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Etiopathogenesis, Diagnosis and Clinical Management of SARS-COV-2

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ABSTRACT

The pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) remained a significant issue for global health, economics, and society. This coronavirus seems to be associated with a substantial number of adult respiratory illnesses especially when rhinovirus infection is infrequent. Patients show flu-like symptoms with a dry cough, sore throat, high fever, and breathing problems. As this spreading virus has no treatment to date therefore prevention and management are the best options. This article focuses on the use of various therapeutic agents and their efficacy in SARS-CoV-2 patients in various levels of severity. The review also discusses the pathogenesis of SARS-CoV-2 along with the basics of oxygen therapy and mechanical ventilation for the patients having severe conditions. Use of Dexamethasone is promising as the new efficient drug for the treatment of SARS-CoV-2. It also depicts the consequences of the children suffering from SARS-CoV-2 which leads to multisystem inflammatory syndrome and Cytokine Release Syndrome (CRS)

1. Introduction

The main objective of this article is to provide unbiased information to the healthcare workers on the aspects of pathogenesis, prevention, management, and treatment of SARS-COV-2.

The worldwide pandemic caused by the novel acute coronary syndrome coronavirus 2 (SARS-CoV 2) has resulted in a new and lethal disease known as coronavirus disease in 2019. It has the potential to cause a devastating social, economic, and political crisis that will leave deep scars. Countries are racing to slow the spread of the virus by testing and treating patients, carrying out contact tracing, limiting travel, quarantine citizens, and canceling large gatherings [1]. It is an enveloped virus with non- segmented with a positive Ribose nucleic acid (RNA) genome which causes a respiratory illness with a clinical severity arising from asymptomatic, mild to a severe acute respiratory disorder and even multi-organ failure. As it has a major and severe threat to the public with the contamination and transmission which is causing severe complications. It does not only cause viral pneumonia but has a major complication for the cardiovascular system as well as the patient having other comorbidities (like diabetes, hypertension) [2]. It is a large spherical pleomorphic particle with bulbous projections. The envelope consists of a lipid bilayer in which the membrane, the envelope, and the spike are anchored on the surface. It belongs to the orthocoronavirinae subfamily and order nidovirales. Members of beta coronavirus subgroup A have a spike-like protein known as Hemagglutinin Esterase (HE) [3].

2. Clinical Presentation

AAs already discussed most of the SARS-CoV-2 cases are asymptomatic for several days on an average this was found to be 14 days described as the incubation period. But this count various and the median value is 4-5 days. From the studies, it is that there are the following symptoms as cough (86%), fever and chills (85%), shortness of breath (80%), diarrhea (27%), nausea (24%), redness of eyes (15%). There include other symptoms even are sputumproduction, headache, rhinorrhea, dysgeusia, sore throat, and vomiting. Still, experiments are going on and new symptoms are being evaluating [4].

3. Pathogenesis

The unique character of SARS-CoV-2 is the fusion cleavage site (RPPA sequence) [5]. After entering into epithelial cells these destroy the cells mainly involved in innate immunity in airways. The three main components of innate immunity include epithelial cells, alveolar macrophages, dendritic cells. SARS-CoV can also bind with dendritic cell-specific intracellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN related protein (DC-SIGNR) [6]. From the data analysis, they have concluded that many patients may die due to excessive response towards the virus by host immune system and release abnormally high quantity of leukocytes, cytokines into the circulating system and lead to a syndrome named as cytokine release syndrome (CRS). This condition leads to severe organ damage in patients with other comorbidities. This phenomenon in which there exist huge amounts

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of cytokines in the blood is termed as a cytokine storm. Cytokines that include are Interleukin (IL-1, IL-2, IL-6, IL-10, IL-12), Tumor Necrosis Factor (TNF-α), Interferon (INF-α). The most important of all is IL-6 as they are also found in ARDS and it is also a pro-inflammatory agent that in turn activates many other inflammatory mediators that worsens the condition [7] in Figure 1.

