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Corona: A Review on Current Clinical Sympathetic

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Abstract **Review Article**

Corona virus (COVID-19) is an enveloped RNA virus that is diversely found in humans and wildlife. A total of six species have been identified to cause disease in humans. They are known to infect the neurological, respiratory, enteric, and hepatic systems. The past few decades have seen endemic outbreaks in the form of Middle East Respiratory Syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome related coronavirus (SARS-CoV). Yet again, we see the emergence of another outbreak due to a new strain called the SARS-CoV-2 virus. The most recent outbreak initially presented as pneumonia of unknown etiology in a cluster of patients in Wuhan, China. The epicenter of infection was linked to *seafood and exotic animal* wholesale markets in the city. SARS-CoV-2 is highly contagious and has resulted in a rapid pandemic of COVID-19. As the number of cases continues to rise, it is clear that these viruses pose a threat to public health. This review will introduce a general overview of coronavirus and describe the clinical features, evaluation, and treatment of COVID-19 patients. It will also provide a means to raise awareness among primary and secondary healthcare providers during the current pandemic. Furthermore, our review focuses on the most up-to-date clinical information for the effective management, prevention, and counseling of patients worldwide. In December 2019, several patients from Wuhan, China were admitted with symptoms of pneumonia. As the number of patients presenting with similar symptoms started to rise, the causative agent was eventually isolated from samples. It was initially called the 2019 novel coronavirus (2019-nCoV) and has been recently relabelled as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); the disease it causes has been named coronavirus disease 2019 (COVID-19). Over the next few weeks, the virus spread from Wuhan to affect different provinces in China and, after a few months, it is now present in 109 countries. As of March 26, 2020, there have been 462,684 confirmed cases globally, and 20,834 deaths have been registered. The World Health Organization (WHO) called COVID-19 a pandemic on March 11, 2020. There are multiple drug trials going on with some positive results. However, since no vaccine is available, the best way to combat the virus is by preventive methods. In this review article, we provide a basic understanding of CoV infections and their potentially detrimental involvement to society.

Keywords: Corona, Clinical Sympathetic, COVID-19, SARS-CoV-2.

INTRODUCTION & BACKGROUND

On February 11, 2020, the World Health Organization (WHO) announced the disease caused by this novel virus as coronavirus disease-2019 (COVID-19). The repeated emergence and outbreaks of CoVs indicate a public health threat. This suggests the possibility of animal-to-human and human-to-human transmission of newly emerging CoVs. The ongoing changes in ecology and climate make future emergence of such infections more likely.

Coronavirus (CoV) is a large family of positive-sense, single-stranded RNA viruses that belong to the Nidovirales order. The order includes Roniviridae, Arteriviridae, and Coronaviridae families. Corona viruses are enveloped; non segmented, positive-sense single stranded RNA virus genomes in the size ranging from 26 to 32 kb, the largest known viral RNA genome. The virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein, which is buried inside phospholipid bilayers and covered by two different types of spike proteins: the spike glycoprotein trimmer (S) that can be found in all CoVs, and the hemagglutinin esterase (HE) that exists in some CoVs. The membrane (M) protein (a type III transmembrane glycoprotein) and the envelope (E) protein are located among the S proteins in the virus envelope. CoVs were given their name based on the

characteristic crown like appearance. The structure of CoV virion is shown in figure 1.

