

COVID-19: Basic Treatment and Impacts

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Abstract

Introduction: A new coronavirus, called SARS-COV-2, was identified in China in late 2019. This virus has been rapidly disseminating from person to person causing COVID-19 that is inducing significant mortality and morbidity worldwide.

Treatment: After taking proper infection control measures, Patients can be treated at home, hospitals or ICU according to the severity of the disease. To date, there is no approved specific treatment for this virus. However, intense several studies have been carried out to find out appropriate treatment or vaccine for COVID-19. Severe infection is usually associated with hypoxemia and requires hospital admission. Those patients require oxygen therapy whether through conventional oxygen, HFNC, NIV or mechanical ventilation.

Conclusion: COVID-19 is a highly contagious disease that needs more research in order to approve appropriate treatment for it. The footprints of COVID-19 on humans are evident even though some populations are underestimating these impacts.

Keywords: SARS-COV-2; Coronavirus; Wuhan City; Seasonal Flu Versus COVID-19

Abbreviations

SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus 2; 2019-nCoV: 2019-New Coronavirus; COVID-19: Coronavirus Disease 2019; HFNC: High Flow Nasal Cannula; NIV: Non-Invasive Ventilation; ICU: Intensive Care Unit; WHO: World Health Organization; PaO₂/FiO₂: Arterial Oxygen Partial Pressure/Fractional Inspired Oxygen; CDC: Centre for Disease Control and Prevention; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; ACEI: Angiotensin Converting Enzyme Inhibitor; ARBs: Angiotensin Receptor Blockers; FDA: Food and Drug Administration; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; SARS: Severe Acute Respiratory Syndrome; ECMO: Extracorporeal Membrane Oxygenation; ARDS: Acute Respiratory Distress Syndrome; PEEP: Positive End Expiratory Pressure

Introduction

In December 2019, a novel coronavirus was detected in Wuhan city where a rush of pneumonia cases was identified. This was followed by an increasing number of cases in other countries worldwide [1]. While the virus was firstly called 2019-nCoV then recently severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the disease caused by this virus is referred to as COVID-19 by the WHO [2]. In January 2020, the WHO declared the first outbreak a 'public health emergency of international concern' [3], then a pandemic on 11 March 2020 [4]. Between December 2019 and April 2020, about three and half million confirmed infected cases and just above 240 000 deaths were reported by the European Centre for Disease Prevention and Control [5]. Researchers have been making concerted efforts to understand the different categories and pathogenesis and, draw a management plan for COVID-19 [6].

Categories: In general, COVID-19 patients can be categorized into five groups [7]:

1. **Asymptomatic or pre-symptomatic:** Patients who tested positive for SARS-CoV-2 but they have not had symptoms.
2. **Mild disease:** Patients with non-specific symptoms like fever, cough, and sore throat but there is no dyspnea and abnormal imaging.
3. **Moderate:** Clinical or radiological evidence of lower respiratory tract infections but oxygen saturation above 93% on room air.
4. **Sever:** If the patient has any of the following:
 - RR > 30.
 - Oxygen saturations < 93% on room air.
 - $\text{PaO}_2/\text{FiO}_2 < 300$.
 - Lung infiltrations > 50%
5. **Critically-ill (about 5% of infected cases):** Any patient with profound respiratory failure, septic shock or multi-organ failure.

Where to treat?

This relies mainly on the severity of the disease at presentation keeping in mind some populations carry a higher risk to rapid progression of the disease.

Home-based care: this should be reserved for asymptomatic and mild cases with no evidence of major respiratory symptoms including significant dyspnea or hypoxemia. However, specific measures ought to be taken for avoidance dissemination of infection and early detection of cases indicated to hospitalization to allow early intervention [8]. Also, groups with a high risk for severe progression should be closely monitored for any deterioration of their symptoms [9].

While patients and their household members should self-isolate themselves, the patients should be kept in separate well-ventilated rooms. These patients, as well as their household members, should be aware of basic infection control measures. The patients should wear masks as much as possible, particularly when contacting others. Also, hand hygiene in the form of frequent hand washing, respiratory hygiene by covering their cough and sterilization of surfaces can minimize the risk of transmission of infection.

