Contemporary Treatment Modalities for the Management of SARS-CoV-2 Positive Patients: An overview

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ABSTRACT
The outbreak of a pandemic, occurring after a hundred years, has taken the world by storm. The knowledge attained from the past epidemics has helped establish various supportive, symptomatic and preventive measures. Some possible therapeutic actions of substances against the concomitant SARS 2 COVID have been tested. However, evidence from randomised controlled trials in humans is not available to support the recommendation of any of the investigational therapies, including vaccines for patients with confirmed or suspected COVID-19 at this time. With the rapid structural changes and the constantly mutating and unpredictable nature of the SARS-CoV-2 virus, the development of a definitive treatment regimen is even more challenging. Hence, management is only aimed at supportive therapy/ symptomatic treatment. In the meantime, community mitigating procedures to keep the sudden surge of cases at bay are in place, and the best healthcare workers are working tirelessly in finding a cure. A significant hurdle faced is the foreboding uncertainty about the virus-host relationship as well as the development and progression of the epidemic even today. The numerous modalities have been discussed to give an overview of the best approach for the treatment of the SARS-CoV-2 positive patients which include the contemporary antiviral drugs, chloroquine and hydroxychloroquine, immunoglobulin therapies, vaccines and homoeopathic remedies.

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INTRODUCTION
The recent epidemics which have been reported in the past twenty years include the SARS- CoV (“Severe acute respiratory coronavirus syndrome”) in 2003, the “H1N1 influenza” in 2009, followed by the MERS- CoV (“Middle Eastern respiratory syndrome coronavirus”) in 2012 and the “Nipah virus” in 2018. The SARS-CoV-2 virus outbreak surpassed all, and assumed the status of a pandemic, as reported by the “World Health Organization” (WHO).

The continuous rise in cases loads the public health services with a significant extra burden putting the world health system in overdrive. The knowledge and treatment options from past epidemics have proven immensely useful and have assisted in the drawing up of protocols to contain the infection at the earliest.

For initial identification of the disease, Chan et al.
carried out genetic tests of patients who had concurring atypical pneumonia, after visiting Wuhan. It was determined that the isolated “HCoV” genome showed 89% resemblance to the “CoVZXC21” and 82% with the “human SARS-CoV”. (Chan et al., 2020)

Hence, this new virus strain has aptly been named as “SARS-CoV-2” or “COVID-19”, an acronym for “coronavirus disease 2019”. The new cases of this infection were believed to have been established from a Zoonotic origin.

The virus is volatile, and the early human-to-human transmissions triggered the ensuing outbreak in the community. (WHO, 2020b) Statistically, an epidemic will continue to increase, as long its R0 “Reproduction number” value exceeds 1. This refers to the rate of replication of the virus from infected individuals. The R0 value of COVID-19 is 2.2, hence the strategy is to limit the spread of the virus, with emphasis on dropping the R0 value to under 1. [Figure 1] (Westman, 2020) A significant hurdle faced is the foreboding uncertainty about the virus-host relationship as well as the development and progression of the epidemic even today. (Cascella et al., 2020)

Figure 2, Scores for each parameter are added together to give a total. If score is greater than 5, urgent medical care is required.

![Figure 1: Significance of R0 in the mitigation of the disease at a Community level](image1)

![Figure 2: National Early Warning Score (NEWS). Each parameter is graded 0–3.](image2)

**Pathophysiology**

The SARS-CoV-2 virus belongs to the β group of coronaviruses. Its dynamics include a genome of approximately 30 kb, diameter up-to 120 nm, with external projections of size 20 nm. They consist of four structural proteins, namely, “S- spike”, “M-membrane”, “E-envelop” and “N- nucleocapsid”. The virus carries out its life cycle in the five stages of “attachment, penetration, biosynthesis, maturation and release”.

The “Spike protein” has two subunits (S1 and S2) for the binding and fusion to the cell receptors and membranes respectively. The “Angiotensin-converting enzyme 2” (ACE2) also acts as a functional receptor and facilitates the binding of the virus. Post this; the Spike protein cleaves at the S1/S2 site (“RPPA” sequence), also known as “furin cleavage sites” which is responsible for the increased pathogenicity of the virus.

Since, the ACE2 is highly expressed in the alveolar spaces, towards the apical side, bonding and destruction at this site is very common, leading to the presentations of mild to severe fever, dry cough, myalgia and fatigue. (Li et al., 2020) Radio graphically, a characteristic “pulmonary ground-glass opacification” has been noted on C.T. scans of the lungs. (Yuki et al., 2020)

Policymakers throughout the world are trying to set up countermeasures to prevent potential catastrophic long term effects. Health organisations have developed guidelines with a detailed outflow of information, including recommendations to help minimise these harmful effects.

