Features, Evaluation, and Treatment of Coronavirus (COVID-19)

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Continuing Education Activity

According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) in 2002-2003, and H1N1 influenza in 2009, have been recorded. Most recently, the Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012. An epidemic of cases with unexplained low respiratory infections was first detected in Wuhan, the largest metropolitan area in China's Hubei province, was first reported to the WHO Country Office in China, on 31 December 2019. Published literature can trace the beginning of symptomatic individuals back to the beginning of December 2019. As they were unable to identify the causative agent, these first cases were classified as "pneumonia of unknown etiology." The Chinese Center for Disease Control and Prevention (CDC) and local CDCs organized an intense outbreak investigation program. The etiology of this illness is now attributed to a novel virus belonging to the coronavirus (CoV) family, COVID-19. This activity describes the evaluation and treatment of COVID-19 and the role of the interprofessional team in managing patients with this condition.

Objectives:

- Identify the etiology of coronavirus in patients.
- Describe the findings expected in patients with coronavirus.
- Summarize treatment options available for coronavirus.
- Discuss interprofessional team strategies for improving care coordination and communication to care for patients with coronavirus and improve outcomes.

Earn continuing education credits (CME/CE) on this topic.

Introduction

According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, and H1N1 influenza in 2009, have been recorded. Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012.

In a timeline that reaches the present day, an epidemic of cases with unexplained low respiratory infections detected in Wuhan, the largest metropolitan area in China's Hubei province, was first reported to the WHO Country Office in China, on December 31, 2019. Published literature can trace the beginning of symptomatic individuals back to the beginning of December 2019. As they were unable to identify the causative agent, these first cases (n=29) were classified as "pneumonia of unknown etiology." The Chinese Center for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation program. The etiology of this illness was attributed to a novel virus belonging to the coronavirus (CoV) family.

On February 11, 2020, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, announced that the disease caused by this new CoV was a "COVID-19," which is the acronym of "coronavirus disease 2019". In the past twenty years, two additional CoVs epidemics have occurred. SARS-CoV provoked a large-scale epidemic beginning in China and involving two dozen countries with approximately 8000 cases and 800 deaths (fatality rate of 9,6%)[1], and the MERS-CoV that began in Saudi Arabia and has approximately 2,500 cases and 800 deaths (fatality rate of 35%) and still causes as sporadic cases[2].

This new virus is very contagious and has quickly spread globally. In a meeting on January 30, 2020, per the International Health Regulations (IHR, 2005), the outbreak was declared by the WHO a Public Health Emergency of International Concern (PHEIC) as it had spread to 18 countries with four countries reporting human-to-human transmission. An additional landmark occurred on February 26, 2020, as the first case of the disease, not imported from China, was recorded in the United States (US).

Initially, the new virus was called 2019-nCoV. Subsequently, the task of experts of the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus as it is very similar to the one that caused the SARS outbreak (SARS-CoVs).

The CoVs have become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species.[3] For reasons yet to be explained, these viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS. Interestingly, these latter viruses have probably originated from bats and then moving into other mammalian hosts — the Himalayan palm civet for SARS-CoV, and the dromedary camel for MERS-CoV — before jumping to humans. The dynamics of SARS-Cov-2 are currently unknown, but there is speculation that it also has an animal origin.

The potential for these viruses to grow to become a pandemic worldwide represents a serious public health risk. Concerning COVID-19, the WHO raised the threat to the CoV epidemic to the "very high" level, on February 28, 2020. On March 11, as the number of COVID-19 cases outside China has increased 13 times and the number of countries involved has tripled with more than 118,000 cases in 114 countries and over 4,000 deaths, WHO declared the COVID-19 a pandemic.

World governments are at work to establish countermeasures to stem the devastating effects and it has been estimated that strict shutdowns may have saved 3 million lives across 11 European countries[4]. Health organizations coordinate information flows and issues directives and guidelines to best mitigate the impact of the threat. At the same time, scientists around the world work tirelessly, and information about the transmission mechanisms, the clinical spectrum of disease, new diagnostics, and prevention and therapeutic strategies are rapidly developing. Many uncertainties remain with regard to both the virus-host interaction and the evolution of the pandemic, with specific reference to the times when it will reach its peak.

At the moment, the therapeutic strategies to deal with the infection are only supportive, and prevention aimed at reducing transmission in the community is our best weapon. Aggressive isolation measures in China have led to a progressive reduction of cases. From China, the disease spread to Europe. In Italy, in geographic regions of the north, initially, and subsequently throughout the peninsula, political and health authorities have made incredible efforts to contain a shock wave that has severely tested the health system. Afterward, the COVID-19 quickly crossed the ocean and as of June 20, 2020, about 2,282,000 cases (with 121,000 deaths) have been recorded in the US, whereas Brazil with more than 1,000,000 cases and about 50,000 deaths is the most affected state in South America and the second in the world after the US. Although over time the lethality rate (total number of deaths for a given disease in relation to the total number of patients) of COVID-19 has been significantly lower than that of the SARS and MERS epidemics, the transmission of the SARS-CoV-2 virus is much larger than that of the previous viruses, with a much higher total number of deaths. It has been estimated that about one in five individuals worldwide could be at increased risk of severe COVID-19 disease if they become infected, due to underlying health conditions[5].

In the midst of the crisis, the authors have chosen to use the "Statpearls" platform because, within the PubMed scenario, it represents a unique tool that may allow them to make updates in real-time. The aim, therefore, is to collect information and scientific evidence and to provide an overview of the topic that will be continuously updated.

