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INVESTIGATIONAL TREATMENT OF COVID 19

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Abstract:
The recent covid 19 outbreak created a panic situation around the world . Covid 19 is the disease caused by a virus named SARS-COV-2 was discovered in december 2019 in Wuhan , China. It is very contagious and has quickly spread around the world . Covid 19 has a profound effect on health of public as well as economy .This review will introduce a general overview of coronavirus and describe its clinical feature, diagnosis and treatment of Covid 19 patient. A number of other drugs and vaccines are under clinical trial pipeline for investigation against COVID-19 infection. Despite multitude of treatment options available, treatment of choice is still NOW well established. Moreover, optimum supportive care and monitoring of seriously ill patients is the need of the hour.

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INTRODUCTION:

The recent COVID 19 pandemic sweeping the globe has caused great concern worldwide. Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a novel RNA coronavirus from the same family as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), was identified in early January2020 as the cause of a pneumonia epidemic affecting the city of Wuhan, the capital of Hubei province, from where it rapidly spread across China. After infecting and causing the death of thousands of persons in China, the virus has spread, reaching Italy and other European countries and the USA, with the number of confirmed new cases currently increasing every day.

Like other RNA viruses, SARS-CoV-2, while adapting to their new human hosts, is prone to genetic evolution with the development of mutations over time, resulting in mutant variants that may have different characteristics than its ancestral strains. Several variants of SARS-CoV-2 have been described during the course of this pandemic, among which only a few are considered variants ofconcern (VOCs) by the WHO, given their impact on global public health. Basedon the epidemiological update by the WHO, five SARS-CoV-2 VOCs have been identified since the beginning of the pandemic

ETIOLOGY

Coronaviruses (CoVs) are positive-stranded RNA(+ssRNA) viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs:

- **Alphacoronavirus** (alphaCoV)
- **Betacoronavirus** (betaCoV)
- **Deltacoronavirus** (deltaCov)
- **Gammacoronavirus (gammaCov)**

SYMPTOMS

- Fever
- Cough
- TirednessShortness of breath or difficulty breathing
- Muscle aches
- Chills
- Sore throat
- Runny nose
  - Headache
  - Chest pain
  - Pink eye (conjunctivitis)
  - Nausea
  - Vomiting

PATHOPHSIOLOGY

Coronaviruses are large, enveloped, single-stranded RNA viruses found in humans and other mammals, such as dogs, cats, chicken, cattle, pigs, and birds. Coronaviruses cause respiratory, gastrointestinal, and neurological disease. The most common coronaviruses in clinical practice are 229E, OC43, NL63, and HKU1, which typically cause common cold symptoms in immunocompetent individuals. SARS-CoV-2 is the third coronavirus that has caused severe disease in humans to spread globally in the past 2 decades.[1] The first coronavirus that caused severe disease was severe acute respiratory syndrome (SARS), which was thought to originate in Foshan, China, and resulted in the 2002-2003 SARS-CoV pandemic.[2] The second was the coronavirus-caused Middle East respiratory syndrome (MERS), which originated from the Arabian peninsula in 2012.[3]

SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona (Figure 2).[4] Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be a natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARS-CoV-2 via an intermediate host, such as the pangolin.

DIAGNOSIS

Diagnosis allows suspected people to understand that they are infected or not. Diagnosis can help them receive the care they need and it can help them take measures to cut back the probability of infecting others. People who don't know they are infected may not occupy at home and thereby risk infecting others.Diagnosis is done by various method given below

RT PCR TEST

Molecular tests (also known as PCR tests) detect the genetic material of the coronavirus. The Panbio™ COVID-19 Antigen Self-Test is an antigen test. Antigen tests detect coronavirus proteins. Antibody tests detect antibodies produced by your body's immune system in response to a previous COVID-19 infection.

