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COVID -19 Pandemic- A Literature Review

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ABSTRACT

The coronavirus pandemic which has originated in Wuhan province of China has brought the whole world on its knees. Despite many scientific advancements since 1900s in the field of medicine the world still remains clueless of controlling this pandemic. U.S.A remains on top with the highest number of cases and counting while the rest of the world is also not far behind. To understand about corona virus disease we did an extensive research of literature and have summed up our findings in our article. SARS-COV2 also known as COVID-19 gains entry via nasopharyngeal route where it attaches itself with the help of ACE 2 receptor thus causing infection. It most commonly affects lungs followed by heart, kidney and liver. Most of the cases present with fever, dry cough, shortness of breath and loss of taste and smell among other manifestations. RT-PCR remains the investigation of choice. Social distancing, practising hand hygiene and use of face mask have been advocated. Many of the drug trials are under way with recent FDA approval of remdesivir. Use of hydroxychloroquine has been debated however trials are underway for a more definite conclusion. The world is fast tracking the approval of vaccine with many of the vaccines in various stages of trials.

Key words- Corona Virus, COVID-19, ACE 2, Lung, Heart, RT-PCR, Social distancing, Vaccine

INTRODUCTION

The coronavirus disease-2019 (COVID-19), which has caused pandemic worldwide and has originated in Wuhan province of china has been caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2). [1] The number of confirmed cases worldwide as of 6 June 2020 are 66,63,204 with over 392802 deaths as per WHO COVID -19 Dashboard. The largest number of cases have been reported in U.S.A with over 18,57,772 cases and 107911 deaths followed by Brazil and Russia with 6,14,941 and 4,58,869 confirmed cases. China where the pandemic began has reported 84,620 confirmed cases with 4,645 deaths till now. In India there has been 2,36,657 total cases with over 6,642 deaths till now (6 June 2020). This pandemic has led to worldwide lockdown, strangling of the global economy and devastation of human life. [1] Scientists and health care workers are working all over the globe for a possible cure of this deadly virus. The world's medical and scientific communities have come together to rapidly expand our knowledge of the pathogenesis, disease manifestations and possible preventive and therapeutic strategies which we will be discussing below. We conducted an extensive research of literature and have summed up our findings in the article.

ORIGIN

The origin of the virus has been attributed to the exposure to the Huanan seafood market which was common among the earliest cases contributing to the SARS-CoV2 epidemic in China. [2] However there has been conflicting reports going on around the world in the social media which suggest that the virus was leaked accidentally from the Wuhan institute of virology prompting the U.S.A government to investigate it, [3,4]

the results of which have not been disclosed so far.

Phylogenetic and virus genome analysis have shown that coding regions of SARS-CoV-2 possess a similar genomic structure to bat-SLCoVZC45, bat-SL-CoVZXC21 (Chinese horseshoe bats in the Zhejiang province in China) and SARS-CoV. [5] Paraskevis et al. also did a complete genome evolutionary analysis of the SARS-CoV-2 and confirmed similar findings with 96.3% sequence similarity to the Bat CoV RaTG13 sequence. [6] Also, no bats are sold in the Hunan sea food market and also most of the bat species in December are hibernating. [1] So even though bats may be the natural reservoir for SARS CoV2, there is likely an unidentified intermediate animal host responsible for animal-to-human transmission in case it has spread from Hunan sea food market.

INCUBATION PERIOD

According to the Centers for Disease Control and Prevention (CDC), the mean incubation period of COVID-2019 is approximately 5.1 days (range 2-14 days). [7]

TRANSMISSION

The main mode of transmission is close or direct contact with infected secretions or large aerosol droplets. [8] The virus can exist in nature on surfaces and can last for up to 4 hours on copper, 24 hours on cardboard and up to 72 hours on plastic and stainless steel surfaces leading to fomite transmission. [9] However there is a possibility that it can even spread through fecal -oral route due to ACE 2 receptor which is present in the epithelium of intestinal lumen to which corona virus binds. [10,11] Zhang et al. from Wuhan University detected the SARS-CoV-2 viral nucleic acids in the fecal samples and anal swabs of COVID19 patients. [9] No vertical transmission has been reported in pregnant women from mother to baby, in vaginal secretions or breast milk. [12-14] Recent evidence also shows that the infection may spread from asymptomatic individuals.