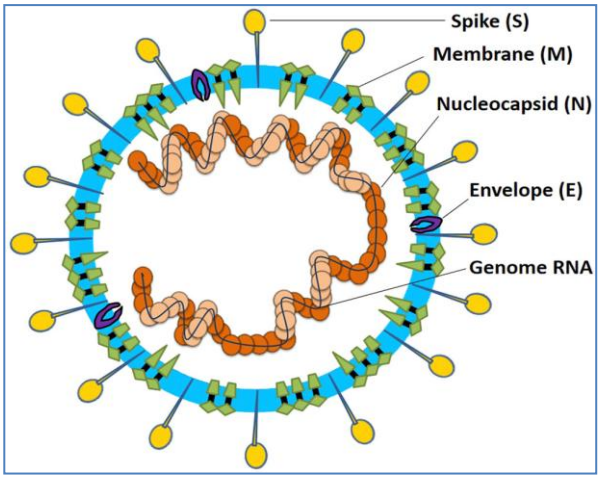


Fig-1: Coronavirus particle

Epidemiology

As of March 3, 2020, the WHO has confirmed 87,317 cases worldwide. Of these confirmed cases, 2,977 (3.42%) patients have succumbed to the virus. The majority of cases and deaths have been reported in China. Of the total number of cases, 79,968 (92%) patients have been identified in China. Likewise, the majority of fatalities (2,873 [96.5%]) have also been reported in China. It is important to note that confirmed cases are clinically diagnosed and laboratory-confirmed. Outside China, a total of 7,169 cases have emerged in 59 countries. Due to the ongoing nature of the pandemic, the number of cases and involved countries are expected to vary. Table 1 provides a comparison of the epidemiological characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2.

Table-1: Comparison of epidemiological characteristics between SARS-CoV, SARS-CoV-2, and MERS-CoV

Features	SARS-CoV-2	SARS-CoV	MERS-CoV
Estimated R0	2.68	2-5	>1
Host of virus	Bats are natural hosts, pangolins are Intermediate hosts, and humans are terminal hosts	Chinese horseshoe bats are natural hosts, masked palm civets are intermediate hosts, and humans are terminal hosts	Bats are natural hosts, dromedary camels are intermediate hosts, and humans are terminal hosts
Transmission mode	Human-to-human through fomites, physical contact, aerosol droplets, nosocomial transmission, zoonotic transmission	Human-to-human through aerosol droplets, opportunistic airborne transmission, nosocomial transmission, fecal-oral transmission, zoonotic transmission	Respiratory transmission, zoonotic transmission, nosocomial transmission, limited human-to-human transmission, aerosol transmission
Incubation period	6.4 days (range: 0-24 days)	4.6 days	5.2 days

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; R0, reproduction number

Etiology

CoVs are a large family of RNA viruses that are found diversely in animal species. They are known to cause diseases of the respiratory, hepatic, nervous system, and gastrointestinal systems in humans. Under the electron microscope, they impart a crown-like appearance due to the presence of envelope spike glycoproteins. CoVs belong to the Roniviridae, Arteriviridae, and Coronaviridae families. The Coronaviridae family can be classified into four genera of alpha-COV, beta-COV, delta-COV, and gamma-COV. Furthermore, beta-COV can be sub-divided into 5 lineages. Gene characterization has helped identify that bat and rodents are the gene source of alpha-COV and beta-COV. On the other hand, avian species are deemed as genetic sources of delta-COV and gamma-COV.

CoVs are responsible for 5-10% of acute respiratory infections. It has been estimated that 2% of the population are deemed healthy carriers of these viruses. Some common human CoVs include HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63. In the immunocompetent, these CoVs clinically present with self-limiting respiratory infections and common colds. In the elderly and immunocompromised, they can involve the lower respiratory tracts. Other human CoVs such as MERS-CoV, SARS-CoV, and SARS-CoV-2 present with pulmonary and extra-pulmonary features.

SARS-CoV-2, which is responsible for the COVID-19 pandemic, is a type of beta-COV. Genomic characterization studies of the new strain have indicated an 89% nucleotide match with bat SARS-like CoVZXC21 . There is also an 82% nucleotide match with the human SARS virus. Therefore, these findings form the basis for the new strain to be called SARS-CoV-2. It has a full genomic length of 29,891 to 29,903 nucleotides. The virus is sensitive to ultraviolet light and heat. SARS-CoV-2 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed in the lungs. Furthermore, these viruses can

be functionally inactivated with the use of ethanol (60%), ether (75%), and chlorine-containing disinfectants.