RAPID ANTIBODY TEST

With the increase in the number of individuals with a suspected COVID-19 infection, it became necessary to adopt more rapid and low-cost diagnostic strategies to carry out extensive surveillance campaigns. To cope with this emergency, various rapid tests have been developed to detect viral antigens or anti-SARS-CoV-2 human antibodies in salivary, nasal or oropharyngeal swabs and blood samples. These tests are currently adopted for the frequent monitoring of personnel operating in at-risk environments such as schools or hospitals or to carry out extensive screening strategies on populations where a new outbreak of infection is suspected (70,71).

Compared to RT-PCR-based methods, rapid antigenic and rapid antibody tests are characterized by more rapid execution times of ~15-30 min, a lower cost and an easier procedure that does not require the presence of highly trained personnel. These tests are mainly built on platforms based on the principle of lateral flow immunoassay (LFIA) for the direct detection of viral proteins (rapid antigen tests) or human antibodies against SARS-CoV-2 antigens (rapid antibody tests). As regards rapid antigen tests, these allow the identification of COVID-19-positive individuals through the detection of SARS-CoV-2 nucleocapsid or Spike proteins (viral antigens) in swabs collected from the upper airways of the subject with suspected infection

Immunoenzymatically serological tests

Most of the immunoenzymatically serological tests used for COVID-19 investigations are based on the principle of indirect enzyme-linked immunosorbent assay (ELISA). Of note, ELISA is a colorimetric, chemiluminescent or fluorescent microwell plate-based assay used for the quantitation and detection of human proteins, immunoglobulins, antigens and other peptides through the binding between the target protein and a specific antibody that results in a detectable signal (85). This technique allows researchers to obtain highly specific and sensitive results in a relatively short time ranging from 1 to 5 h (85).

CT SCAN FINDING OF COVID 19

Typical CT findings of COVID-19 pneumonia are predominantly peripheral, bilateral ground-glass opacities (GGOs), consolidations, combination of GGOs with consolidations, Findings vary and usually progress during the course of the disease. In the early phase, the predominant finding is unilateral or bilateral small peripheral GGOs. While the size and number of GGOs and the number of affected lobes increase, crazy-paving pattern and consolidations appear as the disease progresses. Consolidations become denser at the peak stage (Fig. 1). Approximately after 2 weeks, opacities start to resolve gradually, and residual subpleural curvilinear lines, fibrous stripes, and GGOs may be seen [9, 12, 13].

and GGOs superimposed with interlobular/intralobular septal thickening creating a "crazy-paving" pattern and subpleural linear opacities. Air bronchograms, vascular enlargement, CT halo sign, and reverse halo sign are also reported. Cavitation, pleural or pericardial effusion, and lymphadenopathy are rarely observed [8,9,10,11].

TREATMENT

You test positive and are more likely to get very sick from COVID-19, treatments are available external icon that can reduce your chances of being hospitalized or dying from the disease. Medications to treat COVID-19 must be prescribed by a healthcare provider and started as soon as possible after diagnosis to be effective. Contact a healthcare provider right away to determine if you are eligible for treatment, even if your symptoms are mild right now.tThe various medication for treatment of covid 19 is as follow.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have a long-standing history in the prevention and treatment of malaria and the treatment of chronic inflammatory diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[7] Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.[9,10] Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC_{50}) in the low micromolar range.

Remdesivir

Remdesivir, an RNA polymerase inhibitor, is a monophosphate prodrug that metabolizes to an active C-adenosine nucleoside triphosphate analog and shows activity against RNA viruses, such as Coronaviridae and Flaviviridae . Triphosphate form of remdesivir is a substrate for RNA-dependent RNA polymerase complexes in coronaviruses and blocks viral RNA synthesis. Detailed mechanisms of remdesivir in inhibiting RNA polymerase is discussed in a review article by Saha et al. (2020a). It shows excellent *in vitro* activity against several

coronaviruses, including SARS-CoV-2 with EC_{50} and EC_{90} values of 0.77 and 1.76 µM, respectively. Remdesivir is considered a potential therapy for COVID-19 in the beginning of outbreak (Al-Tawfiq et al., 2020; Wang M. et al., 2020). Holshue et al. reported the first case of COVID-19 treated with remdesivir in the United States; the patient's condition improved one day after initiation of remdesivir . However, it is unclear whether the use of remdesivir resulted in this improvement. After that, remdesivir was compassionately used in 53 cases, of which 68% showed improvement in oxygen support, 47% were discharged, and 13% died (Grein et al., 2020).