Scientists around the world are working relentlessly to gather details on the mechanisms of transmission and the complete range of clinical illness. New treatment protocols incorporating preventive and therapeutic approaches are evolving rapidly to combat the situation. Cascella et al. (2020)

**Risk factors**

The risk factors rendering individuals susceptible to acquiring this disease and subsequently progressing to severe illness may include acute or chronic respiratory, cardiovascular, cerebrovascular, renal and hepatic disorders, cancer, diabetes as well as immuno compromised conditions. Pregnant patients and those of an older age group are also at high risk. (COVID-19, 2020)

**Classification**

The Chinese C.D.C. officials have reportedly subdivided the clinical presentation of the disease based on their level of severities

**Mild disease** - Characterised by “non-pneumonia” and “mild pneumonia”.

**Severe disease** - Characterised by “Dyspnea”, “Oxygen Saturation”: \( \text{SpO}_2 \leq 93\% \), “Respiratory frequency” \( \geq 30 \) cycles/ min, \( \text{PaO}_2/\text{FiO}_2 \) ratio: “Partial pressure of oxygen” - \( \text{PaO}_2 \), divided by the “Fraction
Table 1: Protocol for symptomatic therapy based on the disease severity

| Disease severity          | Symptoms                                                                 | Phase of treatment                                      | Treatment administered                                                                                                                                                                                                 |
|--------------------------|--------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mild COVID-19            | Mild fever, cough and cold: Do not require hospitalisation, but isolation is mandatory, to control the virus Transmission. | Symptomatic treatment and monitoring                     | - Antipyretics for fever.  
- Counselling of patients about signs and symptoms of severe conditions.  
- In case of the severe symptoms develop, the patient should seek urgent care through national referral systems.  
- Empiric antimicrobials to treat all likely pathogens causing SARI and sepsis, within 1 hour of initial patient assessment.  
- Airway management and oxygen therapy during resuscitation to target SpO2 ≥ 94-90%.  
  - Adults: Initiate oxygen therapy at 5 L/min and titrate flow rates.  
  - Face mask with reservoir bag (at 10–15 L/min) if patient is in critical condition (WHO, 2013b,a)  
  - Children: Use of nasal prongs or nasal cannula is preferred, as it may be better tolerated.  
- Oxygen is delivered via a face mask with reservoir bag (flow rates of 10–15 L/min)  
- Endotracheal intubation should be performed  
- Give at 250–500 mL crystalloid fluid as rapid bolus in first 15–30 minutes and reassess for signs of fluid overload after each bolus.  
  - Children: Give 10–20 mL/kg crystalloid fluid (normal saline and Ringer’s lactate) as a bolus in the first 30–60 minutes. |
Critical disease - "Respiratory failure", "Septic shock", and "Multiple Organ Dysfunction" (M.O.D.) or "Multiple Organ Failure" (M.O.F.) (Wu and Mcoogan, 2020)

The decision to manage a patient should be determined based on the individual clinical presentations in an inpatient or ambulatory environment. This treatment protocol also relies on, the willingness of the patient to participate in the surveillance and "home-isolation" after assessing the risk of transmission in the home environment of the patient. (COVID-19, 2020)

Treatment considerations

Often, the affected people with a mild clinical presentation, don’t require medical attention initially. However, in the second week of illness, the typical clinical symptoms may intensify along with the disease progression to the lower respiratory tract. Hence, close supervision of all patients must be done. (COVID-19, 2020)

A professional clinician must carry out the examinations or procedures only after using a Personal Protection Equipment Kits (P.P.E. kits) for containment of infections: utilising disposable gowns, face shields/standard face masks/respirators, gloves, disposable double socks and protective goggles. (Cascella et al., 2020) The clinical operations must comprise of timely and precise execution of the recommended infection prevention protocols and the management of complications which includes advanced organ support if indicated. (COVID-19, 2020)

Close monitoring of patients with COVID-19 for signs and symptoms of clinical deterioration must be actively done to identify the causes of rapidly advancing respiratory failure and sepsis. Immediate response involving supportive care intervention must take place. (Cascella et al., 2020)

The various recommendations for symptomatic treatment to be administered based on the extent of the disease progression have been summarised as follows (WHO, 2020a)

General guidelines

1. All facilities in which SARI patients are treated are required to be fitted with sufficient number of pulse-oximeters, working portable and single-use oxygen devices, such as simple face masks, masks with reservoir bags, nasal cannulas and nasal prongs. (COVID-19, 2020)

2. Patients hospitalised after diagnosis with "COVID-19" require constant vital signs evaluation, and wherever possible, the use of early warning medical scores via "National Early Warning Score" NEWS2 [Figure 2] is promoted, for the early identification in the case of escalating conditions of decline. (Abbott et al., 2015)

3. Haematology, laboratory biochemical testing and Echocardiography is necessary on admission and must be conducted as and when indicated medically. Application of appropriate, efficient and secure supportive treatments for patients who experience severe manifestations of COVID-19 is the fundamental basis of therapy.