CDC suggests two strategies for terminating patients' isolation. The first strategy is test-based which requires patients to be asymptomatic without using any medications and have at least two-negative nasopharyngeal swabs taken at least 24-hour apart. However, the non-test based strategy relies mainly on patients' symptoms. Seven days from starting of the symptoms and at least three days without any symptoms should pass before ending the isolation [10]. For household members, they should be self-isolated for 14 days from the last day of possible contact.

Lastly, all patients should have access to obtain medical advice with any deterioration of their conditions [8].

Hospital-based health care: this can be allocated to patients with moderate, severe and critically-ill patients. Severe cases are recommended to be treated in AIIRs (Air-born infection isolation room) [7]. For any hospitalized patient, the following blood tests have prognostic values in the treatment of COVID-19 patients [6]:

1. D-Dimer > 1000 ng/ml.
2. C-reactive protein (CRP) > 100 mg/L.
3. Lactate dehydrogenase (LDH) > 245 units/L
4. Troponins > 2 X upper limit of normal.
5. Ferritin > 500 mcg/L.

6. Creatine kinase > 2 X upper limit of normal.
7. Absolute lymphocytic count < 800 microL.

ICU-based care: For patients requiring invasive mechanical ventilation and those with multi-organ failure or hemodynamic instability [6].

Therapeutic options

General measures

1. **Empirical antibiotics:** Because superimposed bacterial infection for COVID-19 patients is not a prominent feature, empirical antibiotics prescription is not recommended. However, antibiotics can be prescribed if the diagnosis has not been confirmed when the differentiation between community acquired pneumonia and COVID-19 is not possible. Evidence of superadded bacterial infection including isolation of organisms or new clinical and radiological signs is another indication for antibiotic administration. Low Procalcitonin level can be used as proof to avoid antibiotic therapy [11].
2. **Anti-coagulants:** Starting prophylactic anticoagulants for COVID-19 patients is recommended [12]. Not only have most admitted COVID-19 patients been old-aged with multiple co-morbidities [11] but also Several studies reported an association between COVID-19 and higher levels of D-Dimer suggesting an increased risk for thromboembolism [13-15]. Ideally, low molecular weight heparin is used unless contraindicated. The impacts of prophylactic and therapeutic anticoagulants on the outcome of COVID-19 patients are still under investigation [6]. However, the incidence of coagulopathy and DIC are associated with poor outcomes [15].
3. **NSAIDs:** While there are insufficient recommendations against NSAIDs, more clinical data are required to approve this strategy [6]. As a general rule, Paracetamol is the preferred antipyretic to use in COVID-19 patients. Having said that many organizations do not recommend against NSAIDs if indicated [16-18].
4. **Steroids:** Like influenza and Middle East respiratory syndrome coronavirus (MERS-COV), glucocorticoids are suggestive to be associated with poor outcomes in patients with COVID-19 [19]. Therefore, the WHO and CDC do not recommend systemic steroid use unless there are other indications [20,21]. Also, there are some recommendations against inhaled steroids [6].
5. **Nebulizers:** Whenever possible, nebulizers should be avoided and MDI can be used instead to decrease the incidence of transmission of infection [6].
6. **Handling routine medications:** Unless contraindicated, long-term medications like statins, ACEI and ARBs should be continued as usual [6].
7. **Infection control:** Specific infection control measures including patients' isolation, wearing appropriate PPE and using negative pressure rooms should be incorporated in the management of COVID-19 patients [6].

Potential specific medications

Several cohorts have been investigating some medications that have been utilized to treat other diseases [6]. However, in general, there is no approved safe and effective treatment to COVID-19 [22].

- 1) **Chloroquine and hydroxychloroquine:** It is found that these medications inhibit only the *in vitro* growth of some viruses including SARS [23]. However, there is no strong data to recommend for or against their use [22]. FDA issued an emergency approval for 4-aminoquinolines use in hospitalized adults with COVID-19 if involvement in clinical trials is not possible [24]. 4-aminoquinolines can be used only if there is neither access to clinical trials nor contraindications to their use [6]. Although their side effects are rare, they may be fatal including severe cutaneous reactions [25], fulminant hepatic failure [26] and serious arrhythmias [27]. Because they can trigger long QT intervals, close monitoring of patients should be applied [28], particularly when used with Macrolides [27].