Immunology

The coronavirus subfamily is genotypically and serologically divided into four genera, the, β, γ, and δ coronaviruses. The β-coronavirus can be further classified into four viral lineages, namely lineage A-D. There are nearly 30 recognized CoVs that infect humans, mammals, fowl, and other animals. Human CoV infections are caused by α- and β-CoVs. CoVs are common human pathogens, and 30% to 60% of the Chinese population is positive for anti-CoV antibodies. The viral infections are generally associated with upper respiratory tract infections, of which the signs and symptoms commonly include fever, headache, and cough; some patients may have lower respiratory tract infections. In contrast, SARS-CoV and MERS-CoV infections may remain asymptomatic in the early stage until severe pneumonia, dyspnea, renal insufficiency, and even death (Figure 2).

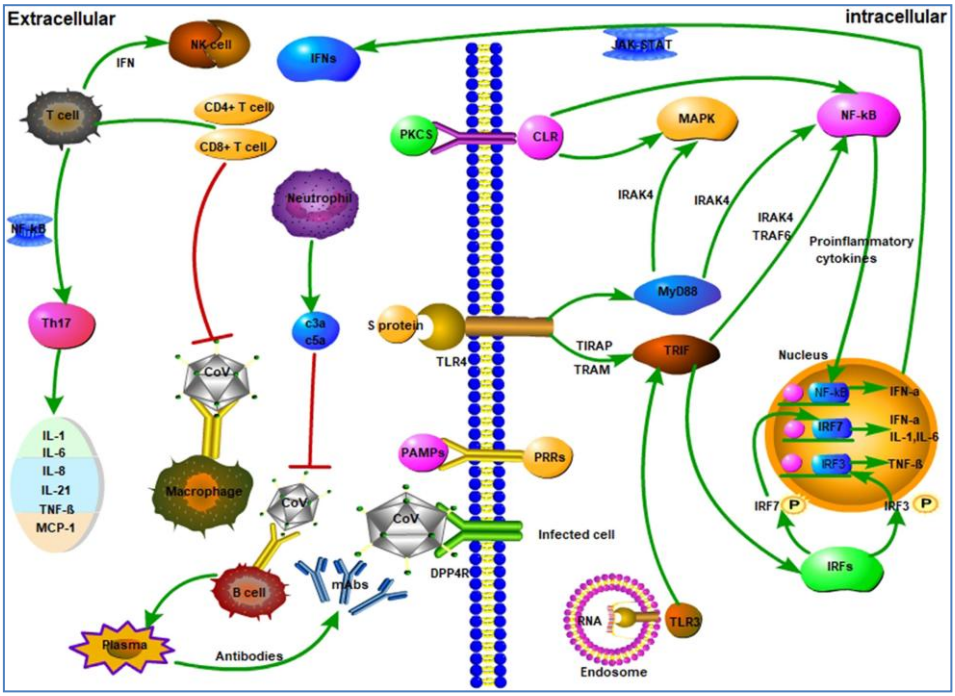


Fig-2

FIGURE 2 the innate immune response and adaptive immune responses of Coronaviruses (CoV) infection during an infection. A, CoV infects macrophages, and then macrophages present CoV antigens to T cells. This process leads to T cell activation and differentiation, including the production of cytokines associated with the different T cell subsets (ie, Th17), followed by a massive release of cytokines for immune response amplification. The continued production of these mediators due to viral persistence has a negative effect on NK, and CD8 T cell activation. However, CD8 T cells produce very effective mediators to clear CoV. B, Attachment of CoV to DPP4R on the host cell through S protein leads to the appearance of genomic RNA in the cytoplasm. An immune response to dsRNA can be partially generated during CoV replication. TLR-3 sensitized by dsRNA and cascades of signaling pathways (IRFs and NF-κB activation, respectively) are activated to produce type I IFNs and proinflammatory cytokines. The production of type I IFNs is important to enhance the release of antiviral proteins for the protection of uninfected cells. Sometimes, accessory proteins of CoV can interfere with TLR-3 signaling and bind the dsRNA of CoV during replication to prevent TLR-3 activation and evade the immune response. TLR-4 might recognize S protein and lead to the activation of proinflammatory cytokines through the MyD88-dependent signaling pathway. Virus-cell interactions lead to the strong production of immune mediators. The secretion of large quantities of chemokines and cytokines (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1) is promoted in infected cells in response to CoV infection. These chemokines and cytokines, in turn, recruit lymphocytes and leukocytes to the site of infection. Red lines refer to inhibitory effects. Green lines refer to activating effects

