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Review Article

Coronavirus 2019: a review of virology, clinical features, diagnosis, and treatment

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ABSTRACT

Coronavirus 2019 (COVID-19) is an enveloped ribonucleic acid (RNA) virus that is diversely found in humans and wildlife. A total of six species have been identified to cause disease in humans. 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 is a declared global pandemic. This review will introduce a general overview of virology and describe the clinical features, diagnostic testing, and management of COVID-19 patients. 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. Our review will also provide a means to raise awareness among primary and secondary healthcare providers during the current pandemic.

Keywords: Coronavirus, COVID-19, Dyspnoea, Pandemic, Pneumonia

INTRODUCTION

Coronavirus (CoV) is a large family of positive-sense, long (30 k base pairs) single-stranded ribonucleic acid (RNA) viruses that belong to the nidovirales order. The order includes roniviridae, arteriviridae, and coronaviridae families. The coronaviridae family is subdivided into torovirinae and coronavirinae subfamilies. Coronavirinae is further subclassified based on phylogenetic clustering into alpha, beta, gamma, and delta COVs.[1] The severe acute respiratory syndrome coronavirus (SARS CoV), which appeared in 2002, and Middle East respiratory syndrome coronavirus (MERS-CoV), which was reported in 2012 are the other significant viruses from the same family.[2]

On 31st December 2019, Wuhan health commission in the Hubei province of the Republic of China notified the National Health Commission, China Centre for Disease Control (CDC), and World Health Organisation (WHO) of a cluster of 27 cases of pneumonia of unknown aetiology which were presented with fever, dyspnoea, and dry cough. The lack of early containment due to the inability to accurately trace the history of exposure in the early patient cases contributed to the rapid rate of spread in Wuhan.[3] After the initial reports of infection, in the following several weeks, COVID-19 outbreaks were reported in South Korea, Iran, and Italy. This was quickly followed by several other European, Asian, and North and South American countries reporting cases. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency. On February 11, 2020, the World Health Organization (WHO) announced the disease caused by this novel virus as coronavirus disease-2019 (COVID-19). On 11th March 2020, due to the global logarithmic expansion of the cases the coronavirus disease 2019 (COVID-19) was declared as a pandemic by the WHO.

So far, the COVID-19 infection is still spreading, and this virus poses a serious threat to public health. Due to a lack of specific management guidelines and antiviral treatments, thousands of severe cases have died every day

worldwide. In this review, we discuss the virology, clinical presentation, diagnosis, and potential management for the treatment of this infection.

VIROLOGY

The name Coronavirus originates from the Latin word corona, meaning "crown" or "halo", due to its characteristic appearance under two-dimensional transmission electron microscopy. Coronaviruses have club-shaped spike peplomers covering their surfaces (Figure 1).[4]

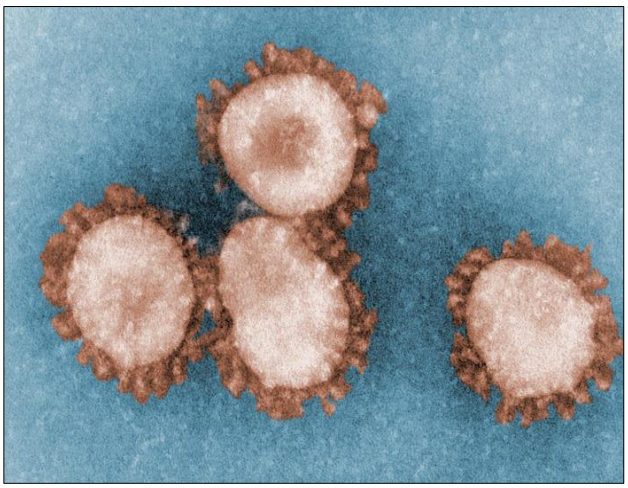

Figure 1: Electron microscopy of SARS-CoV, with the arrow pointing at a single virion. (Photo credit to Dr. Fred Murphy. This media comes from the centers for disease control and prevention's (CDC) public health image library (PHIL), identification number 4814).