- 2) **Remdesivir:** A new nucleotide analog that has antiviral activity, both *in vitro* and in animal models, inhibiting the replication of SARS viruses [29] including SARS-COV-2 [30]. It is found that it can reduce viral loads and mitigate severe lung injury in mice [29]. In the USA, Remdesivir was used for the first time to treat a COVID-19 patient who showed improvement in his clinical condition in 24 hours [31]. Wider Clinical trials have been performed in China-Japan Friendship Hospital to check the impact of Remdesivir on COVID-19 [32]. The most common side effects of Remdesivir are nausea, vomiting and deranged liver enzymes [6].
- 3) **Lopinavir-ritonavir:** Anti-retroviral drugs used to treat HIV and have activity against SARS-COV *in vitro* [33] and MERS-CoV in animal studies [34]. A randomized control study was carried in china and found no benefit of their oral use in treating COVID-19 patients [35]. However, the recovery trial run by Oxford University has been performed comparing the effectiveness of some medications including Lopinavir-ritonavir on COVID-19 patients [36].
- 4) **Favipiravir:** An anti-viral drug that has been manufactured in Japan [36]. It is reported that Favipiravir is more effective than Arbidol against non-sever COVID-19 pneumonia [37]. Clinical trials have been evaluating its use to treat these patients in the USA [6].
- 5) **Interferon β 1a:** An inhaled drug that found to reduce the replication of MERS-COV both *in vitro* and in animals [34]. Interferon β represents part of the natural lung defense mechanism against viruses. Therefore, the idea behind its use in COVID-19 is to improve the lung immune response and reduce the severity of lung injury. The drug is still in the stage of clinical trials [36].
- 6) **Tocilizumab:** Anti-IL6 that has been used to treat rheumatoid arthritis [36]. It is observed that patients with severe COVID-19 have Significantly-high IL6 levels [38]. China's National Health Commission recommends its usage for severe COVID-19 with high IL6 levels. While some case reports revealed favorable outcomes with Tocilizumab [39,40], systemic randomized control trials to support its use are pending [6].
- 7) **Convalescent plasma:** Whereas convalescent plasma therapy showed promising outcomes in the treatment of SARS [41], it did not show significant survival benefits compared to conservative management when used to treat the Ebola virus disease [42]. It is found that convalescent plasma has the ability to neutralize SARS-COV-2 separated from the lungs of a critically-ill patient [43]. To give maximal neutralizing effects, It should be collected within two weeks of patient recovery which represents a challenge to its use [32]. In the USA, the FDA approved its use in clinical trials, expanded access programs and emergency individual use to make it available to sever or life-threatening patients [44]. A case series, including five patients with severe COVID-19, showed promising effects of convalescent plasma in the form of reduced viral loads, decreased severity index and improve oxygenation [45]. However, a causal effect has not been established. For this reason, large cohorts are required to prove its efficacy [6].
- 8) **Combined azithromycin and hydroxychloroquine:** Although there is some evidence supporting the use of this combination for rapid eradication of SARS-COV-2 [46], another study did not show significant effects on virus clearance in severe cases [47]. Additionally, both agents can prolong the QT interval; therefore, simultaneous use of Azithromycin and Hydroxychloroquine may potentiate the risk of development of arrhythmias [6].
- 9) Basic principles of treatment of critically-ill patients:
 - It is proved that while dyspnea starts late in critical patients (around day 6), the rate of progression to ARDS afterward is relatively rapid. The characteristic picture of those is severe hypoxemia. However, hypercapnia is a rare finding. More than 50% of such patients require mechanical ventilation [48].
 - The most common complications associated with COVID-19 patients with ARDS are cardiac affection, acute kidney injury and deranged liver enzymes [49]. Coagulopathy and Neurologic complications including encephalopathy are common in those patients as well whereas sepsis, septic shock and multi-organ dysfunction are relatively less common [50].

