a number of coronaviruses that cause respiratory and intestinal infections in humans.[64,65] Among these coronaviruses are a group of SARS-like bat coronaviruses, including both SARS-CoV and SARS-CoV-2, that comprise a unique clad under the subgenus *Sarbecovirus*.[65,66] Coronaviruses have a number of molecular targets within their positive-sense, single-stranded RNA genome that can be used for PCR assays.[43,65,66]

3. Post-Analytical Issues

Monitoring patients with resolution of COVID-19 pneumonia may also be important in terms of when they should be released from isolation and discharged. If discharged patients are still shedding viable coronavirus, they are likely to infect others.[67] Therefore, self-quarantine for up to one month may be advisable. NP and OP swabs are not sufficient for either test of cure or test of infectivity.[68] The optimal method for test of cure most likely will be two consecutive negative real-time RT-PCR tests from rectal swabs; this suggestion is based on the fact that SARS-CoV-1 has been cultured from stool during the 2002- 2003 SARS outbreak [69,70] and SARS-CoV-2 has been culture from stool during the COVID- 19 outbreak.[71]

Members of the coronavirus family have four structural proteins: the Spike [S], Membrane [M], Envelope [E], and Nucleocapsid [N] proteins. Two of these proteins appear to be important antigenic sites for the development of serological assays to detect COVID-19. Serological methods have focused on detecting serum antibodies against S-proteins from the coronavirus spike.[56] The coronavirus envelope spike is responsible for receptor binding and fusion and determines host tropism and transmission capability.[65,66] S-proteins are determined by the S gene and are functionally divided into two subunits (S1 and S2). The S1 domain is responsible for receptor binding while the S2 domain is responsible for fusion. SARS CoV and SARS-CoV-2 bind to human angiotensin-converting enzyme 2, which is found on human respiratory cells, renal cells, and gastrointestinal cells.[65,72,73] The other proteins that appear to be important antigenic sites for the development of serological assays to detect COVID-19 are the N protein, which is a structural component of the helical nucleocapsid. The N protein plays an important role in viral pathogenesis, replication, and RNA packaging. Antibodies to the N protein are frequently detected in COVID-19 patient,[74,75] suggesting that the N protein may be one of the immunodominant antigens in the early diagnosis of COVID-19.[76]

Rapid lateral flow assays for antibodies (IgM and IgG) produced during COVID-19 infection have been developed.[77] Seroconversion occurred after 7 days in 50% of patients (14 days in all), but was not followed by a rapid decline in viral load. Serological methods, when available, will play an important role in the epidemiology of COVID-19 and in determining the immune status of asymptomatic patients, but are unlikely to play any role in screening or for the diagnosis of early infections.[38,74,75] However, serology may be useful for confirming the diagnosis of COVID-19 infection.[54]

Treatment:

The SARS-CoV2 virus broke out in December 2019.[78] There have been revisions of the Guidelines the [5th] edition of Guidelines advices antiviral like IFN-α, lopinavir/ritonavir as well as ribanivir for treating COVID-19. The particular method for delivering IFN-α is vapouring inhalation at a dose of 5 million units (as well as 2 ml of sterile water for injection) for adults, 2 times/day. Dosage of lopinavir/ritonavir is 400mg/100 mg for adults' 2 times/day. Ribanivir is given as intravenous infusion in a dose of 500 mg for adults 2-3 times/day combined with IFN-α or lopinavir/ritonavir. Chloroquine phosphate is given orally at a dose of 500 mg (300mg for Chloroquine) for adults 2 times/day. Arbidol is delivered orally at 200 mg dose for adults'. Duration of therapy is not higher than 10 days.[78]

Besides these drugs used in above Guidelines, favipiravir is a drug that needs more lime light. It got approved for the therapy of novel influenza on February 15th, 2020, in China. This drug is undergoing clinical trials for treating COVID-19. Favipiravir is a new kind of RNA-dependent RNA polymerase (RdRp) inhibitor. Hence favipiravir might have potential anti viral activities against SARS-CoV2. No significant side effects were observed in the favipiravir treated group, having significantly less side effects as compared to Lopinavir/Ritonavir group.[79]