Histopathological observations of pulmonary lesions in SARS cases not only show nonspecific inflammatory responses such as edema and inflammatory cell infiltration but also exhibit severe exfoliation of alveolar epithelial cells, alveolar septal widening, damage to alveolar septa, and alveolar space infiltration in a distinctly organized manner. Pathologically, inflammation includes degeneration (necrosis), infiltration, and hyperplasia. Thus, SARS-CoV infection can cause pathological changes, degeneration, infiltration, and hyperplasia. Damage to

the pulmonary interstitial arteriolar walls indicates that inflammatory response plays an important role throughout the course of disease in spites of the pathogenic effect of CoVs.

Although the pathologies of SARS and MERS are not yet fully understood, viral and host factors play a key role in SARS-CoV and MERS CoV infections. During virus infection, host factors trigger an immune response against the virus. However, it should be noted that immunopathogenesis is associated with an immune response out of control, which may result in pulmonary tissue damage, functional impairment, and reduced lung capacity. Chemotactic factors are essential to the immune responses against the virus infections, given their regulatory effect on dilations and positions of leukocytes in the host lungs. Therefore, spectral changes in chemotactic factors may lead to severely maladjusted immune responses. Immune insufficiency or misdirection may increase viral replication and cause tissue damages. In contrast, overactive immune responses may induce immune-pathological conditions.

Transmission

The initial cases were presumably linked to direct exposure to infected animals (animal-to-human transmission) at a seafood market in Wuhan, China. However, clinical cases with diversity in exposure history have emerged. This helps further elaborate that human-to-human transmission of the virus is also possible. Therefore, human-to-human transmission is now considered the main form of transmission. Individuals who remain asymptomatic could also transmit the virus. However, the most common source of infection is symptomatic people. Transmission occurs from the spread of respiratory droplets through coughing or sneezing. Data also suggest that close contact between individuals can also result in transmission. This also indicates possible transmission in closed spaces due to elevated aerosol concentrations.

SARS-CoV-2 has a basic reproduction number of 2.2. This suggests that a patient can transmit the infection to two other individuals. Current data suggest that the virus has an incubation period of three to seven days. These findings are based on initial cases. Therefore, further studies are needed to address transmission dynamics and incubation times.

Definition of contact

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protectiveequipment1; OR
4. Other situations as indicated by local risk assessments.

Clinical features

COVID-19 manifests with a wide clinical spectrum ranging from asymptomatic patients to septic shock and multiorgan dysfunction. COVID-19 is classified based on the severity of the presentation. The disease may be classified into mild, moderate, severe, and critical. The most common symptoms of patients include fever (98.6%), fatigue (69.6%), dry cough, and diarrhea.

Mild Disease

Patients with mild illness may present with symptoms of an upper respiratory tract viral infection. These include dry cough, mild fever, nasal congestion, sore throat, headache, muscle pain, and malaise. It is also characterized by the absence of serious symptoms such as dyspnea. The majority (81%) of COVID-19 cases are mild in severity. Furthermore, radiograph features are also absent in such cases. Patients with mild disease can quickly deteriorate into severe or critical cases.

Moderate Disease

These patients present with respiratory symptoms of cough, shortness of breath, and tachypnea. However, no signs and symptoms of severe disease are present.

Severe Disease

Patients with severe disease present with severe pneumonia. acute respiratory distress syndrome (ARDS), sepsis, or septic shock. Diagnosis is clinical, and complications can be excluded with the help of radiographic studies. Clinical presentations include the presence of severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, $SpO2 \leq 93\%$, $PaO2/FiO2 < 300$, and/or greater than 50% lung infiltrates within 24 to 48 hours. Even in severe forms of the disease, fever can be absent or moderate.

In addition, 5% of patients can develop a critical disease with features of respiratory failure, RNAaemia, cardiac injury, septic shock, or multiple organ dysfunction. Data from the Chinese Centers for Disease Control and Prevention (CDC) suggest that the case fatality rate for critical patients is 49%. Patients with preexisting comorbidities have a higher case fatality rate. These comorbidities include diabetes (7.3%), respiratory disease (6.5%), cardiovascular disease (10.5%), hypertension (6%), and oncological complications (5.6%). Patients without comorbidities have a lower case fatality rate (0.9%).