- For those patients, maintaining oxygen saturations above 90%, optimally between 92 and 96% are recommended except for patients with chronic hypercapnia whose target saturations are between 88 and 92% [51]. Oxygen saturations above 96% are found to be associated with poor outcomes [52,53].
- If the patient does not meet the target saturations (> 90%) on low-flow oxygen, elective non-invasive modalities (HFNC or NIV) are preferred to invasive mechanical ventilation. However, some experts recommend directly invasively ventilating those patients, particularly elderly with several comorbidities or confusion [50].
- There is some evidence that HFNC may be superior to NIV in reducing mortality and the need for intubation [51]. Nevertheless, NIV can be more appropriate in specific situations including hypercapnic respiratory failure and cardiogenic pulmonary edema. For both modalities, patients should be closely monitored clinically and with ABGs for any deterioration with a low threshold for intubation [50].
- Some case reports found beneficial effects for the prone position on oxygen saturation [54-56].

Invasive mechanical ventilation

Indications [50]:

- Rapid progression.
- Lack of improvement on > 40 L/min. high-flow Oxygen and $\text{FIO}_2 > 60\%$.
- Pending hypercapnia, increased work of breathing and confusion.
- Multi-organ failure or hemodynamic instability.

Ventilator settings for COVID-19 and ARDS [50,51]:

- Volume-limited assist control mode.
- Low tidal volume ventilation ($V_t \leq 6 \text{ ml/Kg}$ predicted body weight).
- Target Plateau pressure $\leq 30 \text{ cm H}_2\text{O}$.
- High PEEP (> 10 cm H_2O) with close monitoring for barotrauma.
- If the patient is still hypoxemic, prone position for 12 - 16 hours a day should be applied.
- With ventilator dyssynchrony, intermittent IV neuromuscular blockers can be used if required.
- If ventilator dyssynchrony and/or high plateau pressure persist despite deep sedation, continuous IV neuromuscular blockers can be started.
- Recruitment maneuvers can be used to open the atelectatic alveoli if the patient is still hypoxemic.
- ECMO can be used for refractory hypoxemia caused by ARDS.

Personal experience

Based on a lot of discussion with experts and from my personal experience in treating hospitalized patients with COVID-19, most of the previously enumerated medications have made no changes in the mortality, particularly for those with severe disease. Even with NIV, the improvement of most cases is negligible while weaning from NIV is awkward with a high failure rate. Unfortunately, the mortality rate for patients who required mechanically ventilated is high and may reach up to 88% [57].

Some physicians still suggest that this virus is powerless and all these measures of quarantine should not have been taken. They claim that these measures have negative impacts on different aspects mainly the economy and politics. At the same time, they pretend that its mortality has been the same as the seasonal flu.

In my opinion, there is a big difference between both. While there are some similarities in symptoms and mode of transmission, SARS-COV-2 is more vigorous and carries more risk to the human being in several aspects.

SARS-COV-2 is a novel virus that has not been fully identified and there is no acquired immunity against it. Therefore, there are a lot of research is being carried out worldwide to find an effective medication or vaccine that may take months or even years to be prepared. Then, the infectivity of SARS-COV-2 is completely different. Not only can this virus be transmitted from asymptomatic patients as stated in a Chinese study [58] but it is also significantly more contagious than the seasonal flu [59].

Additionally, it is reported that the overall case fatality of COVID-19 is approximately 2.3% [60] and may reach 30% in elderly with chronic diseases [61] compared to about 1 in 1000 of all flu-infected cases [59]. To date, the general figure of COVID-19 related death may be comparable to that of the seasonal flu. However, this has been achieved after taking strict measures of quarantine, isolation and social distancing in most countries worldwide. I think despite being painful, if these measures had not been taken, the death rate would have been terrible with unbearable overburdens on health care systems that are not well-prepared for such pandemics. This can be best explained by the fact that the virus is easily transmissible from person to person and some populations have a higher percentage of elderly people with multiple comorbidities that have a considerably higher mortality rate. Lastly, the COVID-19 pandemic is not a replacement to the seasonal flu; therefore, rather than having one pandemic, currently there are two of them causing at least a double toll of death.

Conclusion

COVID-19 presentation is variable ranging from simple illness with mild symptoms in the majority of cases to very severe disease in about 5% that usually requires ICU admission. From December 2019 until April 2020, all research has failed to approve a specific medication or vaccine for COVID-19. Due to its highly transmissible properties, a lot of measures have been taken in many countries to control the rate of infection. In spite of having several impacts on different aspects of human daily life, I believe these measures are mandatory to save not only lives but also the health care systems.

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