4. In patients with "Severe Acute Respiratory Infection" (SARI), it has been suggested to treat conservatively with intravenous fluids, as the aggressive administration of fluids can exacerbate deoxygenation. Precautions must be taken especially where mechanical ventilation facilities are inadequate for adults as well as children. (Schultz et al., 2017)

5. Observational treatment measures should be increased or decreased based on the clinical findings or from the microbiological reports.

Intubation and protective mechanical ventilation

“Rapid sequence intubation” (RSI) should be performed, as it shows the most favourable outcomes: Preoxygenation (with 100% O₂ every 5 minutes) must be carried out using the "Continuous Positive Airway Pressure" (CPAP) process. The "heat and humidity exchanger" (H.M.E.) must be mounted in between the mask and the ventilation balloon.

Investigational therapies

The use of antibiotics with non-selective mechanisms of action or improper antibiotic administration should be avoided. Although no antiviral drugs have been authorised, various treatment alternatives have been suggested

1. Antiviral drugs
   a. Remdesivir (Dosage in patients with Critical stage of COVID-19: 200 mg I.V. within 30 mins of identification followed up by 100 mg every 24 hours for 2-10 days)
   b. Favipiravir
   c. Lopinavir (Dosage 400 mg every 12 hours)
d. Ritonavir (Dosage 100 mg every 12 hours) (COVID-19, 2020)

2. Chloroquine (500 mg every 12 hours), whereas Hydroxychloroquine (200 mg every 12 hours)

3. Vaccines

4. Other therapies

1. Antiviral drugs

Remdesivir

It is a drug under various clinical trials in both U.S. and China (COVID-19, 2020), for its antiviral activity and was recorded to have in-vitro effectiveness against the “SARS-CoV-2”. (Wang et al., 2020) Preclinical studies have indicated that “Remdesivir-GS5734”, acting by inhibiting R.N.A. polymerase, shows evidence of activity against multiple R.N.A. viruses, including Ebola and for “MERS- CoV” disease in a rhesus macaque template. (de Wit et al., 2020) This drug could be improvised for use in both prophylactic and “HCoV” infection therapy. (Gordon et al., 2020) Certain COVID-19 patients were given the medication intravenously outside of a clinical trial framework, with approval for compassionate use. (COVID-19, 2020)

Favipiravir

This is a prodrug of a purine nucleotide, “favipiravir ribofuranosyl-5’-triphosphate” and was previously known as T-705. It actively inhibits R.N.A. polymerase to stop replication. In vitro, it has shown 50% efficacy against the moderate to severe presentations of SARS-CoV-2. The potency is now actively being tested in clinical trials all over the world as a replacement of Remdesivir. (Irvani, 2020)

Chloroquine & hydroxychloroquine (hcq)

India has produced this drug for the management of malaria and is readily available/ affordable. In the past five years since its approval, H.C.Q. has gained momentum as a third- or fourth-line drug for treating type 2 diabetes in India. Thus, this property has made it a favourable drug in the treatment of the COVID positive patients who are at risk due to diabetes. Mechanism of action of the drug is by changing the pH of endosomes and interfering with the glycosylation of the cellular receptors of the virus. (Singh et al., 2020) Chloroquine blocks the replicative capability of the virus. Evidence shows that it inhibits cathepsins, which induces the formation of autophagosomes; this in-turn degenerates the virus by cleaving the spike protein of the SARS-CoV-2.

In an open-label, clinical study conducted by Gautret et al., in Marseille, it was found that H.C.Q. itself as well as in combination with azithromycin showed significant synergistic action in clearing the viral load in the nasopharyngeal exudates. This was confirmed by a “Polymerase Chain Reaction” in approximately six days in the patients presenting with COVID-19. (Gautret et al., 2020).

3. Immunoglobulin therapy

"Tocilizumab" which is a “humanised IgG1 monoclonal antibody”, is a drug against the IL-6 receptor and is used as a therapeutic medication in rheumatoid arthritis commonly. The “IstitutoNazionaleTumori, Fondazione Pascale di Napoli” in Italy, carried out a study in patients presenting with moderate or severe conditions, where they received one or two doses of 400mg Tocilizumab in addition to antiviral therapies. Evidence of decreased fever, reduced oxygen support and improved lymphocyte levels were seen in the majority of the subjects. Hence, the drug has been included in the regimen by the National Health Commission of China.