ORIGIN

At the end of 2019, COVID-19 emerged in several local hospitals of Wuhan, Hubei province, China. It was first isolated in the bronchoalveolar lavage fluid (BALF) of three COVID-19 patients from Wuhan Jinyintan Hospital on December 30, 2019. Based on clinical manifestations, blood tests, and chest radiographs, this disease was diagnosed as virus-induced pneumonia by clinicians. The public health office traced all these cases to Huanan seafood wholesale market which trades live species of bats, snakes, pangolins, and badgers.[3] As expected, SARS-CoV-2 was isolated in environmental samples of the Huanan seafood market by China CDC, implying the origin of the outbreak. However, such a decisive conclusion was disputed because the earliest case had no reported link connection to the mentioned market.[5] A recently phyloepidemiologic analysis suggests that SARS-CoV-2 at the Huanan seafood market could have been imported from other places.[6] To date, it remains inconsistent concerning the origin of SARS-CoV-2, and epidemiologic and etiologic investigations are being conducted by Chinese health authorities.

Classification and genome

The CoVs family is a class of enveloped, positive-sense single-stranded RNA viruses having an extensive range of natural roots. These viruses can cause respiratory, enteric, hepatic, and neurologic diseases.[7,8] The CoVs are genotypically and serologically divided into four subfamilies: α, β, γ, and δ-CoVs. Human CoV infections are caused by α and β CoVs. SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) are members of β CoVs.[7,8] Genome-wide phylogenetic analysis indicates that SARS-CoV-2 shares 79.5% and 50% sequence identity to SARS-CoV and MERS-CoV, respectively.[9-11] However, there is 94.6% sequence identity between the seven conserved replicase domains in open reading frame 1ab (ORF1ab) of SARS-CoV-2 and SARS-CoV and less than 90% sequence identity between those of SARS-CoV-2 and other β-CoVs implying that SARS-CoV-2 belongs to the lineage B (Sarbecovirus) of β-CoVs.[9,10,12]

Similar to other β-CoVs, the SARS-CoV-2 virion with a genome size of 29.9 kb possesses a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein.[13] The nucleocapsid is buried inside phospholipid bilayers and covered by two different types of spike proteins: the spike glycoprotein trimmer (S) that exists in all CoVs, and the hemagglutinin-esterase (HE) only shared among some CoVs. The membrane (M) protein and the envelope (E) protein are located among the S proteins in the viral envelope.[12] The SARS-CoV-2 genome has 5′ and 3′ terminal sequences (265 nt at the 5′ terminal and 229 nt at the 3′ terminal region), which is typical of β-CoVs, with a gene order 5′-replicase open reading frame (ORF) 1ab-S-envelope(E)-membrane(M)-N-30. The predicted S, ORF3a, E, M, and N genes of SARS-CoV-2 are 3822, 828, 228, 669, and 1260 nt in length, respectively. Similar to SARS-CoV, SARS-CoV-2 carries a predicted ORF8 gene (366 nt in length) located between the M and N ORF genes.[12]

Receptor interactions and cell entry

The angiotensin-converting enzyme 2 (ACE2) receptors on host type 2 pneumocytes have been found to be the target of S proteins.[10,14] The S protein of CoVs exists in a metastable pre-fusion conformation that undergoes a dramatic structural rearrangement to fuse the viral membrane with the host cell membrane. This process is triggered by the S1 subunit and a host–cell receptor binding, which destabilizes the pre-fusion trimer, resulting in the S1 subunit shedding and the S2 subunit transition to a highly stable post-fusion conformation.[8]

The entry of SARS-CoV-2 into the type II pneumocyte is via endocytosis and then multiplies in the cytoplasm. The high protein manufacturing stress induced upon the type II pneumocytes leads to apoptosis. Additionally, the RNA from the SARS-CoV-2 acts as a pathogen-associated molecular pattern (PAMP) and will be recognized by the

pattern recognition receptor or toll-like receptors. This leads to a chemokine surge which causes neutrophil migration and activation. This leads to the destruction of the alveolar-capillary walls. At a microscopic level, this leads to a loss in the interface between the intra-alveolar space and the surrounding stroma. Therefore, fluid leaks through and fills into the alveolar sacs.[15]

