A comprehensive review on COVID-19 with main focus on management and treatment options

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Review Article

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus of the same family as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), has spread globally in leading the World Health Organization to announce it a pandemic. The disease caused by SARS-CoV-2, 2019 coronavirus disease (COVID-19), causes flu-like symptoms that may become severe in people at high risk. Infection is known to spread from human to human and through contact with contaminated surfaces. COVID-19 's main symptoms include nausea, cough, fatigue, mild dyspnea, sore throat, headache and gastrointestinal problems. Real time PCR is used as a diagnostic device using nasal swab, oropharyngeal swab, tracheal aspiration or bronchoalveolar lavage samples. Antiviral medications, steroids, IL-6 antagonist and respiratory support devices are the primary treatments being used to treat the condition. In addition, while several interventions have been suggested, quarantine is the only method that seems to be successful in lowering the risk of infection. The COVID-19 pandemic reflects the present generation's major global public health issue, and likely since the 1918 pandemic influenza epidemic. The pace and frequency of clinical trials conducted to evaluate possible COVID-19 therapies underscore both the need and capacity to deliver high-quality evidence even in the midst of a pandemic. Various vaccines have been developed which are in different phases and we hope to have a vaccine for general population soon, as it could prevent the spread of the disease.

KEYWORDS: Clinical Trials, SARS-CoV-2, Viral pneumonia, Vaccines, Therapeutics

INTRODUCTION

According to the World Health Organization (WHO), viral diseases tend to arise and pose a significant public health problem. Numerous viral epidemics, such as the severe acute respiratory coronavirus syndrome (SARS-CoV) and H1N1 influenza have been recorded in the last two decades [1].

The Middle East respiratory syndrome coronavirus (MERS-CoV) was also identified early in this decade. On 31 December 2019, an outbreak with several cases of unidentified lower respiratory infections was first reported in Wuhan, China's largest metropolitan area in Hubei province. Those first cases were listed as "pneumonia of unknown etiology" since they were unable to classify the causative agent.

The new virus was at first named 2019-nCoV. Eventually, the task of the International Committee on Virus Taxonomy (ICTV) experts named it the SARS-CoV-2 virus, as it is very identical to that which caused the SARS outbreak (SARS-CoVs) [2].

SARS-CoV-2 is a β-coronavirus, enveloped by non-segmented positive-sense RNA virus (subgenus sarbecovirus, subfamily Orthocoronaviridae) [3]. It was figured that SARS-CoV-2's genome sequence is 96.2 % identical to a bat CoV RaTG13, while it represents SARS-CoV's identity at 79.5 %. Based on the results of virus genome sequencing and evolutionary research, bat was believed to be a natural host of virus origin, and SARS-CoV-2 could be transmitted via unspecified intermediate hosts from bats to infect humans. It has become apparent that SARS-CoV-2 may use angiotensin-converting enzyme 2 (ACE2) for its entry into the cell [4].

Scientists are engaged in research works day-in and-out, and knowledge on transmission processes, clinical disease continuum, new treatments, and strategies for prevention are increasingly emerging. The therapeutic approaches for coping with the infection have improved the chances of survival in moderate-severe cases and prevention is aimed at minimizing social transmission and developing an efficacious vaccine.

The present review explores the symptoms, diagnosis, associated complication and the challenges associated with COVID-19. The management strategies and the possible therapeutic interventions that can be employed in the treatment of the disease are also discussed.

LITERATURE REVIEW

Fever, cough, malaise, mild dyspnea, sore throat, and headache are typical symptoms of the disease [5]. Therefore, differentiating COVID-19 from other respiratory disorders is difficult [6]. Gastrointestinal involvement, with diarrhea, nausea and vomiting were documented in a lower percentage of cases. In about 80–90 % of cases, the pattern of the infection is mild or asymptomatic. It only becomes severe in about 10 % of cases, with dyspnea, hypoxemia and significant radiological involvement of the lung parenchyma (> 50%). In about 5 % of cases, a severe condition progresses with respiratory failure, pneumonia, shock, multiorgan failure and, in the most extreme cases, death, which is almost always the case. Typical pathology pattern involves the presence of apparent dyspnea 6 days after the start of flu-like symptoms, hospitalization after another 8 days, and tracheal intubation 10 days after hospitalization [7]. It has been recorded that COVID-19 mortality is about 3% and hence continues to be lower than SARS-CoV (10%) and MERS-CoV (35%) [8]. However, in light of COVID-19's recent and rapid progress, it is far too premature to establish the specific mortality rate of the disease. Ongoing research implies that age, ischemic heart disease, diabetes, hypertension and immunosuppression are the key risk factors for poor outcome [9].