Etiology

CoVs are positive-stranded RNA 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), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages. [6] 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) — capable of infecting humans — 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.[7]

- 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. In this regard, although high temperature decreases the replication of any species of virus. Currently, the inactivation temperature of SARS-CoV-2 must be well elucidated. It seems that this virus can be inactivated at about 27° C. On the contrary, it may resist the cold even below 0°C. 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. 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[8]. 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 the SARS-CoV-2 origins are not entirely understood, genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The genomic comparison between the human SARS-CoV2 sequence and known animal coronaviruses revealed, indeed, high similarity (96%) between the SARS-CoV2 and the betaCoV RaTG13 of bats (Rhinolophus affinis)[9]

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.

Transmission

Because the first cases of the COVID-19 disease were linked to direct exposure to the Huanan Seafood Wholesale Market of Wuhan, the animal-to-human transmission was presumed as the main mechanism. Nevertheless, subsequent cases were not associated with this exposure mechanism. Therefore, it was concluded that the virus is transmitted from human-to-human, and symptomatic people are the most frequent source of COVID-19 spread. Because of the possibility of transmission before symptoms, and thus individuals who remain asymptomatic could transmit the virus, isolation is the best way to contain this epidemic.

As with other respiratory pathogens, including flu and rhinovirus, the transmission is believed to occur through respiratory droplets (particles >5-10 μm in diameter) from coughing and sneezing. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces. Analysis of data related to the spread of SARS-CoV-2 in China seems to indicate that close contact between individuals is necessary. Of note, pre- and asymptomatic individuals may contribute to up 80% of COVID-19 transmission. The spread, in fact, is primarily limited to family members, healthcare professionals, and other close contacts (6 feet, 1.8 meters). Concerning the duration of contamination on objects and surfaces, a study showed that SARS-CoV-2 can be found on plastic for up to 2-3 days, stainless steel for up to 2-3 days, cardboard for up to 1 day, copper for up to 4 hours. Moreover, it seems that contamination is higher in intensive care units (ICUs) than general wards and SARS-Cov-2 can be found on floors, computer mice, trash cans, and sickbed handrails as well as in air up to 4 meters from patients.[10] However, because data so far available have been generated by experimental conditions, they must be interpreted with caution, also taking into account that the presence of viral RNA does not necessarily indicate that the virus is viable and potentially infectious.

Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days (median 5.1 days, similar to SARS [11]) and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18).[12] This data also showed that this novel epidemic doubled about every seven days,

whereas the basic reproduction number (R0 - R naught) is 2.2. In other words, on average, each patient transmits the infection to an additional 2.2 individuals. Of note, estimations of the R0 of the SARS-CoV epidemic in 2002-2003 were approximately 3.[13]

Epidemiology

Data provided by the WHO Health Emergency Dashboard report 8,525,042 confirmed cases of COVID-19, including 456,973 deaths (as of 1:38 pm CEST, 20 June 2020).

To date, there are cases in 215 Countries. Considering case comparison, in Europe there are 2,509,750 confirmed cases; Americas 4,163,813; Eastern Mediterranean 878,428; Western Pacific 203,490; South EastAsia 206,200; Africa 208,000. The highest fatal cases have been recorded in the US (121,130) followed by Brasil (49,156), and UK (42,589).

The most up-to-date source for the epidemiology of this emerging pandemic can be found at the following sources:

- The WHO Novel Coronavirus (COVID-19) Situation Board.
- The Johns Hopkins Center for Systems Science and Engineering site for Coronavirus Global Cases COVID-19, which uses openly public sources to track the spread of the epidemic.

Pathophysiology

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. For addressing pathogenetic mechanisms of SARS-CoV-2, its viral structure, and genome must be considerations. In CoVs, the genomic structure is organized in a +ssRNA of approximately 30 kb in length — the largest known RNA viruses — and with a 5′-cap structure and 3′-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized. The transcription works through the replication-transcription complex (RCT) organized in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Of note, transcription termination occurs at transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as templates for the production of subgenomic mRNAs. In the atypical CoV genome, at least six ORFs can be present. Among these, a frameshift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 with known or predicted RNA synthesis and modification functions non-structural proteins (nsps 1-16). Apart from ORF1a and ORF1b, other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins. [3] and accessory proteic chains. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs.

Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, research underlined that nsp is able to block the host innate immune response.[14] Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described. Other elements on which research must necessarily focus are the ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally different from those of SARS-CoV.

Among the structural elements of CoVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors.[15] Of note, in SARS-CoV-2, the S2 subunit — containing a fusion peptide, a transmembrane domain, and cytoplasmic domain — is highly conserved. Thus, it could be a target for antiviral (anti-S2) compounds or vaccines. On the contrary, the spike receptor-binding domain (RBD) presents only a 40% amino acid identity with other SARS-CoVs. RBD is a fundamental peptide domain in the pathogenesis of infection. It represents a binding site for the human Angiotensin-Converting Enzyme 2 (ACE2) receptor. Although initially assumed, inhibitors of the renin-angiotensin-aldosterone system do not increase the risk of hospitalization for COVID-19 and severe disease[16]. The RBD is the most variable and is decisive for the specificity of species. Although structural and functional analyzes demonstrate that the spike protein RBD domain is highly akin to the human ACE2 receptor, computational analyzes of the corresponding sequence reveal several critical amino acids that are compatible but not ideal for binding the ACE2 receptor. This could be evidence of a series of adaptive mutations, rather of an in vitro manufacture of the virus (the correspondence would have been direct). Interestingly, because there are no differences in ACE2 expression concerning gender, ages, and races, the differences in disease incidence and severity are probably related to different

immune factors rather than receptor binding.[17] On the other hand, cigarette smoking and inflammatory signaling can enhance receptor expression in the lung.[18]

Other factors enter the pathogenetic cascade and need to be better explained. For example, we need to understand why mortality and more severe disease forms are higher in men than in women. Probably, the hormonal structure plays a key role in this difference. In the prostate, for instance, androgens induce the expression of the serine protease TMPRSS2 used by Sars-CoV-2 for the S protein priming[19].