Ecology of SARS-CoV-2

The origin of the SARS-CoV-2 genome has been linked to bats akin to the SARS-CoV-1 and MERS-CoV viruses.[16] Interestingly, the SARS-CoV-2 whole-genome aligned with the genomes of viruses (Bat-CoV and Bat-CoV RaTG13) in Rhinolophus affinis species of Yunnan province with 96% similarity.[10] As seen previously in SARS-CoV-1 and MERS-CoV viruses that undertake residence in the intermediate hosts, it was suspected that in SARS-CoV-2 pangolins were the natural reservoir. This was based on the analysis of the genome contig alignment of SARS-CoV-2 like CoV (Renamed: Pangolin-CoV) harboured in the lung tissue of two dead Malayan pangolins.[17] This Pangolin-CoV's whole genome had 91.02% similarity with SARS-CoV-2 and 90.55% similarity with Bat-CoV RaTG13.[18] Proteomic analysis revealed that the S1 subunit of Spike glycoprotein (S) was more closely related to that of SARS-CoV-2 compared to BaT-CoV RaTG13. Furthermore, five amino acid residues of the S protein of SARS-CoV-2 interacting with the ACE2 receptor are identical in Pangolin-CoV.[18] Contrastingly, only four amino acid residues are identical in the S protein of BaT-CoV RaTG13. Interestingly, both Pangolin-CoV and BaT-CoV RaTG13 have lost the furin recognition motif, vital to the S1/S2 cleavage.[18] This putative furin recognition sequence is still intact within the SARS-CoV-2. A compilation of all these findings portrays that pangolins are the intermediate hosts for SARS-CoV-2 (Figure 2).

Genetic evolution

The phylogenetic analysis by Tang et al of 103 genomes with SARS-CoV-2 indicated that the two major lineages co-exist. These lineages are designated as L-type (T28, 144 is in the codon of leucine) and S-type (C28, 144 is in the codon of serine) and these are defined by the significant linkage ($r2 = 0.954$, and LOD = 50.13) of their SNPs at positions 8782 (ORF1ab: T8517C, synonymous) and 28144 (ORF8: C251T, S84L).[19] Due to severe selective pressure on the L type, the L type might be more aggressive and spread more quickly, while the S type might remain milder due to relatively weaker selective pressure.[19] Due to the unstable nature of RNA viruses, the continuous surveillance of SARS-CoV-2 from humans or animals is extremely important for disease control.

Transmission

The initial cases were presumably linked to direct exposure to infected animals (animal-to-human transmission) at a seafood market in Wuhan, China. At the moment, person-to-person transmission and fomite transmission have been linked with the spread of the illness.[20] Modes of transmission traced in an imported case are through droplet transmission, faecal-oral route, conjunctiva, and fomites.[21,22] Additionally, local transmission can be traced back to the patient's bodily fluids such as respiratory droplets, saliva, faeces, and urine.[22] Individuals who remain asymptomatic could also transmit the virus.[23] The half-life of SARS-CoV-2 in aerosols, copper, cardboard, stainless steel and plastic are 1.5 hours, 1 hour, 3.4 hours, 5.6 hours, and 6.8 hours, respectively. The viable residence time of SARS-CoV-1 in aerosols, copper, cardboard, stainless steel and plastic are 3 hours, 4 hours, 24 hours, 48 hours, and 72 hours, respectively.[24] Incubation periods may vary but have been known to be between 1 and 14 days for other coronaviruses. To date, the median observed incubation period for SARS-CoV-2 appears to be 5.1 days [95% confidence interval (CI): 4.5-5.8 days], with 97.5% of those who develop symptoms doing so within 11.5 days (95% CI: 8.2-15.6 days) of infection.[25] The basic reproduction number (R0), or the number of cases directly generated by one case in a population where all individuals are susceptible, has been reported to be between 2.13 and 4.82, which is similar to SARS-CoV.[26]

Clinical features

COVID-19 presents with a varied range of clinical features having mean incubation period of 14 days, with some cases becoming apparent at shorter duration of time. Most common symptoms in majority of patients are mild fever (80%) cough (60%) and sore throat (40%). Constitutional symptoms such as muscle and bone pains, chills and headache have also been reported in a small number of cases.[27] Patients may be asymptomatic at the start with their condition advancing from fever and mild respiratory illness to multi-organ failure and sepsis. Based on the severity of the symptoms, the disease is classified as mild, moderate, severe and critical.

Mild disease

Mild disease refers to the presence of mild upper respiratory disease presenting as fever, headaches, dry cough, nasal congestion, sore throat and myalgia.[23] Radiographic findings are also absent in most of the cases. Majority of the patients show the symptoms of mild disease which can easily be treated, or the disease may progress to the more severe form in the absence of proper treatment and general health condition of the patient.