4. Stages of Infection

Based on the infection of the virus in the cells SARS-COV-2 can be divided into three different clinical stages. They are described in Table 1.

About 80% of patients, the virus is restricted to the upper and conducting airways. These individuals are monitored at home with therapy [8]. The Reverse Transcription Polymerase Chain Reaction (RT-PCR) is used to detect the virus in this stage by collecting the samples from the nasal cavity. Nasal swabs are more sensitive than the throat swabs [9].

The pathological study reveals that there is alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. This leads to fibrosis and other forms of ARDS [8,10]. Elderly people are at high risk as they have decreased immune response and reduced ability to repair the damaged epithelium, reduced mucociliaryclearance this allows the virus to move to the gas exchange site more easily [11].

5. Laboratory Investigations

Laboratory findings of SARS-COV-2 include leukopenia and lymphopenia, the elevation of aminotransferase levels, C- reactive protein, D-dimer, ferritin, lactate dehydrogenase.

Abnormalities in chest X-ray (bilateral multi-focal; opacities), computed tomography (bilateral peripheral ground-glass opacities) imaging may be normal in the early stage of infection and abnormal in absence of symptoms [4]. The conformation of SARS-CoV-2 is mainly done by two tests that include virological tests that help in diagnosing the symptomatic patient especially in comorbid conditions, focus mainly on detection for the presence of viral genetic material (antigens) and another set is serological tests that are done for indirect detection for antibodies against SARS-CoV-2 [12].

6. Management Of SARS-COV-2

Treatment options:

- Oxygen therapy
- Mechanical ventilation (invasive & non-invasive)