In summary, the spike RBD allows the binding to the ACE2 receptor in the lungs and other tissues. The presence within the spike protein of an amino acid site (polybasic site) allows the functional processing of the same by the human enzyme furin (protease). This process allows the exposure of the fusion sequences and therefore the fusion of the viral and cell membranes, a necessary passage for the virus to enter the cell.

In international gene banks such as GenBank, researchers have published several Sars-CoV-2 gene sequences. This gene mapping is of fundamental importance allowing researchers to trace the phylogenetic tree of the virus and, above all, the recognition of strains that differ according to the mutations. According to recent research, a spike mutation, which probably occurred in late November 2019, triggered jumping to humans. In particular, Angeletti et al. compared the Sars-Cov-2 gene sequence with that of Sars-CoV. They analyzed the transmembrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3 and found that position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine.[20] These data are providing us with important information on the potential origin of the virus. Interestingly, pangolin (Manis javanica) Covs have an RBD domain identical to that of the human SARS-CoV2 spike protein. However, neither bat CoVs nor those present in pangolins have the sequence of the polybasic site for furin, suggesting that natural selection must have also favored the acquisition of this site for the transition to human-human transmission. The matter of viral mutations is key for explaining potential disease relapses.

Mechanisms of SARS-CoV-2-induced Pneumonia

The pathogenic mechanism that produces pneumonia seems to be particularly complex. Clinical and preclinical research will have to explain many aspects that underlie the particular clinical presentations of the disease. The data so far available seem to indicate that the viral infection is capable of producing an excessive immune reaction in the host. In some cases, a reaction takes place which as a whole is labeled a 'cytokine storm'. The effect is extensive tissue damage with dysfunctional coagulation. Just a while ago, Italian researched introduced the term of MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) for underlying the lung viral injury associated with the inflammatory reaction and the microvascular pulmonary thrombosis. [21] While several cytokines such as the tumor necrosis factor α (TNF-α), IL-1β, IL-8, IL-12, interferon-gamma inducible protein (IP10), macrophage inflammatory protein 1A (MIP1A), and monocyte chemoattractant protein 1 (MCP1) are implicated in the pathogenic cascade of the disease, the protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced mostly by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. It also stimulates the production of acute-phase proteins and plays an important role in thermoregulation, in bone maintenance and in the functionality of the central nervous system. Although the main role played by IL-6 is pro-inflammatory, it can also have anti-inflammatory effects. In turn, IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases, and some types of cancer. It is also implicated in the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction. IL-6 is not the only protagonist on the scene. It was proved, for instance, that the binding of SARS-CoV-2 to the Toll-Like Receptor (TLR) induces the release of pro-IL-1β which is cleaved into the active mature IL-1β mediating lung inflammation, until fibrosis.[22]

Histopathology

Tian et al.[23] 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 'accidental' cases showed edema and important proteinaceous exudates as large protein globules. The authors also reported

vascular congestion combined with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes.

More recently, Zhang et al. [24] performed a postmortem transthoracic needle lung biopsy in a patient who died of COVID-19. Immunostaining showed diffuse alveolar injury and an important alveolar expression of viral antigens. In autopsies on COVID-19 cases, the authors [25] offered a detailed picture of the histological patterns in lung and extrapulmonary tissues. This picture was characterized by capillary congestion, necrosis of pneumocytes, hyaline membrane, interstitial edema, pneumocyte hyperplasia, and reactive atypia. Platelet-fibrin thrombi in small arterial vessels were the expression of intravascular coagulopathy. Moreover, in the lung they found infiltrates expressed as macrophages in alveolar lumens and lymphocytes in the interstitium. In summary, similar to SARS and MERS, severe COVID-19 lung damage was manifested in terms of Diffuse Alveolar Disease (DAD) with severe capillary congestion. Again, a lot of findings were suggestive for vascular dysfunction, in lung and other tissues.

History and Physical

The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and support in an ICU, to multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS). In one of the first reports on the disease, Huang et al. illustrated that patients (n. 41) suffered from fever, malaise, dry cough, and dyspnea. Chest computerized tomography (CT) scans showed pneumonia with abnormal findings in all cases. About a third of those (13, 32%) required ICU care, and there were 6 (15%) fatal cases.[26]

The case studies of Li et al. published in the New England Journal of Medicine (NEJM) on January 29, 2020, encapsulates the first 425 cases recorded in Wuhan.[12] Data indicate that the patients' median age was 59 years, with a range of 15 to 89 years. Thus, they reported no clinical cases in children below 15 years of age. There were no significant gender differences (56% male). On the contrary, in other reports, there is a lower prevalence in the female gender.

Clinical and epidemiological data from the Chinese CDC and regarding 72,314 case records (confirmed, suspected, diagnosed, and asymptomatic cases) were shared in the Journal of the American Medical Association (JAMA), providing the first important illustration of the epidemiologic curve of the Chinese outbreak.[27] There were 62% confirmed cases, including 1% of cases that were asymptomatic, but were laboratory-positive (viral nucleic acid test). Furthermore, the overall case-fatality rate (on confirmed cases) was 2.3%. Of note, the fatal cases were primarily elderly patients, in particular those aged ≥ 80 years (about 15%), and 70 to 79 years (8.0%). Approximately half (49.0%) of the critical patients and affected by preexisting comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases, died. While 1% of patients were aged 9 years or younger, no fatal cases occurred in this group.