During February–March 2020, the first randomized, placebo-controlled trial of remdesivir in China showed no virological benefits or clinical effect in reducing the recovery time and deaths compared with the placebo group. Moreover, it caused several adverse effects leading to early termination of the trial (Wang Y. et al., 2020). Other clinical trials of remdesivir are ongoing; preliminary data from an international multicenter, placebo-controlled double-blind randomized trial suggest that remdesivir is effective in reducing the recovery time from 15 to 11 days in hospitalized patients (Beigel et al., 2020). On April 29, 2020, based on the Adaptive COVID-19 Treatment Trial, the National Institute of Allergy and Infectious Diseases in the United States announced that remdesivir was better than placebo in reducing recovery time in hospitalized patients with advanced COVID-19 and lung involvement (National Institute of Allergy and Infectious Diseases, 2020). Currently, remdesivir is being tested as a specific treatment for COVID-19 and has been authorized for emergency use in people with severe symptoms in the United States (Food and Drug Administration, 2020c).

The dosage regimen of remdesivir under investigation is a single 200 mg loading dose, followed by 100 mg daily infusion. Remdesivir demonstrated linear pharmacokinetics within this dose range and an intracellular half-life of more than 35 h . Dose adjustment for patients with impaired hepatic or kidney function is not recommended. However, remdesivir therapy is not recommended in patients with an estimated glomerular filtration rate less than 30 ml/min .Adverse effects, including gastrointestinal and hepatic (elevated transaminase levels) dysfunction, and infusion site reactions were reported to be associated with remdesivir therapy .In a study without placebo, prolonged courses of 10-days remdesivir therapy did not show a significant difference from 5-days courses in patients with severe

COVID-19 (oxygen saturation ≤94% in ambient air) not requiring mechanical ventilation .

Lopinavir/itonavir and Other Antiretrovirals
Lopinavir/ritonavir, a US Food and Drug Administration (FDA)–approved oral combination agent for treating HIV, demonstrated in vitro activity against other novel coronaviruses via inhibition of 3-chymotrypsin-like protease.[21,22] No published SARS-CoV-2 in vitro data exist for lopinavir/ritonavir.[44] A systematic review of lopinavir/ritonavir for the treatment of SARS and MERS found limited available studies, with most of these investigating SARS. Clinical studies in SARS were associated with reduced mortality and intubation rates, but their retrospective, observational nature prevents definitive conclusions. The timing of administration during the early peak viral replication phase (initial 7-10 days) appears to be important because delayed therapy initiation with lopinavir/ritonavir had no effect on clinical outcomes.

Convalescent Plasma
Passive antibody administration for infectious diseases was introduced in the 1890s and has been largely replaced by antimicrobial agents in the 20th century (Casadevall and Scharff, 1995). CP became a treatment option for severe viral diseases such as SARS, Middle East respiratory syndrome, influenza A H1N1/2009, and Ebola virus disease with variable results, because no specific treatment was available for these diseases (Cheng et al., 2005; Yeh et al., 2005; Hung et al., 2011; Mair-Jenkins et al., 2015; van Griensven et al., 2016).

Many physicians hope that CP transfusion would be effective in treating COVID-19. In addition, the FDA (United States) accepted applications for expanded access and single patient emergency use of CP (Food and Drug Administration, 2020b). Up to 33% of patients who recovered from COVID-19 generated very low titers of SARS-CoV-2 neutralizing antibodies. Therefore, neutralizing antibody testing is highly recommended for CP donors (Robbiani et al., 2020; Wu et al., 2020).