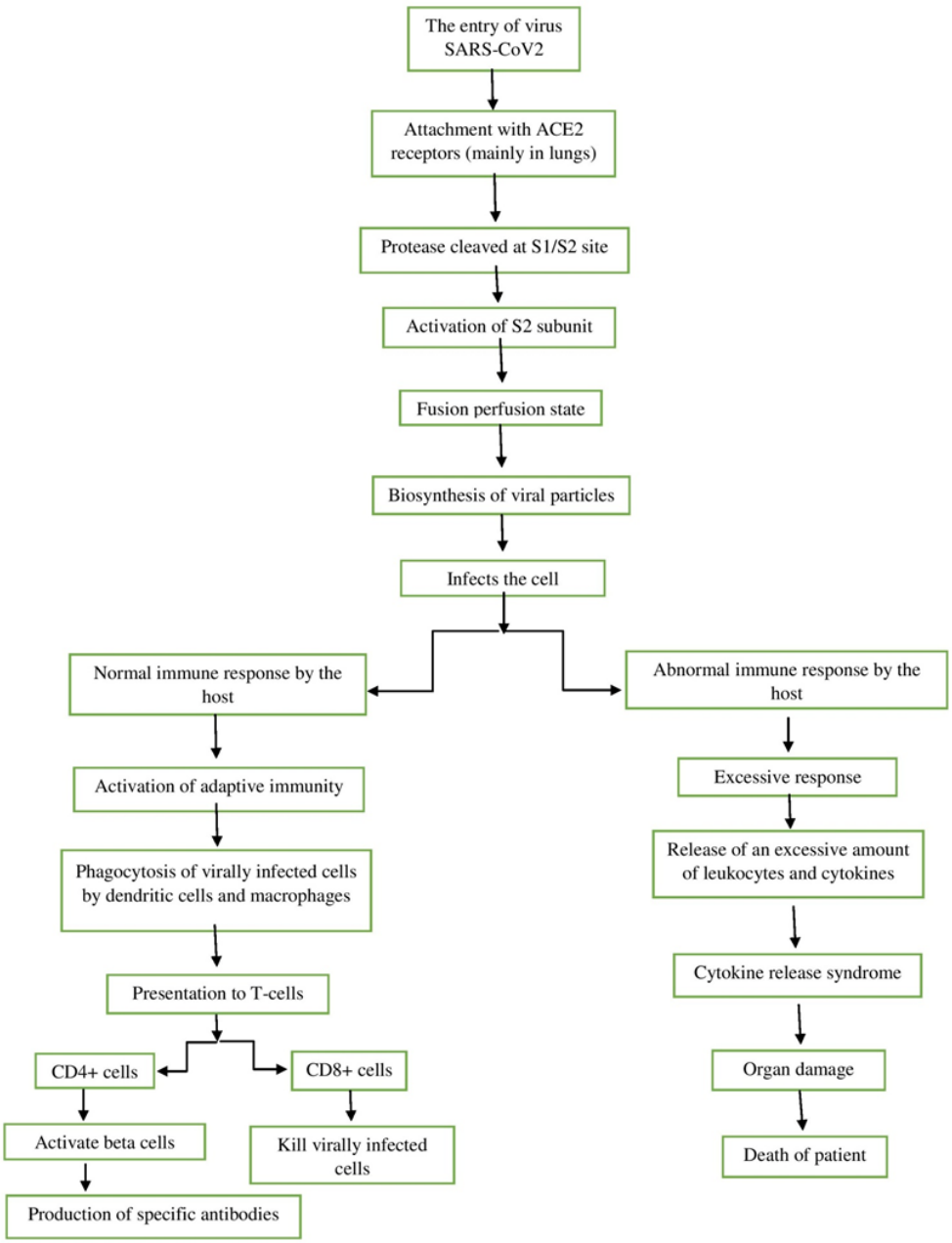

Figure 1: Pathogenesis of SARS-CoV-2

Table 1: Stages of Infection of SARS-CoV-2

Stage	Stage-1	Stage-2	Stage-3
Characteristics	Asymptomatic (for 1-2 days).	The response of upper and conducting airways (Next few days).	Hypoxia and progression to Acute Respiratory Distress Syndrome (ARDS).
Location Of Virus	In epithelial cells of the nasal cavity bound with ACE2.	Conducting airways.	Alveolar Type 2 cells, Apical cilia, Microvilli.
Host Immune Response	Limited innate immunity.	Interferon Responsive Gene C-X-C motif chemokine ligand 1 (CXCL)10 is produced (disease marker of SARS).	Progressive immune response (In elderly due to decreased immunity condition progress to ARDS).

- Antibiotics (e.g. Azithromycin)
- Hydroxychloroquine
- Antivirals (e.g. Remdesivir, Lopinavir, Ritonavir, Favipiravir)
- Corticosteroids (e.g. Dexamethasone)
- Convalescent Plasma
- Non-SARS-CoV-2 specific I.V Immunoglobulin

7. Oxygen Therapy

This oxygen therapy depends on the condition as well as the presentation of the patient. WHO guidelines recommend supplemental oxygen therapy for patients with respiratory distress, hypoxia, or shock with a target of SpO_2 > 94%. Sometimes nasal cannulas are not recommended as they may cause a higher spread of droplets. In SARS-CoV-2 19 patients there is a high risk of hypoxia where there is a need for increased intubation and invasive mechanical ventilation. Therefore, close monitoring is advised. SpO_2 levels depend on the condition of the patient. High Flow Nasal Oxygen (HFNO) is useful for patients with hypoxemic respiratory failure and even it can prevent the intubation of some patients. Negative pressure rooms are preferable for patients receiving HFNO. The risk of airborne transmission is low if the staff wearing the Personal Protective Equipment (PPE) [13]. In adults with SARS-CoV-2 and acute hypoxemic respiratory failure, SpO_2 target should not be maintained higher than 96% [14].

8. Mechanical Ventilation

8.1 Non-Invasive:

It is a procedure where a patient is given a proper face mask or nasal mask under positive pressure and is used for the treatment of hypercapnic Respiratory Failure. Negative prognostic factor includes overall severity, renal failure, and hemodynamic instability. Routine use of Non-Invasive Ventilation (NIV) is not recommended as there is a high failure rate [13]. Amount of pressure alternates depending upon the pressure of inhalation or exhalation. It may improve oxygenation but doesn't change the original disease course and doesn't play an important role in severe hypoxemic Respiratory Failure. Current studies say that non-invasive ventilation for SARS-CoV-2 19 is associated with a high failure rate delayed intubation and possibly increased risk of aerosolization with poor mask fit. In deteriorating patient endotracheal intubation should be used [15].