The authors of the Chinese CDC report divided the clinical manifestations of the disease by there severity:

- Mild disease: non-pneumonia and mild pneumonia; this occurred in 81% of cases.
- Severe disease: dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] < 300, and/or lung infiltrates > 50% within 24 to 48 hours; this occurred in 14% of cases.
- Critical disease: respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); this occurred in 5% of cases.[27]

From the subsequent reports, it is estimated that in 70% of patients the disease is asymptomatic or with very mild symptoms, while in the remaining 30% there is a respiratory syndrome with high fever, cough until severe respiratory failure is reached who may require ICU admission. Thus, data obtainable from reports and directives provided by health policy agencies, allow dividing the clinical manifestations of the disease according to the severity of the clinical pictures. The COVID-19 may present with mild, moderate, or severe illness. Among the severe clinical manifestations, there are severe pneumonia, ARDS, as well as extrapulmonary manifestations and Systemic complications such as sepsis, and septic shock. The clinical course of the disease seems to predict a favorable trend in the majority of patients. In a percentage still to be defined of cases, after about a week there is a sudden worsening of clinical

conditions with rapidly worsening respiratory failure and MOD/MOF. As a reference, the criteria of the severity of respiratory insufficiency and the diagnostic criteria of sepsis and septic shock can be used.[28]

Uncomplicated (mild) Illness

These patients usually present with symptoms of an upper respiratory tract viral infection, including mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain, or malaise. New loss of taste and/or smell, diarrhea, and vomiting are usually observed. Signs and symptoms of a more serious disease, such as dyspnea, are not present.

Moderate Pneumonia

Respiratory symptoms such as cough and shortness of breath (or tachypnea in children) are present without signs of severe pneumonia.

Severe Pneumonia

Fever is associated with severe dyspnea, respiratory distress, tachypnea (> 30 breaths/min), and hypoxia (SpO2 < 90% on room air). However, the fever symptom must be interpreted carefully as even in severe forms of the disease, it can be moderate or even absent. Cyanosis can occur in children. In this definition, the diagnosis is clinical, and radiologic imaging is used for excluding complications.

Acute Respiratory Distress Syndrome (ARDS)

The diagnosis requires clinical and ventilatory criteria. This syndrome is suggestive of a serious new-onset respiratory failure or for worsening of an already identified respiratory picture. Different forms of ARDS are distinguished based on the degree of hypoxia. The reference parameter is the PaO2/FiO2 or P/F ratio:

- Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg. In not-ventilated patients or in those managed through non-invasive ventilation (NIV) by using positive end-expiratorypressure (PEEP) or a continuous positive airway pressure (CPAP) ≥ 5 cmH2O.
- Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg.
- Severe ARDS: PaO2/FiO2 ≤ 100 mmHg.

When PaO2 is not available, a ratio SpO2/FiO2 ≤ 315 is suggestive of ARDS.

Chest imaging utilized includes chest radiograph, CT scan, or lung ultrasound demonstrating bilateral opacities (lung infiltrates > 50%), not fully explained by effusions, lobar, or lung collapse. Although in some cases, the clinical scenario and ventilator data could be suggestive for pulmonary edema, the primary respiratory origin of the edema is proven after the exclusion of cardiac failure or other causes such as fluid overload. Echocardiography can be helpful for this purpose.

Extrapulmonary Manifestations and Systemic Complications

The involvement of other organs is an important aspect of the disease. For example, an understanding of pathophysiology and mechanisms of kidney damage and AKI is emerging in the context of critical forms of COVID-19, although further research is needed to identify patients at risk of AKI and guide management strategies. The clinical presentation ranges from mild proteinuria (>40% of patients have abnormal proteinuria at hospital admission[29]) to acute progressive renal injury (AKI) which represents a marker of MOD and disease severity and often requires renal replacement therapy (RRT) with the possible use of cytokine removal approaches[30]. Up to 20% of ICU patients with COVID-19 require RRT.[31]

Sepsis

According to the International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis represents a life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction.[32] The clinical pictures of patients with COVID-19 and with sepsis are particularly serious, characterized by a wide range of signs and symptoms of multiorgan involvement. These signs and symptoms include respiratory manifestations such as severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs expressed as laboratory

data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia. The reference for the evaluation of multiorgan damage and the related prognostic significance is the Sequential Organ Failure Assessment (SOFA) score, which predicts ICU mortality based on lab results and clinical data.[33] A pediatric version of the score has also received validation.[34]

Septic Shock

In this scenario, which is associated with increased mortality, circulatory, and cellular/metabolic abnormalities such as serum lactate level greater than 2 mmol/L (18 mg/dL) are present. Because patients usually suffer from persisting hypotension despite volume resuscitation, the administration of vasopressors is required to maintain a mean arterial pressure (MAP) ≥ 65 mmHg.

The Peculiar History of this New Disease In some patients, the clinical history of this disease occurs with particular characteristics. It foresees that the patient manifests above all fever, which is not very responsive to antipyretics, and a state of malaise. A dry cough is often associated. After 5-7 days, older patients with already impaired lung function begin to experience shortness of breath and increased respiratory rate. In more fragile patients, however, dyspnea may already appear at the onset of symptoms. On the other hand, in younger subjects and in those who do not have basic respiratory impairments or other comorbidities, dyspnea may appear later. In these patients experiencing worsening inflammatory-induced lung injury, there is a decrease in oxygen saturation (<93%). This seems to be the crucial phase of the disease, from this point onwards, there may be a rapid deterioration of respiratory functions. The scenario is truly incredible because, for patients who are paucisymptomatic and slightly hypoxic, the first therapeutic approach is oxygen therapy. Although this strategy is effective, the worsening of respiratory failure may occur in some patients. With the drive preserved, the next step, according to logic, is the NIV. This therapy has a rapid success by increasing the P/F. In some patients, however, there is a sudden, unexpected worsening of clinical conditions. Patients collapse under the operator's eyes and require rapid intubation and invasive mechanical ventilation. However, after 24-48 hours the patient can have a rapid improvement with an increase in P/F. Operators are therefore tempted to proceed with weaning. But very often, after an initial success, there is a new worsening of respiratory conditions, such as to require a new invasive therapy. Therefore, mechanical ventilation has also been suggested for 1-2 weeks.