Moderate disease

These patients have dyspnoea and tachypnoea, termed as COVID pneumonia, in addition to the common symptoms of mild disease, but there are no signs or symptoms of severe disease.[23]

Severe disease

Patients with severe disease have tachypnoea, respiratory distress with central cyanosis, spO_2 <93% with presence of lung infiltration greater than 50% radiologically.[23]

Critical disease

It manifests as very morbid complications of the previously poorly managed disease, which can be in the form of acute respiratory distress syndrome (ARDS) or sepsis leading to multiorgan failure, encephalopathy or coagulation disorders.[23] Main factors leading to lethal outcomes of corona virus infection include history of cigarette smoking, old age with poor immunity and other co-morbid conditions like diabetes, hypertension, coronary artery disease (CAD) and cerebrovascular accident (CVA).

DIAGNOSIS

Two kinds of tests are available for COVID-19: diagnostic tests and antibody blood tests. Diagnostic tests check samples from the respiratory system (such as swabs of the inside of the nose) to tell if a person currently an infection with SARS-CoV-2, the virus that causes COVID-19. Antibody blood tests, also called serologic tests, check the blood for antibodies that would show if you have had a previous infection.[28] The United States CDC has developed criteria for persons under investigation (PUI).[23] If a person is deemed a PUI, immediate prevention and infection control measures are undertaken.

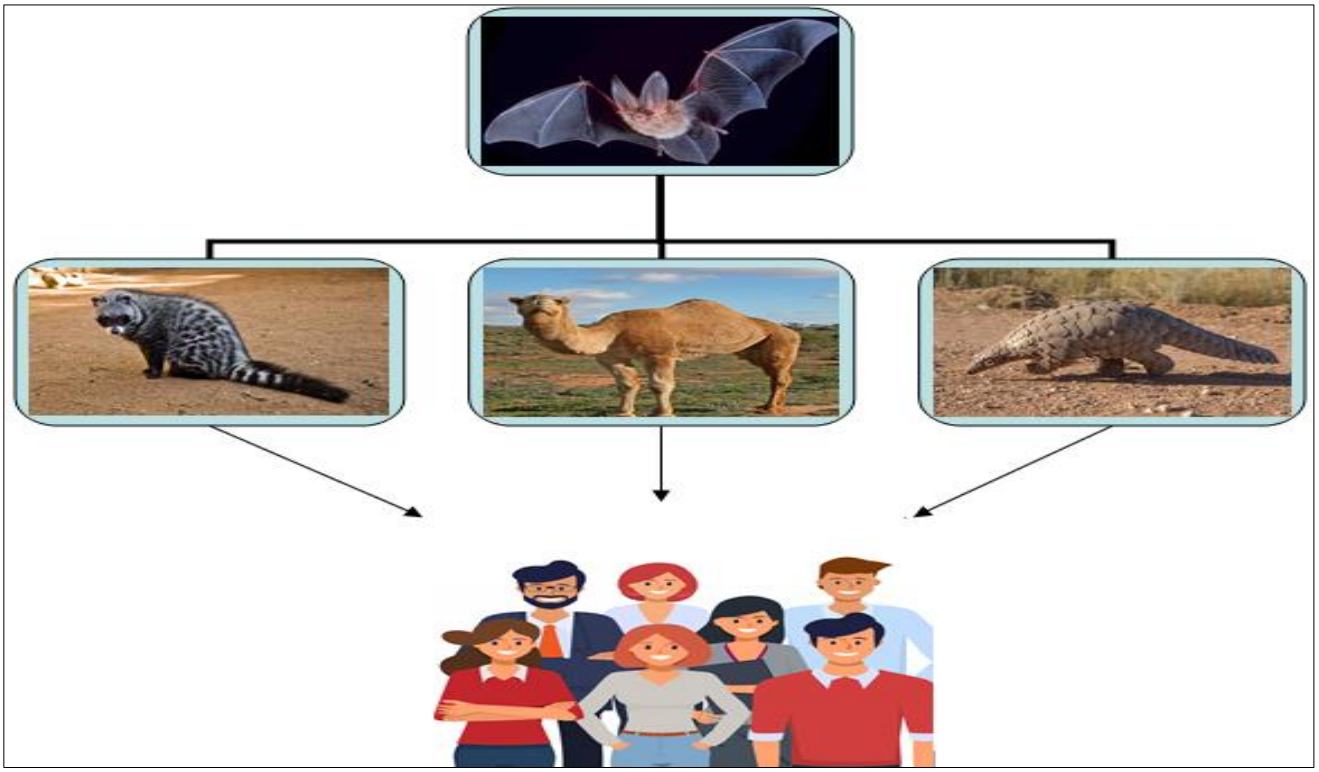

Figure 2: The natural reservoir, intermediate host and target in coronavirus.