Similar trials have been carried out in other countries like the United States, where they have assessed the action of “Sarilumab” (NCT04315298). This is also an anti-IL-6R which has a protective action and prevents “anaphylactic toxicity” or a “cytokine storm” of the immune system and so far the trial has shown favourable results. (Buonaguro et al., 2020)

IVlg mediates the immune response through diverse pathways, including the blockade of a wide range of cytokines, “Fc-gamma receptors” (FcRs), and “leukocyte adhesion molecules” that restrict the pathogenic action of the “pTh1” and “Th17” subsets and neutralise the autoantibodies. IVlg can also alleviate the mechanism of regulatory T-cells by inducing the secretion of “cyclo-oxygenase-2-dependent prostaglandin E2” in dendritic cells. (Jawahara, 2020)

4. Vaccines

Candidate vaccines, as well as therapeutics for COVID-19, are being developed by the “National Institutes of Health” (N.I.H.) among other collaborators in the US. (COVID-19, 2020) The “Kaiser Permanente Washington Health Research Institute” (KPWHRI) at Seattle has a clinical trial in its Phase 1, aimed at assessing an experimental vaccine, to protect against the COVID-19.

The test is being financed by the “National Institute for Allergy and Infectious Diseases” (NIAID) a unit of the “National Institutes of Health”. The open-label study enrolled about 155 stable adults of age 18 to 55 years, who will be vaccinated in 2 doses and will
be followed up for 12 months, to evaluate its safety and reactogenicity.

This vaccine is named “mRNA-1273”, has been developed at the Cambridge, Massachusetts-based biotechnology firm Moderna, Inc. The vaccine directs the cells of the body to release a protein against the virus. This requires a strong immune response. The “mRNA-1273” vaccine proved promising in animal samples, and hence human trials have started. (Covid-19, 2020)

Some in-vitro or in-vivo studies indicate possible therapeutic action of substances against concomitant coronaviruses. Still, evidence from randomised controlled trials in humans is not available to support the recommendation of any of the investigational therapies for patients with confirmed or suspected COVID-19 at this time.

5. Homeopathic remedies

Homoeopathic remedies namely: Arsenicum Album 30 have shown to be effective in COVID-19 positive patients. It is being used as a prophylactic as well as a therapeutic agent. However, no studies have established its effectiveness, and in certain countries like the U.S., the Food and Drug Association has banned the sale of the drug due to lack of clinical trials.

6. Other therapies

Observational therapy on the administration of “neuraminidase inhibitor” should also be considered for the management of patients developing severe lung infections such as influenza. (Rhodes et al., 2016)

Currently, due to numerous ongoing investigations and the significant lack of any approved vaccine, social preventive and mitigation measures are the only resort to reduce the exponential spread of SARS-CoV-2. Strict policies to ensure the adherence to the recommended “infection control policies” devised by the respective countries or states can, in due time, reduce the burden of SARS-CoV-2. (COVID-19, 2020)

Absolute contraindications

1. Corticosteroids

As per the “Surviving Sepsis guidelines for adults and children”, regardless of their potential in prolonging viral replication, the use of corticosteroids should be avoided, unless otherwise indicated. Since they may cause exacerbation of conditions such as “Chronic Obstructive Pulmonary Disorder”. (Zumla et al., 2015; Arabi et al., 2018)

2. Ibuprofen

Specific evidence contradicts the use of Ibuporfen and advocates the use of Acetaminophen monotherapy for its antipyretic effect in COVID-19 patients. This has been established by the WHO recommendations as well. If the lone action of Acetaminophen is not sufficient, the coadministration of Ibuporfen with Acetaminophen remains controversial, and its action in the morbidity of COVID 19 must be further investigated. (Sodhi and Etminan, 2020)

CONCLUSIONS

Various therapeutic approaches have been developed to deal with the infection caused by the SARS 2 COVID virus. However, they are only aimed at supportive therapy/ symptomatic treatment. With the rapid structural changes of the COVID-19 virus, the development of a definitive treatment regimen is even more challenging.

Scientists and biotechnologists across the globe are working hard, and the numerous clinical trials aimed at finding a cure to eradicate the disease are being conducted worldwide. In India, Bharat pharmaceuticals have received the regulatory approval for its first domestic vaccine trial.

In the meantime, preventive measures directed at minimising social transmission is our best weapon to curtail the situation. World-wide, the adoption of strict and aggressive isolation measures has led to a progressive reduction of cases.

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Conflict of interest

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