Evaluation

Most countries are utilizing some type of clinical and epidemiologic information to determine who should have testing performed. In the US, criteria have been developed for persons under investigation (PUI) for COVID-19. According to the U.S. CDC, most patients with confirmed COVID-19 have developed fever and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing). If a person is a PUI, it is recommended that practitioners immediately put in place infection control and prevention measures. Initially, they recommend testing for all other sources of respiratory infection. Additionally, they recommend using epidemiologic factors to assist in decision making. There are epidemiologic factors that assist in the decision on who to test. This includes anyone who has had close contact with a patient with laboratory-confirmed COVID-19 within 14 days of symptom onset or a history of travel from affected geographic areas (presently China, Italy, Iran, Japan, and South Korea) within 14 days of symptom onset.

Diagnosis

Molecular Test

The WHO recommends collecting specimens from both the upper respiratory tract (naso- and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period. The samples require storage at four degrees celsius. In the laboratory, amplification of the genetic material extracted from the saliva or mucus sample is through a reverse polymerase chain reaction (RT-PCR), which involves the synthesis of a double-stranded DNA molecule from an RNA mold. Once the genetic material is sufficient, the search is for those portions of the genetic code of the CoV that are conserved. The probes used are based on the initial gene sequence released by the Shanghai Public Health Clinical Center & School of Public Health, Fudan University, Shanghai, China on Virological.org, and subsequent confirmatory evaluation by additional labs. If the test result is positive, it is recommended that the test is repeated for verification. In patients with confirmed COVID-19 diagnosis, the laboratory evaluation should be repeated to evaluate for viral clearance prior to being released from

observation. The availability of testing will vary based on which country a person lives in with increasing availability occurring nearly daily.

Serology

Despite the numerous antibody tests designed, to date serologic diagnosis has limitations in both specificity and sensitivity. Again, results from different tests vary. A CDC research on a test developed by the US Vaccine Research Center at the National Institutes of Health is ongoing. Of note, this test seems to have a specificity higher than 99% with a sensitivity of 96%.

Research is providing us with a lot of data on the role of serology. For example, it has been shown that there is no cross-reactivity between autoantibodies collected from serum samples from patients with autoimmune disease and SARS-CoV-2 antibodies. Nevertheless, further research is needed for elucidating several aspects of the matter. In particular:

- If IgG antibodies will provide immunity from future SARS-CoV-2 infection.
- On the protective titer of antibodies.
- On the duration of the protection.

Serologic, however, can have an important role in broad-based surveillance.

Laboratory Examinations

Concerning laboratory examinations:

- In the early stage of the disease, a normal or decreased total white blood cell count (WBC) and a decreased lymphocyte count can be demonstrated. Interestingly, lymphopenia appears to be a negative prognostic factor.
- Increased values of liver enzymes, lactate dehydrogenase (LDH), muscle enzymes, and C-reactive protein can be detected.
- Unless a bacterial overlap, a normal procalcitonin value is found.
- The elevated neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR) [neutrophil count divided by the result of WBC count minus neutrophil count], and platelet-to-lymphocyte ratio, can be the expression of the inflammatory storm. [35] The correction of these indices is an expression of a favorable trend.
- Increased D-dimer
- In critical patients, D-dimer value is increased, blood lymphocytes decreased persistently, and laboratory alterations of multiorgan imbalance (high amylase, coagulation disorders, etc.) are found.

Imaging

Chest X-ray Examination

Since the disease manifests itself as pneumonia, radiological imaging has a fundamental role in the diagnostic process, management, and follow-up. Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes and in the initial stages of the disease. At this stage, it can be completely negative. In the more advanced stages of infection, the chest X-ray examination generally shows bilateral multifocal alveolar opacities, which tend to confluence up to the complete opacity of the lung. Pleural effusion can be associated.

Chest Computed Tomography

Given the high sensitivity of the method, chest computed tomography (CT), in particular high-resolution CT (HRCT), is the method of choice in the study of COVID-19 pneumonia, even in the initial stages. Several non-specific HRCT findings and patterns can be found. Most of these findings may also be observed in other lung infections, such as Influenza A (H1N1), CMV, SARS, MERS, streptococcus, and Chlamydia, Mycoplasma. The most common findings are multifocal bilateral "ground or ground glass" (GG) areas associated with consolidation areas with patchy distribution, mainly peripheral/subpleural and with greater involvement of the posterior regions and lower lobes. The "crazy paving" pattern can be also observed. This latter finding is characterized by the presence of GG areas with superimposed interlobular septal thickening and intralobular septal thickening. It is a non-specific finding that can be detected in different conditions. Other findings are the "reversed halo sign" which is a focal area of GG delimited by a peripheral ring with consolidation, and the finding of cavitations, calcifications, lymphadenopathies, and pleural effusion.

Lung Ultrasound

Ultrasound can allow evaluating the evolution of the disease, from a focal interstitial pattern up to "white lung" with evidence often of subpleural consolidations.It should be performed within the first 24 hours in the suspect and every 24/48 hours and can be useful for patient follow-up, choice of the setting of mechanical ventilation, and for the indication of prone positioning.The main sonographic features are:

- Pleural lines often thickened, irregular, and discontinuous until it almost appears discontinuous; subpleural lesions can be seen as small patchy consolidations or nodules.
- B lines. They are often motionless, coalescent, and cascade and can flow up to the square of "White lung".
- Thickenings. They are most evident in the posterior and bilateral fields especially in the lower fields; the dynamic air bronchogram within the consolidation is a manifestation of disease evolution.
- Perilesional pleural effusion

In summary, during the course of the disease, it is possible to identify the first phase with focal areas of fixed B lines, a phase of numerical increase of the lines B up to the white lung with small subpleural thickenings, and further progress until evidence of posterior consolidations.

Treatment / Management

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 first step for addressing respiratory impairment. Non-invasive (NIV) and invasive mechanical ventilation (IMV) may be necessary in cases of respiratory failure refractory to oxygen therapy. Again, intensive care is needed to deal with complicated forms of the disease.