8.2 Invasive:

Lung protective mechanical ventilation is the recommended strategy for the management of Acute Respiratory Failure. It's in process with the use of low tidal volume strategy (4-8 ml/kg) predicted body weight and limiting plateau pressure to less than 30 cm H_2O. Alternate modes of ventilation such as APRV may be considered based on clinical preference and local experience [16]. Patients of SARS-CoV-2 19 are kept in deeper sedation to reduce the risk of ventilator desynchrony and control respiratory drive neuromuscular blockade are recommended for the patient with worsening hypoxic or hypercapnia. In most SARS-CoV-2 19 patient endotracheal tubes are used with very few requiring tracheostomies [17].

9. Azithromycin and Hydroxychloroquine

Although antibiotics have no role in the treatment of coronavirus infection Azithromycin and hydrochloroquinine played an important role in viral replication in vitro and block infection by increasing the endosomal pH and by blocking glycosylation of the cellular receptors of SARS-COV2. QT Interval (QTC) prolongation is a known adverse effect of hydrochloroquinine [18].

10. Antivirals

There are no Food and Drug Administration (FDA) approved drugs for the treatment of SARS-CoV-2 but there are many drugs under investigation that include the following:

10.1 Remdesivir:

Remdesivir, a nucleotide analog, has shown efficacy against SARS-CoV-2 *in vitro*. Adverse effects include nausea, vomiting, and transaminitis.

10.2 Lopinavir:

Lopinavir, an antiviral used in the treatment of HIV infection, was initially shown to have in vitro activity against SARS in 2003.

10.3 Ritonavir:

Ritonavir is added to lopinavir to increase the plasma half-life through the inhibition of cytochrome P-450. Despite initial enthusiasm, a randomized control trial failed to show mortality benefits [19].

10.4 Favipiravir:

It is an oral antiviral approved for treatment for influenza in Japan. It selectively inhibits RNA polymerase which is necessary for viral replication. Now the same drug is used in SARS-CoV-2 treatment clinical trials are going on by japan in phase-3 and united states in phase-2 with approximately 50 patients has started in may 2020 [20].

11. Convalescent Plasma

The use of plasma from individuals who have recovered from SARS-COV-2 has the potential to provide passive immunity through the transfer antibodies.(1)Randomised clinical trials are under evaluation fo the use of plasma in treating SARS-COV-2 under FDA guidance but few adverse effects include transfusion-associated acute lung injury, transfusion-associated circulatory overload, allergic transfusions keeping all these into consideration clinical trials are still in progress [4].

12. Non-SARS-CoV-2-Specific I.V. Immunoglobulin

Intravenous immunoglobulin is a type of product obtained from plasma used in treating primary and secondary immunodeficiency disorders. The mechanism in this therapy is to lessen inflammatory response in host also IgG dimers helps in blocking the activation of FcγR on immune effector cells. From the previous studies, this gave significant recovery from the condition of infection so it has become potential treatment in SARS-COV-2 [21].

FDA has approved this in consideration with some indications that are:

- Primary immune disorders
- Thrombocytopenic purpura
- Kawasaki disease
- Motor neuropathy
- Prophylaxis of various bacterial and viral infections [4].

13. Corticosteroids

Based on data from SARS-CoV (2002-2003), Middle Eastern Respiratory Syndrome (MERS), influenza, and respiratory syncytial virus, the WHO issued interim guidance in January 2020 against the routine use of corticosteroids in the treatment of SARS-COV-2. However, as with ARDS, there is a possible role for corticosteroid administration as it suppresses tissue inflammation in the lungs but runs the risk of delaying clearance of SARS-CoV-2 [1].