STRUCTURE

It belongs to genus Coronaviridae which is a family of single stranded, enveloped, positive sense, RNA viruses. They are divided into alpha- and beta- (cause human diseases- respiratory infections), gamma- and delta- genera based on genetic clustering. The SARS-CoV1 and SARS-CoV2 are beta-CoV. [15-17] The CoV genome consists of two parts-

1. Structural proteins

The structural proteins are the constituent proteins of the transmissible viral particle. The key structural CoV proteins are-

I. Nucleocapsid protein (N)
II. Transmembrane proteins [15-19]
- Spike protein (S)
- Membrane protein (M)
- Envelope protein (E)

While Spike protein is responsible virus - cell receptor interaction, [20-24] Membrane and Envelope protein are responsible for membrane structure and fusion. The N protein binds viral RNA and mediates its interaction with the S, E, and M proteins for genome encapsulation. [15,25]

2. Non structural Proteins

They are responsible for viral replication within the cell. CoV genomes encode 16 non structural proteins. Critical proteins for viral replication include-

I. Protease (nsp5)
II. Papain-like protease (nsp3)
III. RNA-dependent RNA polymerase (nsp12, RdRp).

3. Accessory Proteins

PATHOGENESIS

SARS-CoV2 uses Angiotensin Converting Enzyme 2 as its receptor to gain entry in airway epithelial cells which is the same as SARS-Cov1. The virus interacts with the receptor through its spike protein (protein S). This ACE2-Spike interaction leads to endocytosis of virus particles through internalization with ACE2, induces the fusion of virus with host cells, [Figure 1] and establishes SARS-CoV infection. [26] ACE2 is present in lung alveolar or bronchial epithelial cells, enterocytes of the

small intestine, arterial and venous endothelial cells and arterial smooth muscle cells. [27] ACE2 is also expressed in different organs such as kidneys, myocardium, GI tract and spleen potentially explaining the multi-organ injury observed with SARS-CoV2 infection. [1] ACE 2 functions as a negative regulator of renin angiotensin system. It catalyses both angiotensin I and angiotensin II to form Angiotensin 1-9 and Angiotensin 1-7 respectively and have vasodilator and cardioprotective effects [Figure 2].

Once SARS-CoV establishes infection and the virus replicates in these cells, new virions are released into the blood. The infected cells under the stimulation of SARS-CoV and some uninfected cells induced by viral antigens or Proinflammatory cytokines regulatory factors eg nuclear factor-kappaB (NF-κB) and p38 (a mitogen-activated protein kinase) produce high levels of Proinflammatory cytokines to mediate inflammatory responses for combating the virus (Figure 3). However, these Proinflammatory cytokines can also damage the host cells. Some of the Proinflammtory cytokines, e.g. monocyte chemoattractant protein-1 (MCP-1), attract monocytes in blood to migrate to the alveolar cavities, where the monocytes are stimulated by other Proinflammatory cytokines to become proliferative and/or activated macrophages. The activated macrophages can produce more Proinflammatory cytokines and may transmit SARS-CoV to other sites. Some of the Proinflammatory cytokines, including TGF-β1 and TNF-α, may induce apoptotic death of the epithelial cells, pneumocytes, and lymphocytes, or mediate pulmonary fibrosis, resulting in Acute lung injury (ALI) and Acute respiratory distress syndrome (ARDS). The cell-free and Macrophage associated SARS-CoV in the blood can be transmitted from the lung to other organs to infect the ACE2-expressing cells in the local sites such as myocardium, GIT, kidney, spleen etc. More Proinflammatory cytokines including IL-1β and IL-6 are produced and the level of proinflammatory cytokines in the blood is rapidly elevated. [28]