Concerning ARDS treatment, accumulating knowledge on the pathophysiology of lung damage, have gradually induced clinicians to review strategies for dealing with respiratory failure. As Gattinoni et al. suggested, COVID-19-induced ARDS (CARDS) is not a "Typical" ARDS.[36] This aspect of the disease is of fundamental importance and has probably negatively affected the therapeutic approach in the early stages of the pandemic. Indeed, despite at beginning of the pandemic, early IMV was postulated as the better strategy for addressing CARDS, in COVID-19 pneumonia the typical ARDS respiratory mechanics featuring reduced lung compliance (i.e., ability to stretch and expand lungs) cannot be found. On the contrary, in CARDS, good pulmonary compliance can be demonstrated. As a consequence, and in contrast to what was initially believed, NIV can have a key role in CARDS therapy.

O2 Fast Challenge

In a patient with a SpO2 < 93-94% (< 88-90% if COPD) or a respiratory rate > 28-30 / min, or dyspnoea, the administration of oxygen by a 40% Venturi mask must be performed. After a 5 to 10 minutes reassessment, if the clinical and instrumental picture has improved the patient continues the treatment and undergoes a re-evaluation within 6 hours. In case of failure improvement, or new worsening, the patient undergoes a non-invasive treatment, if not contraindicated.

HFNO and Non-invasive Ventilation

In regards to HFNO or 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.[37]

HFNO

Because this procedure has a greater risk of aerosolization, it should be used in negative pressure rooms.

Suggested ways to manage HFNO:

- Indication: when it is difficult to maintain SpO2 > 92% and/or not improved dyspnoea through standard oxygen.
- Setting: 30-40 L / min and FiO2 50-60%; adjust according to clinical response.
- Switch to NIV if the symptomatology is not improved after 1 hour with flow > 50 L / min and FiO2> 70%.

- HFNO can also be used for CPAP breaks (between CPAP cycles) and for assisted fibreoptic tracheal intubation in critically ill patients.[38]
- Contraindication to HFNO: hypercapnic patient.

Non-invasive ventilation and Continuous Positive Airway Pressure

NIV/CPAP has a key role in managing COVID-19-associated respiratory failure.

Suggested ways for performing NIV/CPAP:

- Interface: Helmet is preferred for minimizing the risk of aerosolization. In the case of NIV with face mask (full-face or oronasal), the use of expiratory valve integrated and non-tubes with exhalation port, and insert an antimicrobial filter on the expiratory valve is recommended.
- Setting:

  ◦ Continuous Positive Airway Pressure (CPAP): start with 8-10 cmH2O and FiO2 60%
  ◦ NIV (e.g., Pressure support ventilation, PSV): start with PEEP 5 cmH2O checking the tolerance of the patient and bring to 8-10 cmH2O, FiO2 60%, PS 8-10 cmH2O

- Management: do not make any changes in the first 24 hours; after at least 4-6 hours, if stabilized, detach for max 1 hour and allow the intake of small quantities of fluids; during the night, NIV continuously

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.

Lung-protective ventilation. 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. Lung-protective ventilation can also reduce the risk of new or worsening AKI by preventing ventilator-induced hemodynamic effects.

Other Therapies

Corticosteroids

Among other therapeutic strategies, although systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) were not recommended, in severe CARDS these drugs are usually used (e.g., methylprednisolone 1 mg/Kg/day). Of note, a recent large-size RCT (the RECOVERY trial) demonstrated that dexamethasone reduces deaths by one-third among critically ill COVID-19 patients. In the intervention group, 2,100 patients received dexamethasone (6 mg/day for 10 days) whereas in the control group patients (n=4,300) received standard care for the disease.[39]

Antiviral Agents

Although no antiviral treatments have been approved, several approaches have been proposed such as lopinavir/ritonavir (400/100 mg orally every 12 hours)[40]. Nevertheless, a recent randomized, controlled, open-label trial demonstrated no benefit with lopinavir/ritonavir treatment compared to standard care.[41] 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.[42] This drug was positively tested in a rhesus macaque model of MERS-CoV infection[43] and

recently in macaques infected with SARS-CoV-2[44]. Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) was also used.

Several anti-flu drugs such as oseltamivir have been used for the treatment of COVID-19 patients[45]. Another anti-flu medication, favipiravir demonstrated a certain efficacy against SARS-CoV-2 in vitro. Again, a retrospective investigation showed that the broad-spectrum antiviral arbidol can improve the discharging rate and decrease the mortality rate of COVID-19 patients.[46]

Antiviral/Immunomodulatory Drugs

Chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours) were proposed as immunomodulatory therapy. Of note, in a non-randomized trial, Gautret et al.[47] showed that hydroxychloroquine was significantly associated with viral load reduction until viral disappearance and this effect was enhanced by the macrolides azithromycin. In vitro and in vivo studies, indeed, have shown that macrolides may mitigate inflammation and modulate the immune system. In particular, these drugs may induce the downregulation of the adhesion molecules of the cell surface, reducing the production of proinflammatory cytokines, stimulating phagocytosis by alveolar macrophages, and inhibiting the activation and mobilization of neutrophils.[48] However, further studies are needed for recommending the use of azithromycin, alone or associated with other drugs such as hydroxychloroquine, outside of any bacterial overlaps. Again, attention must be paid with the concomitant use of hydroxychloroquine with azithromycin as the association can lead to a higher risk of QT interval prolongation and cardiac arrhythmias.[49] Chloroquine can also induce QT prolongation.

Serotherapy

Antibodies taken from the blood of healed individuals represent a therapeutic option currently under study. It is calculated that the dose of antibodies necessary for the treatment of a single patient with SARS-CoV-2, requires the removal of antibodies carried out by at least three patients recovered from the SARS-CoV-2 infection. A clinical trial has been launched (June 11, 2020) for investigating an antibody cocktail for the prevention and treatment of COVID-19.

