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**A COMPREHENSIVE REVIEW OF COVID-19**

 Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the ongoing 2019–20 coronavirus pandemic. Common symptoms include fever, cough, and shortness of breath. Other symptoms may include fatigue, muscle pain, diarrhea, sore throat, loss of smell, and abdominal pain. The time from exposure to onset of symptoms is typically around five days but may range from two to fourteen days. While the majority of cases result in mild symptoms, some progress to viral pneumonia and multi-organ failure. The virus is primarily spread between people during close contact, often via small droplets produced by coughing, sneezing, or talking. While these droplets are produced when breathing out, they usually fall to the ground or onto surfaces rather than being infectious over long distances. People may also become infected by touching a contaminated surface and then touching their eyes, nose, or mouth. The virus can survive on surfaces up to 72 hours. It is most contagious during the first three days after the onset of symptoms, although spread may be possible before symptoms appear and in later stages of the disease.

AETIOLOGY

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope 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), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages. Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.

Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) have been identified. Some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium.

In general, estimates suggest that 2% of the population are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections.

 Common human CoVs: HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alphaCoVs). They can cause common colds and self-limiting upper respiratory infections in immunocompetent individuals. In immunocompromised subjects and the elderly, lower respiratory tract infections can occur.

Other human CoVs: SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively). These cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations. Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 10% and 35%, respectively.

Thus, SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.

In genetic terms, (Chan *et al,*2020) have proven that the genome of the new HCoV, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV. For this reason, the new virus was called SARS-CoV-2. Its single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 amino acids. Although its origins are not entirely understood, these genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The potential amplifying mammalian host, intermediate between bats and humans, is, however, not known. Since the mutation in the original strain could have directly triggered virulence towards humans, it is not certain that this intermediary exists.

PATHOGENESIS

The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities specially in the epidemic region of China. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 the death cases increased to 56 deaths. The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years.

Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection. The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed. The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury. Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity.

HISTOPATHOLOGICAL FEATURES

(Tian *et al* 2020) and others reported histopathological data obtained on the lungs of two patients who underwent lung lobectomies for adenocarcinoma and retrospectively found to have had the infection at the time of surgery. Apart from the tumors, the lungs of both cases showed edema and important proteinaceous exudates as large protein globules. They also reported vascular congestion combined with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes.

CURRENT THERAPIES

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.

Among these recommendations, we report the strategies for addressing respiratory failure, including protective mechanical ventilation and high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV).

Intubation and protective mechanical ventilation

Special precautions are necessary during intubation. The procedure should be executed by an expert operator who uses personal protective equipment (PPE) such as FFP3 or N95 mask, protective goggles, disposable gown long sleeve raincoat, disposable double socks, and gloves. If possible, rapid sequence intubation (RSI) should be performed. Preoxygenation (100% O2 for 5 minutes) should be performed via the continuous positive airway pressure (CPAP) method. Heat and moisture exchanger (HME) must be positioned between the mask and the circuit of the fan or between the mask and the ventilation balloon.

Mechanical ventilation should be with lower tidal volumes (4 to 6 ml/kg predicted body weight, PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H2O. PEEP must be as high as possible to maintain the driving pressure (Pplat-PEEP) as low as possible (< 14 cmH2O). Moreover, disconnections from the ventilator must be avoided for preventing loss of PEEP and atelectasis. Finally, the use of paralytics is not recommended unless PaO2/FiO2 < 150 mmHg. The prone ventilation for > 12 hours per day, and the use of a conservative fluid management strategy for ARDS patients without tissue hypoperfusion (strong recommendation) are emphasized.

Non-invasive ventilation

Concerning HFNO or non-invasive ventilation (NIV), the experts' panel, points out that these approaches performed by systems with good interface fitting do not create widespread dispersion of exhaled air, and their use can be considered at low risk of airborne transmission. Practically, non-invasive techniques can be used in non-severe forms of respiratory failure. However, if the scenario does not improve or even worsen within a short period of time (1–2 hours) the mechanical ventilation must be preferred.

Other therapies

Among other therapeutic strategies, systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) are not recommended. Moreover, unselective or inappropriate administration of antibiotics should be avoided, although some centers recommend it. Although no antiviral treatments have been approved, several approaches have been proposed such as lopinavir/ritonavir (400/100 mg every 12 hours), chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours). Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) is also used.

Preclinical studies suggested that remdesivir (GS5734) — an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola — could be effective for both prophylaxis and therapy of HCoVs infections. This drug was positively tested in a rhesus macaque model of MERS-CoV infection.

In Italy, a great investigation led by the Istituto Nazionale Tumori, Fondazione Pascale di Napoli is focused on the use of tolicizumab. It is a humanized IgG1 monoclonal antibody, directed against the IL-6 receptor and commonly used in the treatment of rheumatoid arthritis.

When the disease results in complex clinical pictures of MOD, organ function support in addition to respiratory support, is mandatory. Extracorporeal membrane oxygenation (ECMO) for patients with refractory hypoxemia despite lung-protective ventilation should merit consideration after a case-by-case analysis. It can be suggested for those with poor results to prone position ventilation.

FUTURE OF COVID-19 ON PUBLIC HEALTH

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its subsequent spread has lived up to and surpassed many of the warnings and has caused an evolving global public health and economic crisis. Significantly, no pharmaceutical agents are known to be safe and effective at preventing or treating coronavirus disease 2019 (COVID-19), the resulting illness. This leaves the medical and public health community with only nonpharmaceutical interventions (NPIs) to rely on for reducing the burden of COVID-19. These measures aim to reduce disease transmission both locally and globally and include bans on public gatherings, compulsory stay-at-home policies, mandating closures of schools and nonessential businesses, face mask ordinances, quarantine and cordon sanitaire (ie, a defined quarantine area from which those inside are not allowed to leave), among others.

A common finding of these studies is that implementing NPIs, especially when done rapidly after initial detection of a new contagious pathogen, can reduce transmission.

In a study published in JAMA, (Pan *et al*, 2020) examined the epidemiologic outcomes following implementation of NPIs during the COVID-19 outbreak in Wuhan, China, shortly after the disease was identified. As it appears that the US and other nations will be living with NPIs to varying degrees during the immediate future,the suggestion that their application can quickly reduce COVID-19 transmission if applied effectively is reassuring.

Based on their sophisticated evaluation, (Pan *et al*,2020) suggest that this series of multifaceted NPIs was associated with improved control of the COVID-19 outbreak in Wuhan. The daily confirmed case rate per million people increased from 2.0 before January 10, to 45.9 between January 10 and 22, and to 162.6 between January 23 and February 1. The rate then decreased to 77.9 between February 2 and 16 and to 17.2 after February 16. In addition, the proportion of severe or critical cases decreased gradually over time: 53.1%, 35.1%, 23.5%, 15.9%, and 10.3%, respectively, for the 5 periods.

 Regardless, for the time being, NPIs are the only tool for controlling COVID-19, and this report in JAMA serves to quantify important metrics suggesting their potential effectiveness.

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