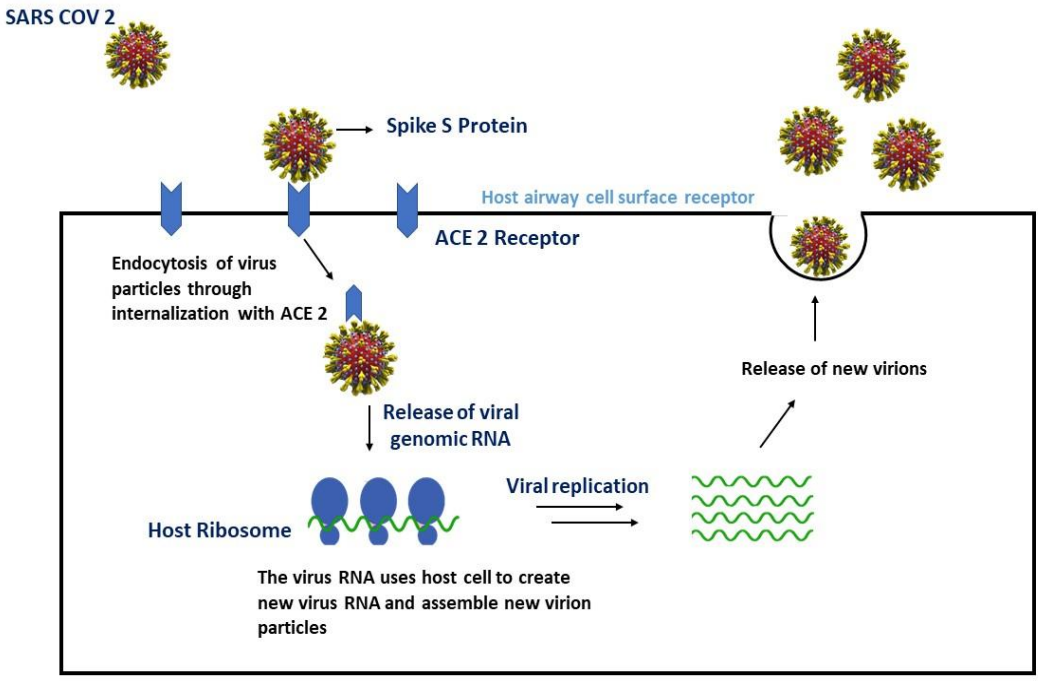

Figure 1: SARS-CoV2 gains entry in airway epithelial cell through ACE 2 receptor by its spike protein. This ACE2-Spike interaction leads to endocytosis of virus particles, induces fusion of virus with host cells and establishes SARS-CoV infection. The virus then replicates in these cells and new virions are released into the blood.