The positioning of oxygen therapy equipment is also important as they increase the ease of breathing, reduce oxygen expenditure, and optimize oxygenation this includes high supported sitting for adults and prone position in case of the conscious condition.

Investigating hematology and biochemistry reports, Electrocardiogram (ECG) and chest imaging should be preferred in cases of severe complications like acute respiratory distress syndrome, acute kidney failure, acute cardiac injury, intravascular coagulation, a shock to evaluate the condition of patients and their management.

Patients with stroke, venous thrombosis, pulmonary embolism, the acute coronary syndrome should be checked with the signs of venous and arterial thromboembolism and then proceed for management of SARS-COV-2.

Cautions should be taken with fluid management in the case of SARS-COV-2 patients without tissue hypoperfusion. In both adults and children, intravenous fluids should be administered cautiously as they may lead to worsening the oxygenation especially in case of settings where there is limited availability of mechanical ventilation [22].

Management of SARS-CoV-2 varies depending on the individual and the stage of the patient. The algorithm for management is given Figure 2.

14. CRS In SARS-COV-2

From previous studies, it was proven that the efficacy of IL-6 and L-6R antagonists have potent significance in the treatment of CRS and secondary hemophagocytic lymphohistiocytosis which also similar to cytokine storm now it became a potential target in SARS-COV-2 therapy. But the use of these antagonists in case of SARS-COV-2 associated with severe respiratory complications are still in clinical trials [7].

14.1 Special Considerations in Children

Data on disease severity and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children are limited. Overall, several large epidemiologic studies suggest that acute disease manifestations are substantially less severe in children than in adults. Recently it is found that it is associated with a severe disease like Multisystem Inflammatory Syndrome. Severe cases of SARS-COV-2 in children were associated with younger age and underlying conditions. Specific guidance on the diagnosis and management of SARS-COV-2 in neonates born to mothers with known or suspected SARS-CoV-2 infection is provided by the centers for Disease Control and Prevention (CDC).

Based on adult data and extrapolation from other pediatric respiratory viruses, severely immunocompromised children and those with the underlying cardiopulmonary disease may be at higher risk for severe disease. Children with risk factors recognized in adults, including obesity, diabetes, and hypertension, may also be at risk. Currently, there are no FDAapproved agents for the treatment of SARS-COV-2. Based on preliminary clinical trial data, the investigational antiviral agent remdesivir is recommended for the treatment of SARS-COV-2 in hospitalized patients with severe disease. Remdesivir is available for children through an FDA Emergency Use Authorization or a compassionate use program.

14.2 Multisystem Inflammatory Syndrome in Children

Emerging reports from Europe and the United States have suggested that SARS-COV-2 may be associated with MIS-C (also referred to as pediatric multisystem inflammatory syndrome–temporally associated with SARS-CoV-2 [PMIS-TS]). The syndrome was first described in the United Kingdom, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified.

15. Future Hopes

Many clinical trials are going on finding the treatment of SARS-COV-2 but the safest and efficacy drug found to be Dexamethasone by performing several experiments which are listed below:

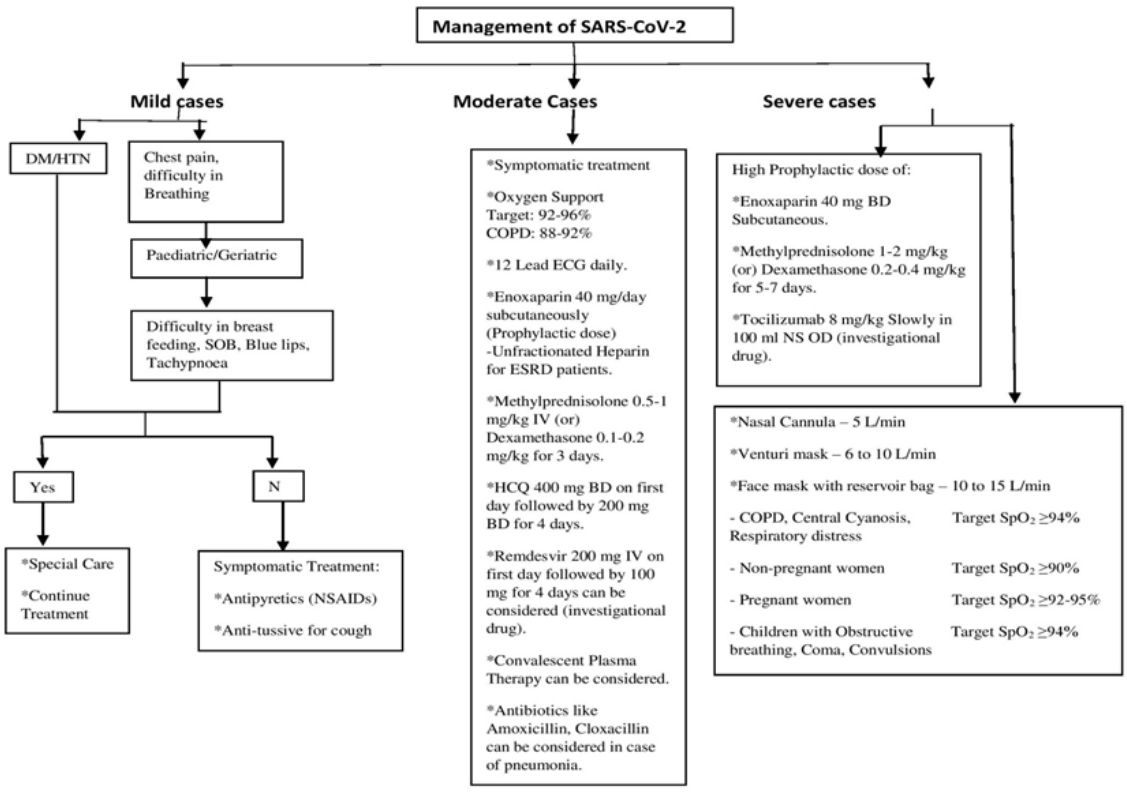

Figure 2: Algorithm of management of SARS-CoV-2

- From the study on the efficacy of dexamethasone for patients with ARDS in the multicenter, randomized, controlled, open-label trial involving mechanically ventilated adult patients with ARDS caused by confirmed SARS-COV-2 infection with 200 participants started on April 3, 2020, in phase 4 is being done with the administration of dexamethasone intravenously 20 mg once daily from day 1 – day 5, then followed by 10 mg once daily from day 6-day 10 or they are given dexamethasone plus standard intensive care. The primary outcome is 60-day mortality and a secondary outcome is several ventilator-free days at day 28 [23].
- From the study on dexamethasone treatment for severe acute respiratory distress syndrome induced by SARS-CoV-2 in the randomized area with ages from 18-80 years by administering dexamethasone 20 mg for 5 days followed by 10 mg for 5 days combined with 600 mg per day of hydroxychloroquine for 10 days will potentially reduce 28-day mortality compared to hydroxychloroquine alone with severe ARDS related with SARS-COV-2. The primary outcome is day-28 mortality and secondary is ventilator-free days for a time frame of 28 days is calculated as (Ventilation Free Days (VFD) = 0, when the patient dies within 28 days of mechanical ventilation; VFD = 28-x, when successfully liberated from ventilation after x days), Intensive care unit mortality for a time frame of 60 days, day-60 mortality for a time frame of 60 days, nosocomial pneumonia for a time frame of 60 days after randomization along with bacteremia up to 60 days. This study also specifies other outcomes like extracorporeal membrane oxygenation for 60 days, tracheostomy, prone position for 60 days after randomization [24].
- From dexamethasone for SARS-COV-2 related ARDS a multicenter, randomized clinical trial in phase-3 it has been intervened that anti-inflammatory corticosteroids shorten the duration of respiratory failure and improves prognosis so dexamethasone was given parenteral route at 16 mg from day 1 to 5 and 8 mg from day 6 to 10. The primary outcome is ventilator-free days at 28 days and their mortality rate [25].
- From a study conducted in France on patients with age 18 and more those who are admitted to Intensive Care Unit (ICU) within 48 hours and confirmed with SARS-COV-2 and acute hypoxemic respiratory failure, the need for invasive mechanical ventilation is. They are associated with a high mortality rate. This study has two hypotheses that include the benefit of corticosteroid therapy on severe SARS-COV-2 infection admitted on ICU and also either continuous positive airway pressure(CPAP) or HFNO allows to reduce intubation rate safely during SARS-CoV-2 related to acute hypoxemic respiratory failure. Procedures include the administration of a variety of drugs to different groups and intervening them. Drugs are given to them include:

- Dexamethasone injection: These include a 1 ampule of dexamethasone 20 mg / 5 ml, solution for injection in an ampule of 5 ml for 10 days continuously.
- Drug placebo: One NaCl 0.9%, solution for injection in an ampoule of 5 ml for 10 days.
- Conventional oxygen to maintain SpO2 92% or more
- CPAP plus oxygen assigned to patients to maintain SpO2 92% measured by pulse oximetry
- HFNO delivered with help of heated humidifier applied continuously through large-bore binasal prongs at a flow rate of 30 liters per minute.
- Mechanical ventilation

All these groups are studied thoroughly for the outcome of time-to-death for 60 days and time to need mechanical ventilation for 28 days analysis [26].

There are many studies still in the process to know more about SARS-COV-2.

16. Conclusion

It has been observed that oxygen therapy, corticosteroid therapy, and therapy with nonspecific antivirals like Remdesivir, Favipiravir have been approved to be effective in COVID-19 patients has therapeutic support. Following this protocol led to the improvement in recovery rate in patients suffering from severe SARS-CoV-2 condition. Also, several studies are being carried out on treatment with dexamethasone which are showing promising results as per early reports. However further evaluation has to be carried out in this context.

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Conflict Of Interest

None

Ethical Statement

Not required

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

RNA: Ribonucleic Acid

ACE: Angiotensin-converting Enzyme

DC-SIGN: Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin

CRS: Cytokine Release Syndrome

IL: Interleukin

TNF: Tumor Necrosis Factor

IFN: Interferon

RT-PCR: Reverse Transcription Polymerase Chain Reaction

CXCL: C-X-C motif chemokine ligand 1

ARDS: Acute Respiratory Distress Syndrome

COPD: Chronic Obstructive Pulmonary Disease

ECG: Electrocardiogram

HFNO: High Flow Nasal Oxygen

PPE: Personal Protective Equipment

NIV: Non-Invasive Ventilation

QTc: QT Interval

MERS: Middle Eastern Respiratory Syndrome

ICU: Intensive Care Unit

CDC: the centers for Disease Control and Prevention

FDA: Food and Drug Administration

MIS-C: Medicatioal Interaction for Sensitizing Caregivers

VFD: Ventilation Free Days

CPAP: Continous Positive Airway Pressure

References

1. Sahu P. Closure of Universities Due to Coronavirus Disease 2019 (COVID-19): Impact on Education and Mental Health of Students and Academic Staff. Cureus. 2020 Apr 4;12(4).
2. Chahrour M, Assi S, Bejjani M, Nasrallah AA, Salhab H, Fares MY, *et al*. A Bibliometric Analysis of COVID-19 Research Activity: A Call for Increased Output. Cureus. 2020 Mar 22;12(3).
3. Saisujay V, Singh M, Aamer Nawaz S. Conventional Drug Targets of Corona Virus. [cited 2020 Jul 11]; Available from: www.ijsart.com
4. Guidelines T. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Disponible en: https://covid19treatmentguidelines.nih.gov/. 2019;2019.
5. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol [Internet]. 2020 Apr 20;215:108427. Available from: https://pubmed.ncbi.nlm.nih.gov/32325252
6. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A

review. Clin Immunol. 2020 Apr;215:108427.