Anticoagulant

Because COVID-19 patients have a higher incidence of venous thromboembolism and anticoagulant therapy is associated with reduced ICU mortality, it is suggested that patients should receive thromboprophylaxis. Moreover, in the case of known thrombophilia or thrombosis, full therapeutic-intensity anticoagulation (e.g., enoxaparin 1 mg/kg twice daily) is indicated.[50]

Inflammation Inhibitors

In Italy, a great investigation led by the Istituto Nazionale Tumori, Fondazione Pascale di Napoli is focused on the use of tocilizumab in addition to standard therapies. It is a humanized IgG1 monoclonal antibody, directed against the IL-6 receptor and commonly used in the treatment of rheumatoid arthritis, juvenile arthritis, giant cell arthritis, Castleman's syndrome, and for managing toxicity due to immune checkpoint inhibitors. Moreover, in the US, a Phase 2/3, randomized, double-blind, placebo-controlled study on sarilumab that is another anti-IL-6 receptor antibody, is ongoing.[51] Other similar strategies have been tested. Anakinra is a recombinant IL-1 receptor antagonist used to treat autoinflammatory disorders such as adult-onset Still's disease, systemic-onset juvenile idiopathic arthritis, and familial Mediterranean fever. The authors of a retrospective analysis showed that in patients with moderate-to-severe ARDS, and hyperinflammation (C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both), the use of anakinra induced clinical improvement in 72% of patients[52].

Targeting excessive host inflammation can be also addressed in another way. Acalabrutinib is a selective Bruton tyrosine kinase inhibitor, which regulates macrophage signaling and activation. Roschewski et al.[53] tested this agent on 19 patients hospitalized with severe COVID-19 in a prospective off-label clinical study. The proved that the treatment improved oxygenation in a majority of patients, ameliorating measures of inflammation such as C-reactive protein and IL-6.

Other Therapies

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.

Unselective or inappropriate administration of antibiotics should be avoided, although some centers recommend it.

Prevention

Preventive measures are the current strategy to limit the spread of cases. Because an epidemic will increase as long as R0 is greater than 1 (COVID-19 is 2.2), control measures must focus on reducing the value to less than 1.

Preventive strategies are focused on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient. For instance, droplet, contact, and airborne precautions should be adopted during specimen collection, and sputum induction should be avoided.

The WHO and other organizations have issued the following general recommendations:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen, in particular, in emergency medicine departments, the application of strict hygiene measures for the prevention and control of infections.
- Individuals that are immunocompromised should avoid public gatherings.

The most important strategy is to frequently wash the hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment.

Isolation and contact tracing alone represent insufficient measures to control the spread of the disease. Nevertheless, their efficacy increases with the distancing. To this regard, a modeling study with data from over 40,000 participants in the UK, demonstrated that the combination of isolation and contact tracing with physical distancing measures can be effective for reducing the accounting of cases that would need to self-isolate and of contacts that would need to be traced, controlling in turn, the disease transmission. [54]

Healthcare workers caring for infected individuals should utilize contact and airborne precautions to include PPE such as N95 or FFP3 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.

The Vaccine

Meanwhile, scientific research is growing to develop a Sars-CoV-2 vaccine. There are more than 100 candidate vaccines in development worldwide, of those 8-10 under clinical investigation. In this 'vaccine gaming', Chinese researchers appear to be ahead, having completed a phase I investigation. Nevertheless, several studies are ongoing, especially in the US, and the UK.

First-in-Human Trial

The results of a phase I clinical trial carried out in a single center in Wuhan (China), designed to evaluate the safety, reactogenicity and immunogenicity of a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the spike glycoprotein have been published. Between 16 and 27 March 2020, 108 healthy adults aged 18-60 years were consecutively enrolled and assigned to one of the three study groups according to the dose of vaccine administered (intramuscular injection). The primary outcome was the evaluation of adverse events in the 7 days following vaccination. Safety was assessed over 28 days after vaccination. The specific antibodies were measured with the enzyme-linked immunosorbent assay (ELISA) method. Of the 108 enrolled subjects, 36 received a low dose, 36 a medium dose, and 36 a high dose of vaccine. Among participants, 87 (81%) reported at least one adverse reaction within the first 7 days of vaccination: 30 (83%) in the low-dose group, 30 (83%) in the medium-dose group and 27 (75%) in the low-dose group high dose group, with no significant difference in the overall number of adverse reactions between groups. The most common injection-site adverse reaction was pain, while the most commonly reported systemic adverse reactions were fever, fatigue,

headache, and muscle pain. No serious adverse events were reported within 28 days. On the 7th day after vaccination, 9 participants (8%) had a mild to moderate increase in total bilirubin, 10 (9%) an increase in alanine aminotransferase, and 4 (4%) fasting hyperglycemia, but no cases were considered clinically significant. The specific antibody responses against SARS-CoV-2 peaked 28 days after the administration of the vaccine dose and the specific immune response of T lymphocytes was evident from the 14th day. The phase II trial (NCT04341389) currently ongoing will provide additional information on the safety and immunogenicity of this vaccine[55].

Other Ongoing Investigations

A Chinese phase II, randomized, double-blinded, placebo-controlled clinical trial was designed to evaluate the immunogenicity and safety of Ad5-CoV which encodes for a full-length spike protein of SARS-CoV-2. the estimated study completion date is January 31, 2021 (NCT04341389). In the US, a company study is aimed at evaluating the safety, tolerability, immunogenicity, and potential efficacy of up to 4 different SARS-CoV-2 RNA vaccine candidates against COVID-19. The spike sequence is included in two of the candidate vaccines, while the other two include the RBD. This Phase 1/2, randomized, placebo-controlled, observer-blind, dose-finding, study will end in March 2023 (NCT04368728). Another Phase I study was designed to assess the safety, tolerability, and immunological profile of a vaccine administered by intradermal injection followed by electroporation which is a technique used to facilitate the passage of drugs into the cell membrane, through the use of a specific device (NCT04336410). A study promoted by the National Institute of Allergy and Infectious Diseases (NIAID) divides the participants into three parallel arms based on the dose of a lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for the spike protein of SARS-CoV-2 (mRNA-1273). It is administered through an intramuscular injection on day 1 and day 29 and the subjects will be followed in follow-up for a period of 12 months after the second administration. The study completion date is scheduled for June 1, 2021 (NCT04283461).