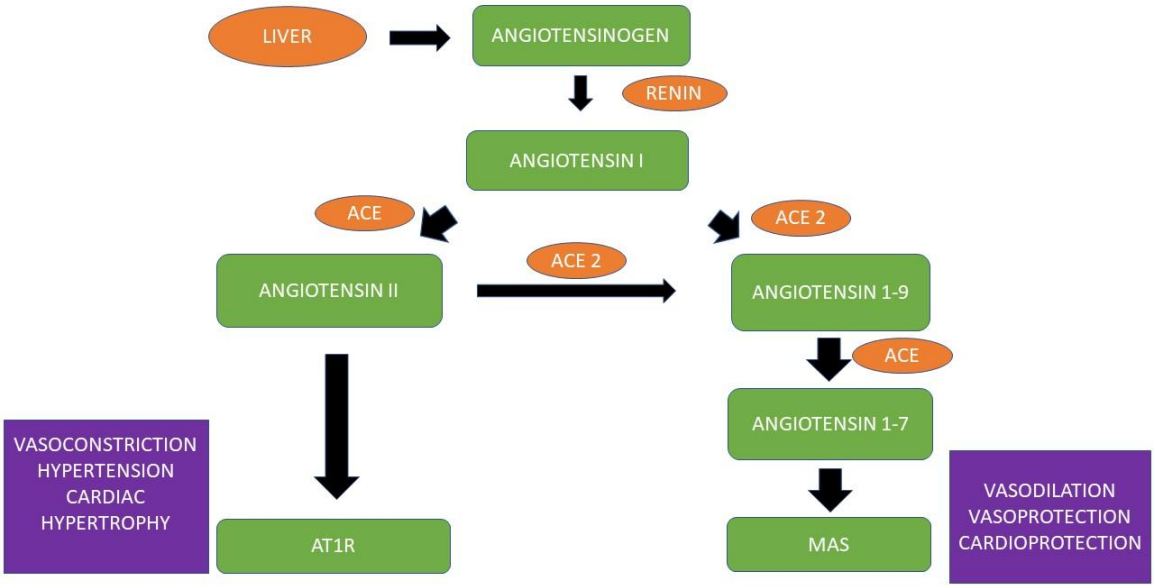

Figure 2: Renin acts on angiotensinogen to produce Angiotensin I which is converted to Angiotensin II by angiotensin converting enzyme. Angiotensin converting enzyme 2 functions as a negative regulator of renin angiotensin system. It catalyses both angiotensin I and angiotensin II to form Angiotensin 1-9 and Angiotensin 1-7 respectively and have vasodilator and cardioprotective effects

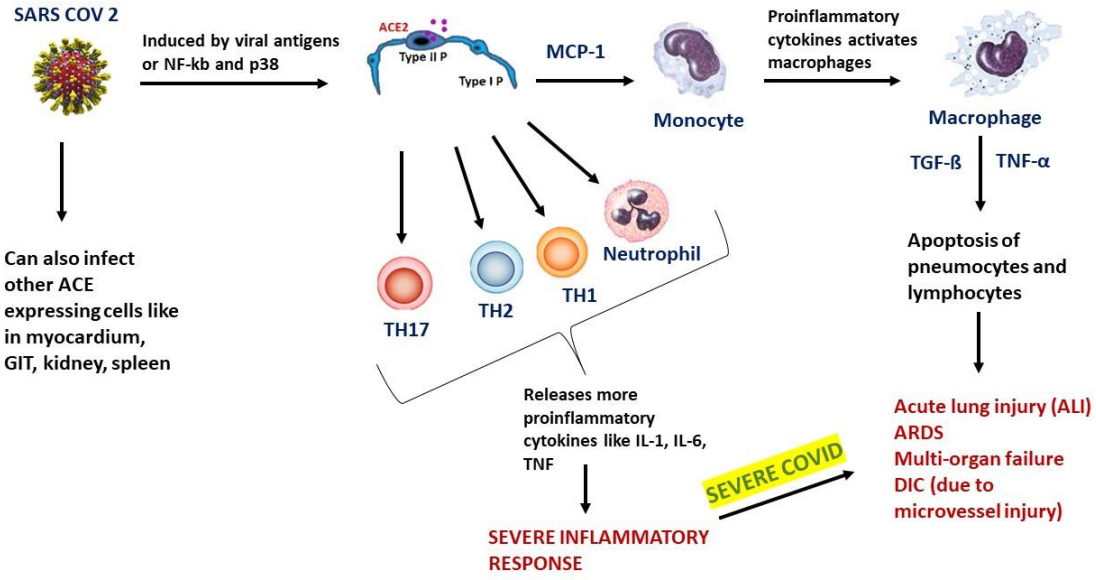

Figure 3: SARS- Cov 2 acts on pneumocyte and produce MCP-1. It attract monocytes to alveolar cavities, converting them to activated macrophages producing more cytokines such as TGF-β1 and TNF-α which induce apoptotic death of pneumocytes and lymphocytes resulting in ALI and ARDS. ACE2 also mediates the activation of neutrophils, NK cells, Th17 cells, Th2, Th1, dendritic and TNFα secreting cells, leading to severe inflammatory response which can result in DIC and multi organ failure. The virus can also infect the ACE2-expressing cells in the local sites such as myocardium, GIT, kidney, spleen.

In addition, blood hypo-oxygenation due to ARDS and disseminated intravascular coagulation resulting from impairment of micro vessel endothelial cells may further damage the structure and function of different organs in SARS patients, resulting in multi-organ dysfunction.