Acute Respiratory Distress Syndrome

The development of ARDS indicates new-onset or worsening respiratory failure. It occurs as a complication within one week of known clinical insult. The values of PaO2/FiO2 are used to distinguish ARDS based on varying degrees of hypoxia. PaO2/FiO2 ≤ 100 mm Hg is indicative of severe ARDS. PaO2/FiO2 values between 100 mm Hg and 200 mm Hg are diagnostic for moderate ARDS. PaO2/FiO2 values between 200 mmHg and 300 mmHg support the diagnosis of mild ARDS. Levels of AST (aspartate transaminase) and ALT (alanine transaminase) at the time of admission correlate with clinical deterioration to ARDS. Therefore, higher levels at admission result in rapid clinical deterioration to ARDS.

In addition to the clinical and ventilatory criteria, chest imaging modalities such as chest X-ray, computed tomography (CT) scan, and lung ultrasound can be used to support the diagnosis. The most frequent finding on CT scan includes ground-glass opacity (86%), consolidation (29%), crazy paving (19%), bilateral disease distribution (76%), and peripheral disease distribution (33%). It is important to note that a chest X-ray has a lower sensitivity (59%) to detect subtle opacities. A CT scan can further detect mediastinal lymphadenopathy, nodules, cystic changes, and pleural effusion. The aforementioned abnormalities might be detectable before the onset of symptoms.

Sepsis and Septic Shock

Patients with COVID-19 and sepsis are deemed the most critical of them all. The accompanying multiorgan dysfunction results as a consequence of dysregulated host response to infection. Signs of organ dysfunction include severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, and hypotension, cold extremities, skin mottling, and altered mentation. Laboratory evidence of other homeostatic dysregulation includes acidosis, high lactate, hyperbilirubinemia, thrombocytopenia, and evidence of coagulopathy.

Patients with septic shock are persistently hypotensive despite volume resuscitation. They may also have an accompanying serum lactate level of >2 mmol/L.

Laboratory Features

Laboratory findings specific to COVID-19 include elevated prothrombin time, LDH (lactate dehydrogenase), D-dimer, ALT, C-reactive protein (CRP), and creatine kinase. In the early stages of the disease, a marked reduction in CD4 and CD8 lymphocytes can also be noted. Patients in the intensive care unit have shown higher levels of interleukin (IL) 2, IL-7, IL-10, GCSF (granulocyte colony-stimulating factor), IP10 (interferon gamma-induced protein 10), MCP1 (monocyte chemotactic protein 1), MIP1A (macrophage inflammatory protein alpha), and TNF-α (tumor necrosis factor-α). They also displayed other abnormal findings indicative of coagulation activation, cellular immune deficiency, myocardial injury, renal injury, and hepatic injury. In critical patients, amylase and D-dimer levels are significantly elevated. However, blood lymphocyte counts progressively decreased. Common to non-survivors are the elevations in ferritin, neutrophil count, D-dimer, blood urea, and creatinine levels. Elevations in procalcitonin levels are not a feature of COVID-19. Therefore, an elevated level of procalcitonin may suggest an alternative diagnosis such as bacterial pneumonia. Levels of CRP correlate directly with disease severity and progression.

Diagnosis

The U.S. CDC has developed criteria for persons under investigation (PUI). If a person is deemed a PUI, immediate prevention and infection control measures are undertaken. Epidemiological factors are used to assess the requirement of testing. These include close contact with a laboratory-confirmed patient within 14 days of symptoms or travel history to an infected area within 14 days of symptom onset.

The WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, bronchoalveolar lavage, or endotracheal aspirate. These samples are then assessed for viral RNA using polymerase chain reaction (PCR). If a positive test result is achieved, it is recommended to repeat the test for re-verification purposes. A negative test with a strong clinical suspicion also warrants repeat testing.