Differential Diagnosis

The symptoms of the early stages of the disease are nonspecific. Differential diagnosis should include the possibility of a wide range of infectious and non-infectious (e.g., vasculitis, dermatomyositis) common respiratory disorders.

- Adenovirus
- Influenza
- Human metapneumovirus (HmPV)
- Parainfluenza
- Respiratory syncytial virus (RSV)
- Rhinovirus (common cold)

For suspected cases, rapid antigen detection, and other investigations should be adopted for evaluating common respiratory pathogens and non-infectious conditions.The Mayo Clinic proposed a COVID-19 self-assessment tool designed for establishing a potential candidate for a COVID-19 diagnostic test (https://www.mayoclinic.org/covid-19-self-assessment-tool).

Pertinent Studies and Ongoing Trials

Multiple studies globally are investigating the use of remdesivir, a broad-spectrum antiviral as well as immunomodulation strategies such as the IL-6-targeting therapies tocilizumab [NCT04317092], sarilumab [NCT04315298]

Prognosis

Preliminary data suggests the reported death rate ranges from 1% to 2% depending on the study and country. The majority of the fatalities have occurred in patients over 50 years of age. Young children appear to be mildly infected but may serve as a vector for additional transmission.

Complications

Long term complications among survivors of infection with SARS-CoV-2 having clinically significant COVID-19 disease are not yet available. The mortality rates for cases globally remain between 1% to 2%. Follow-up studies will clarify the extent of the sequelae on organ functions, such as respiratory, renal, cardiovascular, as well as psychological/psychiatric, and related to chronic pain problems [56].

Deterrence and Patient Education

Patients and families should receive instruction to:

- Maintaining good social distance is mandatory for preventing the spread of the disease.
- Strict personal hygiene measures (hands wash) are necessary for the prevention and control of this infection.
- Avoid close contact with subjects suffering from acute respiratory infections.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes, and wash their hands.
- Immunocompromised patients should avoid public exposure and public gatherings. If an immunocompromised individual must be in a closed space with multiple individuals present, such as a meeting in a small room; masks, gloves, and personal hygiene with antiseptic soap should be undertaken by those in close contact with the individual. In addition, prior room cleaning with antiseptic agents should be undertaken and performed before exposure. However, considering the danger involved to these individuals, exposure should be avoided unless a meeting, group event, etc. is a true emergency.

Pearls and Other Issues

The following pearls have been provided by health professionals in Italy, the UK, and the U.S. and are based on anecdotal experience.

- The disease is not a 'typical' adult respiratory distress syndrome (ARDS).
- Microvascular thrombosis in the pulmonary circulation can lead to an increased dead space. Early pulmonary fibrosis following the disease has been reported from Italy. This could be oxygen-related or inflammation-related. Pulmonary thrombosis has been associated with wedge-shaped infarcts in the lungs on imaging, without the evidence of deep vein thrombosis.
- In both NIV and MIV, prone positioning of the patient can be essential and should be done early. This procedure should be done more than once a day. Keep a lower threshold for proning even if the usual threshold is a PF ratio of 130. The benefit of proning lasts less than 4 hours in the early phase, but as the disease advances into ARDS, the beneficial effects become long-lasting. Prone positioning in MIV should be followed by HNFO or NIV (preferably in the prone position) if the saturation is not maintained. There should be a low threshold for intubation if NIV fails for more than an hour.
- Many centers use inhaled nitric oxide and prostacyclin with good effect. Tachyphylaxis with nitric oxide is usually seen after 4-5 days.
- Maintain euvolemia. There is a high risk of acute kidney injury with hypovolemia.
- Extubation should be delayed more than usual, especially if the inflammatory markers are remaining high. Always perform a leak test before extubation.
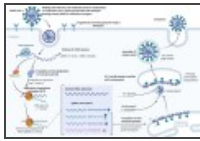
Enhancing Healthcare Team Outcomes

Since the first outbreak of coronavirus (COVID-19) in Wuhan, China, the disease is spreading worldwide. Individuals at the extreme of ages and those that are immunocompromised are at the most significant risk. All health care workers should understand the presentation of the disease, workup, and supportive care. Further, health professionals should be aware of the precautions necessary to avoid the contraction and spread of the disease. [Level 5]
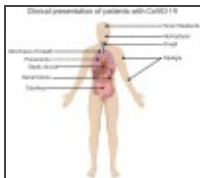
Continuing Education / Review Questions

- Access free multiple choice questions on this topic.

- Access free CME on this topic.
- Comment on this article.

Figure

Covid 19, Corona Replication. Contributed by Rohan Bir Singh, MD
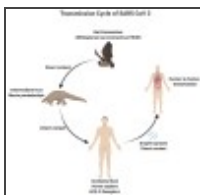

Figure

Clinical Presentation of Patients with CoVID-19. Contributed by Rohan Bir Singh, MD; Made with Biorender.com
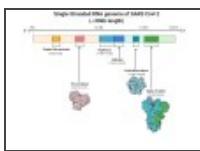

Figure

SARS- CoV 2 Structure. Contributed by Rohan Bir Singh, MD; Made with Biorender.com

Figure

Transmission Cycle of SARS CoV 2. Contributed by Rohan Bir Singh, MD; Made with Biorender.com

Figure

Single-stranded RNA genome of SARS-CoV2. Contributed by Rohan Bir Singh, MD; Made with Biorender.com

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