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CLINICAL PRESENTATION

The patients infected with COVID 19 can either be asymptomatic (without any symptoms) or symptomatic. The most commonly reported symptoms are-

RESPIRATORY SYMPTOMS [29]

- FEVER
- Dry Cough
- Shortness of breath
- Sore throat
- Sputum Production
- Nasal Congestion

GI SYMPTOMS [30]

- Diarrohea
- Vomiting
- Nausea
- Abdominal Pain
- Anorexia

Both adults and children can present with GI symptoms in absence of respiratory symptoms

NEUROLOGICAL SYMPTOMS [31]

Peripheral nervous system

- Ageusia
- Anosmia

Central nervous system

- Dizziness
- Headache
- Impaired consciousness
- Acute cerebrovascular disease
- Ataxia
- Seizure

CUTANEOUS MANIFESTATIONS [32]

- Erythematous Rash
- Localised/ Widespread Urticaria

OCULAR MANIFESTATIONS [33]

- Redness
- Foreign Body Sensation
- Tears

DISEASE PROGRESSION

LUNGS

The most prominent complication of COVID-19 is respiratory failure. [1] In lungs the infection may progress to either pneumonia or acute respiratory distress syndrome. ARDS tends to occur ~1-2 weeks into illness and is often precipitous and protracted. [34-36]

RENAL

Acute kidney injury has also been reported in COVID 19 infection. It occurs in the first few days after admission in patients with baseline chronic kidney disease, and after 7-10 days in patients with normal baseline renal function. [37] Mechanisms of renal injury have been hypothesized to include both acute tubular necrosis (ATN), direct cytotoxic effects of the virus itself, and immune-mediated damage. [37]

LIVER

Acute liver injury (more than three times upper limit of normal ALT or AST levels) has also been although less frequently in a number of cases. [36]

CARDIAC

Acute cardiac injury has been reported as an important manifestation in a large number of cases. Arrhythmias comprising of sustained ventricular tachycardia or ventricular fibrillation have also been reported. [40] Heart failure and myocardial dysfunction (myocarditis) have also been described in COVID-19 cases. [34,35,39,40]

One of the possible mechanisms for acute cardiac injury is due to presence of ACE2 receptors on the myocardium and vascular endothelial cells which provides a mechanism for direct viral infection of the heart with resultant myocarditis. [1] Another hypothesized mechanism of direct viral injury to the myocardium is through an infection-mediated vasculitis. [1] The ACE2 receptor is highly expressed in arterial and venous endothelial cells. Either direct viral entry into myocardial endothelial cells could trigger a vasculitis or presence of virus could lead to an indirect immunological response and resulting hypersensitivity reaction. [41,42] Systemic hyperinflammatory responses have also been thought as an important mechanism for cardiac injury in severe COVID-19 patients. [1]

THROMBOSIS

COVID 19 infection is also thought to be associated with venous or arterial thrombi though incidence has not been

published. Patients with moderate and severe infection have prolonged prothrombin time (PT), elevated D-dimer, and activated partial thromboplastin time (APTT levels) [2,38,43] resembling a DIC like picture. >70% of non-survivors of COVID 19 patients meet the criteria for DIC. [45] This picture is likely due to the hyperinflammation and immune activation seen in severe COVID-19 infection. [1]

INVESTIGATIONS

REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION (RT - PCR)

Polymerase Chain Reaction method is considered as the 'gold standard' for the detection of some viruses because of its high sensitivity, specificity and rapid detection. So, real-time reverse transcriptase-PCR (RT-PCR) has been used for the detection of SARS-CoV-2 due to these benefits. [44-47] However, the sensitivity and specificity of the real-time RT-PCR test is not 100% and it has its own disadvantages which include false negative and false positive results. [48]

RT-PCR uses primers in different genes for detection which can be affected by the variation of viral RNA sequences. False-negative results may occur by mutations in the primer and probe target regions in the SARS-CoV-2 genome. [48] So RT-PCR should be combined with other diagnostic modality like computed tomography (CT) of the chest in an appropriate clinical setting to best investigate any patient. [7]

Respiratory specimen collection method

1. Lower respiratory tract
   - Bronchoalveolar lavage (not routinely used due to logistic and medical reason)
   - Tracheal aspirate
   - Sputum (highest positive rate Yang et al) [49]
2. Nasopharyngeal and oropharyngeal swab (Commonly used)

A patient is declared negative if RT-PCR is negative from respiratory tract samples on two consecutive occasions which are 24 hours apart. [7]

Serum based testing such as rapid diagnostic kits, ELISA using IgM / IgG antibodies have been developed throughout the world [Abott laboratories, Roche, Biomediomics, ICMR-NIV]. The test detects both early marker and late marker, IgM/IgG antibodies in human finger-prick (capillary) or venous whole blood, serum, and plasma samples.