Management

Isolation remains the most effective measure for containment of COVID-19. No specific anti-viral medication or vaccine is currently available. Therefore, the treatment of COVID-19 includes symptomatic care and oxygen therapy. Patients with mild infections require early supportive management. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements, and anti-bacterial therapy. Critically ill patients require high flow oxygen, extracorporeal membrane oxygenation (ECMO), glucocorticoid therapy, and convalescent plasma. The administration of systemic corticosteroids is not recommended to treat ARDS. Moreover, unnecessary administration of antibiotics should also be avoided. ECMO should be considered in patients with refractory hypoxemia despite undergoing protective ventilation. Patients with respiratory failure may require intubation, mechanical ventilation, high-flow nasal oxygen, or non-invasive ventilation. Treatment of septic shock requires hemodynamic support with the administration of vasopressors. Organ function support is necessary for patients with multiple organ dysfunctions.

Therapeutically, aerosol administration of alpha-interferon (5 million units twice daily), chloroquine phosphate, and lopinavir/ritonavir have been suggested. Other suggested anti-virals include ribavirin and abidor. In Singapore, confirmed cases that were hospitalized were also given the combined antiviral therapy of lopinavir and ritonavir.The use of three or more anti-viral drugs simultaneously is not recommended. Ongoing clinical studies suggest that remdesivir (GS5734) can be used for prophylaxis and therapy. Furthermore, a fusion inhibitor targeting the HR1 domain of spike protein is reported to have the potential to treat COVID-19.

Recommendation for empiric use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection

Background:

Hydroxy-chloroquine is found to be effective against coronavirus in laboratory studies and in-vivo studies. Its use in prophylaxis is derived from available evidence of benefit as treatment and supported by pre-clinical data. The following recommendation for the use of hydroxy-chloroquine as a prophylactic agent against SARS-CoV-2 infection is based on these considerations, as well as risk-benefit consideration, under exceptional circumstances that call for the protection of high-risk individuals.

The National Taskforce for COVID-19 recommends the use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection for selected individuals as follows:

Eligible individuals:

- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19
- Asymptomatic household contacts of laboratory confirmed cases

Dose:

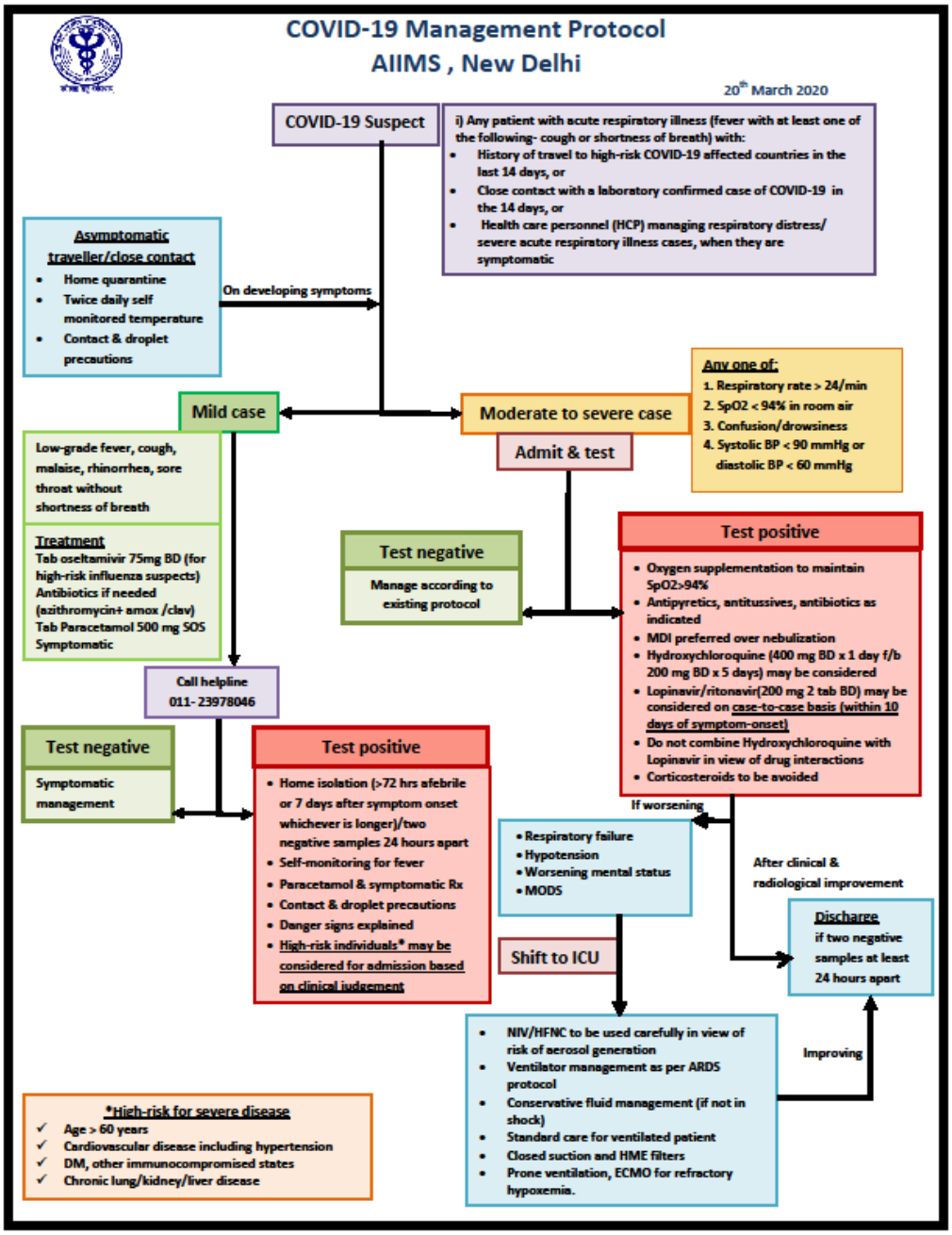
- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: *400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals*
- Asymptomatic household contacts of laboratory confirmed cases: *400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals*