Oxygenation And Ventilation Management In COVID-19Conventional Oxygen Therapy
Venturi mask must be administered to maintain oxygen saturation (SpO2) between 92 to 96% COVID-19 patients with associated respiratory insufficiency should be monitored closely with continuous pulse oximetry. Supplemental oxygen supplementation via nasal cannula or (< 88-90% if COPD). If there is improvement in clinical and oxygen saturation, supplemental oxygen should be

continued with periodic reassessment. If there is no clinical improvement worsening of symptoms and/or oxygen saturation, noninvasive treatments such as High-Flow Nasal Cannula (HFNC) or Noninvasive Positive Pressure Ventilation(NIPPV) are recommended. **Management of Acute Hypoxemic Respiratory Failure in COVID-19**

Flow Nasal Cannula (HFNC) and Noninvasive Positive Pressure Ventilation (NIPPV)

HFNC and NIPPV are noninvasive enhanced respiratory support modalities available in managing COVID-19-associated acute hypoxemic respiratory failure and are instrumental in avoiding invasive mechanical ventilation in carefully selected patients. A meta-analysis study evaluating the effectiveness of HFNC compared to conventional oxygen therapy and NIPPV before mechanical ventilation reported that HFNC, when used before mechanical ventilation, couldimprove the prognosis of patients compared to conventional oxygen therapy andNIPPV

VACCINES
COVID-19 vaccines are safe and effective. COVID-19 vaccination helps protect adults and children ages 6 months and older from getting severely ill with COVID-19 and helps protect those around them.Some people who are vaccinated against COVID-19 will still get sick and have a vaccine breakthrough infection because no vaccine is 100% effective. Vaccine effectiveness is a measure of how well vaccination protects people against outcomes such as infection, symptomatic illness, hospitalization, and death. Vaccine effectiveness is typically measured through observational studies specifically designed to estimate individual protection from vaccination under "real-world" conditions.

COVIDSHIELD VACCINE
It is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Following administration, the genetic material of part of corona virus is expressed which stimulates an immune response. Covishield Vaccine has been developed by AstraZeneca with Oxford university in the UK and is being manufactured by the Serum Institute of India (SII) in Pune. Successful clinical trials have been conducted in S.Africa, Brazil, and the UK with bridging study results in the Indian population based on which the approval was granted by DCGI (Drugs Controller General of India).

Covishield Vaccine is given as an injection into the muscle of the upper arm. The vaccination course consists of two separate doses. The government of India has extended the gap between the first and the second dose to 12-16 weeks. Taking just a single dose is not enough as it is insufficient to produce a protective level of antibodies in the body to prevent the infection. So make sure you turn up for the second dose.

PFIZER VACCINE
This is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that works against the S protein of the SARS-CoV-2 virus.[9] Thisvaccine allows for the body to create an antibodies response to neutralise the virus which is dependent on the S protein for entry via theACE2 receptor on type 2 alveolar cells.

MODERNA VACCINE
The nucleoside-modified mRNA in the Moderna COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 Spike antigen. The vaccine elicits an immune response to the Spike antigen, which protects against COVID-19

JOHNSON AND JOHNSON VACCINE
The COVID-19 vaccine from Johnson & Johnson uses existing technology that involves a virus called adenovirus, a common cause of respiratory infections. The DNA in the adenovirus is modified so that it produces a key part of the SARS-CoV-2 virus particle to which the body then develops an immune response.

CONCLUSION:
The situation of covid 19 is under control in India . The situation in China is still worse is under lockdown. Various drugs used in the treatment of covid 19 are not specially designed for Covid 19 treatment . Various research is still going on various drugs. Many aspects of transmission , infection and treatment remain unclear. Advances in prevention and effective management of COVID 19 will require basic and clinical investigational and public health and clinical interventions .

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