CHEST X-RAY FINDINGS

The most common findings on chest radiographs are multifocal ground-glass opacities and consolidation with a peripheral and lower lung zone predilection. Lung involvement may or may not be bilateral .Although chest x ray provides a cheap modality it lacks sensitivity and specificity for patients who have no/mild symptoms. [50]

CHEST ULTRASOUND

Chest ultrasound is primarily performed in some centers to triage patients, to monitor treatment effects, and for diagnosing complications of COVID-19 pneumonias, such as pleural effusions (uncommon). However ultrasound examinations should be kept to a minimum to avoid the risk of infection of the medical personnel. Transthoracic ultrasound is done usually as COVID19 affects lungs periphery. It detects subpleural consolidation and so called B-LINES (vertical reverberation artifacts that originate from the pleura) in a variety of patterns (focal, multifocal, consolidated). [50]

CT CHEST

CT chest findings although characteristic are nonspecific, however if properly correlated with other clinical findings, CT findings are highly suggestive of COVID -19.

The common CT imaging findings include ground-glass opacities (GGOs) (multifocal, patchy, bilateral in the lung periphery with basal predominance), consolidation which is seen in one-third of

the cases and interlobular thickening. As the disease progresses Linear opacities, ground glass superimposed with reticular abnormalities (crazy paving), and ground glass surrounded by ring of consolidation (reverse halo) can be seen commonly. [50,51] In severe cases, CT shows diffuse heterogeneous consolidation with ground-glass opacities, air bronchograms, and bronchiectasis, presenting as "white lung" when most lung lobes are affected.

OTHER LAB INVESTIGATIONS

The other common laboratory investigations include complete blood count, coagulation profile, serum biochemical tests (KFT, LFT, creatine kinase, lactate dehydrogenase, and electrolytes), myocardial enzymes, and procalcitonin. The most common reported laboratory findings include leucopenia (WBC count$<4 \times 10^9$/L), lymphopenia ($<1{\cdot}0 \times 10^9$/L), dearranged coagulation profile with increase in PT, INR and D-dimer levels. Increase in ALT, AST, Creatine Kinase (CK), Lactate dehydrogenase (LDH), ESR and C- reactive protein have been reported while there has been decrease in albumin levels. [2,52] Cardiac Troponin I has also been reported to be raised in patients who additionally suffer from virus related cardiac injury. [2] Procalcitonin values would remain within the reference range in several patients with non-complicated SARS-CoV-2 infection, whereas its substantial increase suggests bacterial coinfection in those developing severe form of disease. [53]

PREVENTION

No effective treatment / vaccination is available till date. As the infection spreads through droplets and close contact so following preventive measures have been advocated.

SOCIAL DISTANCING

Social distancing is a prevention and control intervention implemented to decrease/ avoid contact between those who are infected with a disease and those who are not to decrease or stop the disease transmission in a community. WHO recommends to maintain at least 1 metre (3 feet) distance between yourself and others.

HAND HYGIENE

Frequent and proper hand hygiene is a must for prevention of COVID 19. Like any other coronaviruses SARS-COV-2 has a lipid envelope which on washing with soap can break that fat in the envelope apart thereby making it impossible or difficult for the virus to infect human cells. Hence, handwashing with soap and water is by far the more powerful weapon than any other preventive measure. [7]

USE OF FACEMASK

According to WHO 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.

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. [54]

A surgical mask provides only "one-way protection" and prevents the spreading of droplets during sneezing and coughing from a wearer to the surrounding areas. In contrast, health care providers who are taking care of suspected or proven cases of COVID-19 must wear a specialized respirator, N95 which technically is a good fit mask preventing the entry of droplets and thereby minimizing the chance of acquiring the infection. [7]

TREATMENT

Till date no effective cure (vaccination /antiviral drugs) are available. However on May 1 2020 FDA issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. The investigational drug has been shown in a clinical trial to shorten the time to recovery in some patients. [55] Various other drugs which have been used as treatment with variable benefits include interferon α and β, Lopinavir/ritonavir, Faviparivir, Umifenovir, Darunavir, Sarilumab, chloroquine and hydroxychloroquine. [56]