Exclusion/contraindications:

- The drug is not recommended for prophylaxis in children under 15 years of age.
- The drug is contraindicated in persons with known case of retinopathy, known hypersensitivity to hydroxychloroquine, 4-aminoquinoline compounds

Key considerations:

- The drug has to be given only on the prescription of a registered medical practitioner.
- Advised to consult with a physician for any adverse event or potential drug interaction before initiation of medication
- The prophylactic use of hydroxychloroquine to be coupled with the pharmacovigilance for adverse drug reactions through self-reporting using the Pharmacovigilance Program of India (PvPI) helpline/app.
- If anyone becomes symptomatic while on prophylaxis he/she should immediately contact the health facility, get tested as per national guidelines and follow the standard treatment protocol.
- All asymptomatic contacts of laboratory confirmed cases should remain in home quarantine as per the national guidelines, even if they are on prophylactic therapy.
- Simultaneously, proof of concept and pharmacokinetics studies be taken up expeditiously. Findings from these studies and other new evidence will guide any change in the recommendation.



Prevention

Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. The WHO has advised against close contact with patients, farm animals, and wild animals. Patients and the general public must cover coughs and sneezes to help prevent aerosol transmission. Frequent handwashing with soap and water is also required. As an alternative measure, hand sanitizers can also be used. Immunocompromised individuals are advised to avoid public gatherings. Emergency medicine departments must apply strict hygiene measures for the control of infections. Healthcare personnel must use personal protective equipment such as N95 masks, FFP3 masks, gowns, eye protection, gloves, and gowns.

CONCLUSIONS

The COVID-19 pandemic is spreading across the globe at an alarming rate. It has caused more infections and deaths as compared with SARS or MERS. Based on R0 values, it is deemed that SARS-CoV-2 is more infectious than SARS or MERS. Elderly and immune-compromised patients are at the greatest risk of fatality. The rapid spread of disease warrants intense surveillance and isolation protocols to prevent further transmission. No confirmed medication or vaccine has been developed. Current treatment strategies are aimed at symptomatic care and oxygen therapy. Prophylactic vaccination is required for the future prevention of COV-related epidemic or pandemic.

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