7. COVID-19 and the Cytokine Storm the crucial role of IL-6 - Enzo Life Sciences [Internet]. [cited 2020 Jun 11]. Available from: https://www.enzolifesciences.com/science-center/technotes/2020/april/covid-19-and-the-cytokine-storm-the-crucial-role-of-il-6/
8. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020;55(4).
9. Lau SKP, Che XY, Woo PCY, Wong BHL, Cheng VCC, Woo GKS, *et al*. SARS coronavirus detection methods. Emerg Infect Dis. 2005;11(7):1108–11.
10. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;
11. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Vol. 170, American Journal of Pathology. Elsevier Inc.; 2007. p. 1136–47.
12. Interpretation of laboratory results for COVID-19 diagnosis, 6 May 2020 [Internet]. [cited 2020 Jul 7]. Available from: https://iris.paho.org/handle/10665.2/52138
13. Thibodeaux K, Speyrer M, Raza A, Yaakov R, Serena TE. Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: a retrospective case series. J Wound Care. 2020 May 1;29(Sup5a):S4–8.
14. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, *et al*. COVID-19 diagnosis and management: a comprehensive review. J Intern Med [Internet]. 2020 May 13 [cited 2020 Jun 11];joim.13091. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/joim.13091
15. Meng L, Qiu H, Wan L, Ai Y, Xue Z, Guo Q, et al. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. Anesthesiology. 2020 Jun 1;132(6):1317–32.
16. Nicola M, O'Neill N, Sohrabi C, Khan M, Agha M, Agha R. Evidence based management guideline for the COVID-19 pandemic - Review article. Vol. 77, International Journal of Surgery. Elsevier Ltd; 2020. p. 206–16.
17. Mash B. Primary care management of the coronavirus (Covid-19). South African Fam Pract. 2020;62(1).
18. Weiss SR, Navas-Martin S. Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus. Microbiol Mol Biol Rev. 2005 Dec 1;69(4):635–64.
19. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020 Apr 10;
20. Symptoms and Management of Coronavirus Disease 2019 (COVID-19) FAQ: What are the signs and symptoms of coronavirus disease 2019 (COVID-19)?, What are the signs and symptoms of severe or critical coronavirus disease 2019 (COVID-19)?, How is mild coronavirus disease 2019 (COVID-19) managed? [Internet]. [cited 2020 Jun 20]. Available from: https://emedicine.medscape.com/article/2500122-overview#a13
21. Nguyen AA, Habiballah SB, Platt CD, Geha RS, Chou JS, McDonald DR. Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution! Vol. 216, Clinical Immunology. Academic Press Inc.; 2020. p. 108459.
22. COVID-19: Clinical/Therapeutic Staging Proposal and Treatment - REBEL EM - Emergency Medicine Blog [Internet]. [cited 2020 Jun 11]. Available from: https://rebelem.com/covid-19-clinical-therapeutic-staging-proposal-and-treatment/
23. Villar J, Belda J, Añón JM, Blanco J, Pérez-Méndez L, Ferrando C, et al. Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: Study protocol for a randomized controlled trial. Trials. 2016 Jul 22;17(1).
24. Dexamethasone Treatment for Severe Acute Respiratory Distress Syndrome Induced by COVID-19 - Tabular View - ClinicalTrials.gov [Internet]. [cited 2020 Jun 19]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04347980?term=DEXAMETHASONE&cond=COVID&draw=2&rank=2
25. Dexamethasone for COVID-19 Related ARDS: a Multicenter, Randomized Clinical Trial - Tabular View - ClinicalTrials.gov [Internet]. [cited 2020 Jun 19]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04395105?term=DEXAMETHASONE&cond=COVID&draw=2&rank=3
26. Dexamethasone and Oxygen Support Strategies in ICU Patients With Covid-19 Pneumonia - Tabular View - ClinicalTrials.gov [Internet]. [cited 2020 Jun 20]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04344730?term=DEXAMETHASONE&cond=COVID&draw=2&rank=4