However, supportive care to help alleviate symptoms is the best current approach being followed by all the medical centers worldwide. Supportive care includes isolating the patient to a negative pressure isolation room, and providing adequate rest, hydration, nutritional support and electrolyte balance. Complicated cases developing respiratory failure, ARDS, heart failure and septic shock also require a high level of care and other life support like invasive ventilation, extracorporeal membrane oxygenation (ECMO), renal replacement therapy and so on. [7]

USE OF CHLOROQUINE OR HYDROXYCHLOROQUINE

Chloroquine is a widely used anti-malarial drug which blocks viral infections by increasing endosomal pH which then interferes with virus/cell fusion. This drug also interferes with the glycosylation of cellular receptors for SARS-CoV and hence decreases virus-cell binding. [57]

HCQS has the same mechanism of action but a better safety profile than chloroquine and hence makes it a more preferable drug. Both these drugs have also shown to have immunomodulatory effects and can suppress the increase immune factors, which may play a role in reducing the severity of coronavirus disease. [58] Notably, CQ and HCQ prolong the QT and may induce arrhythmia; significant caution should be used in starting these agents in patients with a QTc>500 ms. [1]

Hydroxychloroquine with azithromycin has also showed significant reduction in viral load on day 6 of the treatment and much lower average carrying duration of the virus. [59] Currently many trials are underway to study the effect both for prophylaxis and treatment. [58] In India use of hydroxychloroquine as a prophylaxis has been approved for high risk population (Asymptomatic health care workers involved in the care of suspected or confirmed cases of COVID 19, Asymptomatic house hold contacts of laboratory confirmed cases) by ICMR.

USE OF CONVALESECENT PLASMA THERAPY

The plasma of recovered patients have been used to treat severely ill COVID 19 patients as it contains antibodies developed by the body in response to COVID 19 infection . Although it has not been approved by FDA it is being regulated under the investigational product. [56] India's Central Drugs Standard Control Organisation (CDSCO) has permitted the Indian Council of Medical Research (ICMR) to conduct a clinical trial of convalescent plasma for the treatment of Covid-19 patients.

CURRENT STATUS OF VACCINES

A number of vaccines are in different phases of clinical trials: Moderna vaccine (mRNA-1273 vaccine under phase 2 clinical trials, developed by US based moderna therapeutics approved by U.S FDA); Novavax Vaccine (NVX-CoV2373 vaccine); INO-4800 vaccine (DNA based vaccine developed by INOVIO pharmaceuticals (cleared phase 1 trials , to start phase 2 trials), Pfizer and BNTECH vaccine (BNT162 based on mRNA technology under collaboration of U.S company Pfizer and German company BNTECH, to start clinical trials in JULY); Johnson and Johnson Vaccine (working on an adenovirus-based vaccine and plans to

initiate a Phase 1 clinical study in September 2020), Ad5-nCoV vaccine (by Can Sino Biologics Inc under phase 1 clinical trial); PiCoVacc (By Sinovac Biotech under phase 1 clinical trial); ChAdOx1 nCoV-19 (developed by the University of Oxford and it has partnered up with UK-based AstraZeneca (Clinical trial on humans started in late April); Sanofi Vaccine (French pharmaceutical group in partnership with U.K. rival GlaxoSmithKline Plc); vaccine developed by British American Tobacco (vaccine developed using protein from tobacco leaves, to start Phase 1 clinical trials after approval from U.S FDA). [60]

VACCINE STATUS IN INDIA

India is set to begin clinical trials of its Bacille Calmette-Guérin (BCG) vaccine (used against tuberculosis to boost the immunity of the individual) on 6000 high-risk individuals.

It shall be done to understand its safety and efficacy in boosting immunity in the fight against COVID-19 disease and whether or not the BCG shots can reduce the severity of this highly infectious disease.

Bharat Biotech International Ltd (BBIL) has also teamed up with the Indian Council for Medical Research (ICMR) to develop a COVID-19 vaccine. Pune's Serum Institute of India (one of the largest vaccine maker of the world by volume)is working with the University of Oxford to make millions of potential coronavirus vaccine doses. [60]

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