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.[23] Following methods of varying sensitivity and specificity can be used to aid diagnosis;

Nucleic acid-based testing

On 12th January 2020, the China CDC shared the genetic sequence of the SARS-CoV-2. This enabled countries to develop primers against the SARS-CoV-2 genome and utilize reverse transcriptase-polymerase chain reaction (RT-PCR) assays to make a diagnosis of COVID-19. Subsequently, many biotechnology companies have successfully developed nucleic acid detection kits, and the China Food and Drug Administration (CFDA) has urgently approved a batch of fluorescent quantitative kits and sequencing systems.[29] 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.[23] The main concern related to the nucleic acid test is false negatives. To solve the problem of low detection efficiency, some improved rapid viral nucleic acid diagnostic tests have been invented. Moreover, negative tests with strong suspicions, such as clinical symptoms or exposure, can be repeated using samples from other respiratory sites.[30,31]

Serologic testing

It has been shown that patients with SARS-CoV-2 infection possess acute serological responses.[11] Combined with immunochromatography, colloidal gold, and other technologies, relevant detection reagents have been developed rapidly.[32,33]

Recently, the centres for disease control and prevention (CDC) has developed a new laboratory test to assist with efforts to determine how much of the U.S. population has been exposed to SARS-CoV-2, the virus that causes COVID-19. The serology test looks for the presence of antibodies, which are specific proteins made in response to infections. Antibodies can be found in the blood and in other tissues of those who are tested after infection. The antibodies detected by this test indicate that a person had an immune response to SARS-CoV-2, whether symptoms developed from infection or the infection was asymptomatic. Antibody test results are important in detecting infections with few or no symptoms. The results of these studies will allow us to estimate how many people have been infected nationally. The results will also provide information about the percentage of U.S. residents who have not had COVID-19 and are still at risk for infection. This research is designed to help us understand who has been infected with SARS-CoV-2 and determine factors that confer protection against this virus.[28]

Radiologic testing

Chest radiograph or computed tomography (CT) is an important tool for COVID-19 diagnosis in clinical practice. Computed tomography (CT) findings include bilateral multi-lobar ground-glass opacities, with peripheral posterior distribution, mainly in the lower lung lobes.[34] Less commonly, septal thickening, bronchiectasis, pleural thickening, and subpleural involvement have been reported. As disease progression occurs, a repeat CT scan may show multifocal consolidations with a paving pattern (Figure 5).[35] The largest study (n = 1014) showed that CT-chest had a 95% sensitivity in making an early diagnosis of COVID-19 through the identification of ground-glass opacities.[36] This finding was also consistent in a case series of 51 COVID-19 patients wherein the sensitivity of CT was 98%.[36]

Prevention

To lessen the transmission rate of R0 about 2-3 of COVID-19 (currently) to R0 less than 1, prevention is the need of hour.[23] To attain this level, prevention at different levels including personal, for healthcare professionals, for the general population as well as prevention at international level is mandatory.

Personal prevention

Frequent hand washing and cleaning with alcohol-based products preferably but washing hands with any soap with water for 20 seconds is also recommended. Soap and sanitizer of any brand are recommended but a 60% alcohol-based product is preferred for controlling and spreading coronavirus.[37] WHO civic rules must follow for coughing or sneezing at the elbow or using tissue papers which must be disposed of into a closed dust bin to avoid its reuse. Much emphasis is made on not touching the mucosal surfaces which are more prone to getting an infection like eyes, nose, and mouth. Avoid touching these crucial areas so that minimal exposure of the virus to the respiratory tract is done. The social distancing of at least 1 foot (3 m) must be followed to avoid contact with any person having symptoms of COVID-19. The WHO has advised against close contact with patients, farm animals, and wild animals.[23] Isolation must be followed if having any symptoms of coronavirus or consult your corona hospital if symptoms become severe. Properly quarantined, using a surgical mask, avoid sharing utensils and clothes, and properly sterilizing the regularly touchable surfaces are the best means to stop the spread of COVID-19.