Remdesivir is another drug which has potential benefits for treating COVID-19. It is a nucleoside analogue as well as broad spectrum antiviral. Animal experiments [80] pointed that Remdesivir can efficaciously reduce the viral load in lung tissue of mice infected with MERS-CoV, improve lung function as well as ameliorate pathological damage to lung tissue. The trial is expected to finish by end of April 2020. Currently, Remdesivir have been used maximum in treating severe patients with respiratory involvement needing ventilator.[81] Further studies have also demonstrated that darunavir, which is a second generation of HIV1 protease inhibitor, inhibited SARS-CoV2 infection *in vitro*.[82] Cell experiments pointed that darunavir inhibited viral replication markedly.[82] A research team of the Shanghai Institute of Material Medica did drug screening in silicon as well as enzyme activity test, revealing 30 compounds which have potential anti-viral activities against SARS-CoV2.[83] They also observed that Chinese herbal medicines might contain active ingredients against SARS-CoV2.[84]

Ivermectin is an FDA-approved broad spectrum antiparasitic agent,[85] which recently has been shown to have antiviral activity against a wide range of viruses *in vitro*.[86] Initially, was found as an inhibitor of interaction between the HIV-1 integrase protein (IN) and the importin (IMP) α/β1 heterodimer that causes IN nuclear import.[87] Since then, Ivermectin has been confirmed to inhibit IN nuclear import as well as HIV-1 replication.[88] It is suggested that Ivermectin has antiviral activities against SARS-CoV2 clinical isolates *in vitro*; with a single dose able to control viral replication within 24-48 h in their system.[89]

The structure of SARS-CoV2 S protein has been attained, which should help in the rapid generation as well as examination of medical countermeasures for tackling the continuing public health crises.[90] Most of the vaccines getting developed for Coronaviruses target the spike glycoproteins or S proteins.[91] Vaccines formation is a long process, and with no vaccine available at the time a pandemic outbreak. There are 18 biotechnology companies as well as Universities in China working on SARS-CoV2 vaccine. Even with Indo US collaboration efforts are being made to develop vaccines, some in trials till animal level, while development of nasal vaccines are also ongoing. Zhang et al detailed on the progress as well as our prospects on the field of vaccine developed against SARS-CoV2.[92]

Convalescent plasma transfusion was delivered early following symptoms onset in the therapy of SARS and the pooled odds of mortality after treatment.[93] The National Health of China appealed to convalescent patients to donate blood for the therapy of COVID-19 infection. Convalescent plasma needs to be collected within 2 weeks following recovery time to make sure a high neutralization antibody titer is recovered. The problem in getting plasma in the convalescence limits its clinical application. Well designed clinical trials are required to further examine the effectiveness as well as safety of convalescent plasma transfusion in patients with COVID-19 infection.

CONCLUSION

The CoVs have become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species. For reasons yet to be explained, these viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS. The potential for these viruses to grow to become a pandemic worldwide seems to be a serious public health risk. COVID-19 can be transmitted between humans. Preventive measures are the current strategy to limit the spread of cases. Wear masks, washing hands as well as disinfecting surfaces aid in decreasing the infection. Diagnosis using RT-PCR or antibodies is very important to decide the appropriate therapy. There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock. Different novel treatments are getting tried including remdesivir, favipiravir, hydroxychloroquin with azithromycin, ivermectin and in serious case acetazolamide, nifedipine along with PDE Inhibitors. Further convalescent plasma is being tried in USA along with other countries. Efforts are being made to get a vaccine as early as possible and lockdown the infection. The social distancing contact tracing and early testing to reduce the spread and mortality are now the main keys to prevent the infection. Individuals at the extreme of ages and those that are immunocompromised are at the most significant risk. All health care workers should understand the presentation of the disease, workup, and supportive care. Further, health professionals should be aware of the precautions necessary to avoid the contraction and spread of the disease.

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