Healthcare professionals

Most critical and much-exposed individuals require critical care to get themselves safe from getting infected. Double layered nonwoven personal protective equipment (PPE) including surgical masks, gloves, full-sleeved gowns, head covers, shoe covers, and eye shield-like goggles must be used and disposed of properly after dealing with a diseased person.[37] N95 is usually recommended as it prevents about 95% droplets to getting into the mask and must be used while dealing with high-risk persons as well as for high-risk procedures like taking OP or nasal swabs.[37] If exposed to any positive individual, one must get himself tested and proper isolation must be followed to avoid spread to any other healthcare individual or any member of his family.

General population

Strict hygienic conditions must be followed including repeated handwashing, proper usage of surgical masks for symptomatic as well as for the non-symptomatic individual, proper coughing technique at the elbow, or using tissue paper, self-isolation, avoid going to areas of an outbreak, disinfection techniques must be followed. WHO also recommends closing all public gatherings including schools, colleges, universities, and malls to avoid the spread. In some countries, lockdown is also implemented to spread the infection at the mass level. In a community, immunocompromised individuals require

strict precautionary measures to cope in such a situation. This self-isolation must be extended to pets as well, as there is a recorded case of a human-to-dog transmission.[38] Frequent disinfection and cleaning are advised for groups that are at risk of contracting the virus.[39]

Prevention at the international level

All countries should have proper screening methods at their respective airports for international travellers. The suspected individual must be isolated and managed accordingly. All airports, airplanes, cargo must be properly disinfected with proper disinfection agents. Unnecessary flights and flights to a pandemic affected country must be avoided.

Management

One thing to keep in mind is that till today there are neither any specific antiviral drugs nor any vaccine for COVID-19 available.[23] Thus, management is predominantly supportive and symptomatic.

Primarily, the symptoms are fever and non-productive cough, therefore treated with over the counter antipyretic agents (paracetamol) and antitussive drugs (guaiphenesin, an expectorant), respectively.[40] Moreover, external cooling, oxygen therapy, nutritional supplements, and anti-bacterial therapy is also used.[41] Later in the course of COVID-19, superimposed microbial infection (bacterial, fungal) happens, thus empiric anti-microbial coverage must be given. In severe respiratory distress, supplementary oxygen (assisted oxygen ventilation) is given to maintain oxygen saturation >92% in pregnant and >90% in other patients.[42] In spite of high flow oxygen therapy, critical patients also require extracorporeal membrane oxygenation (ECMO), glucocorticoid therapy, and convalescent plasma.[41] ECMO should be considered in such critical patients having refractory hypoxemia despite being on a ventilator.[41]

Complications like septic shock and acute kidney injury should be managed accordingly. Septic shock requires hemodynamic support with the administration of vasopressors.[45] Acute kidney injury (AKI) should be managed with renal replacement therapy (RRT). Renal function tests and fluid balance measurements will tell which patient requires RRT.[42]

Many anti-viral drugs are being used to help the patient with severe viral symptoms, with satisfactory results. In the USA and China, a randomized clinical trial has been initiated to test the efficacy of remdesivir.[43] However, oseltamivir and a neuraminidase inhibitor are among the drugs using extensively.[20] Anti-malarial drug chloroquine also showing promising effects in treating COVID-19, but due to its side effects, Zhou suggests hydroxychloroquine as an alternative treatment.[44] Hydroxychloroquine is less toxic as compared to chloroquine and potentially effective. Tocilizumab, a humanized monoclonal antibody, has shown success in treating some of the severe cases of COVID-19. A small study showed that tocilizumab decreased fever, oxygen requirements, and C-reactive protein (CRP), along with improved CT findings.[45] Nitazoxanide, a broad-spectrum antiparasitic and antiviral agent, found to inhibit SARS-CoV-2 at low micromolar concentrations in vitro.[46] However, further studies are still required for action.

Cautions

NSAIDs, especially ibuprofen, cause an uplift in ACE-2 receptors but at present, there is no specific study available that suggests its increased risk for SARS-CoV-2.[47] Thus, it is recommended for the patients on ACEI or ARBs to continue their drug regimen. Care must be taken while using corticosteroids in COVID-19. No mortality benefit has been appreciated in non-ARDS COVID-19 patients.

CONCLUSION

The SARS-CoV-2 is spreading across the world at an alarming rate. The elderly and immune-compromised patients are most vulnerable to the virus. The health care systems risk collapsing due to the increasing number of confirmed patients who need intensive care and the spread of the disease in health providers. Currently, no confirmed medication and vaccine is available. Due to the lack of available and validated therapeutics, most of the countermeasures rely on the usage of public health containment and quarantine approaches.

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