DIAGNOSTIC APPROACH

The diagnosis of COVID-19 at a clinical stage is centred on epidemiological evidence, clinical symptoms and certain complementary tests, namely blood analysis, nucleic acid detection, CT screening, immune-related tests (IgM or IgG levels) and enzyme-linked immunosorbent tests (ELISA) [10]. RT-PCR is a diagnostic test which uses specimens of nasal swab, oropharyngeal swab, tracheal aspirate, or bronchoalveolar lavage (BAL). The predominant, and favoured, diagnostic method is to obtain the upper respiratory samples through nasopharyngeal and oropharyngeal swabs [11]. The gene targets for RT-PCR test are one or more of nucleocapsid (N), envelope (env), spike (S), RNA-dependent RNA polymerase (RdRp) and ORF1 genes [12]. RT-PCR positivity is highest in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%) and pharyngeal swab (32%) [13]. Specificity of this test has been 100% as the primer design is specific to the genome sequence of SARS-CoV-2 and false positivity may be seen due to technical errors and reagent contamination. Serological diagnosis of SARS-CoV-2 infection could be especially important in patients with mild-moderate illness who present late i.e. after 2 weeks of onset of illness [12]. IgM and IgG seroconversion occurred in almost all patients between 3rd and 4th

week of clinical illness [14, 15]. There is decline of IgM levels by week 5 and disappearance by week 7, whereas IgG persists for more than 7 weeks [16]. The combined sensitivity of PCR and IgM ELISA directed at nucleocapsid (NC) antigen was 98.6% vs. 51.9% with a single PCR test in a study done on 140 patients highlighting the importance of combined testing for SARS-CoV-2 infection. Quantitative PCR had a higher positivity rate than IgM ELISA during the first 5.5 days of illness [17]. High-resolution computed tomography (HRCT) of the thorax should be considered in all patients with hypoxia to grade the severity of lung involvement.

ASSOCIATED COMPLICATIONS

Acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute kidney injury, acute myocardial injury, liver disease, stroke, pulmonary thromboembolism and secondary infection are reported to be the major complications [18]. The inconsistent clinical result is associated with the severity of the disease. The disease tends to progress faster in the elderly (age 65 or older) [19, 20].

The elderly male with ARDS and comorbidities had an increased risk of death [21]. Furthermore, many children were diagnosed with the infection, the youngest being 30 hours after childbirth [22]. Neonates and the elderly do need care and treatment, given their weak or impaired immune system.

CHALLENGES

COVID-19 has raised high health concerns worldwide. Specific approaches should be introduced at the national and global levels in the healthcare settings to prevent the spread of the disease. However, irrespective of stringent measures taken to curtail the spread, still huge challenges persist which paves the way that leads to controlling the spread. Antiviral medications, steroids, tocilizumab along with oxygen therapy, ventilatory management, fluid control and the use of broad-spectrum antibiotics to ameliorate secondary infections continues to remain the most viable management strategy. Huge research efforts are underway which would culminate in the development of potential vaccines which would prove to be a viable effective prevention technique in limiting the spread.

POSSIBLE STRATEGIES TO CONTROL THE SPREAD

Various strategies are adopted in every sphere to control the spread of the disease. The strategies which need to be followed upon are discussed below.

Unfortunately, the health care environments may be a significant origin of viral transmission. Suspected patients with signs of respiratory infections at clinics and hospitals need to wear a face mask and stick explicitly to triage protocol. They should not be required to wait at the hospitals with other patients in the waiting zones for availing medical treatment. Instead they should be put in a distinct, completely ventilated space, about 2 m from the other patients with adequate respiratory hygiene supplies [23]. Additionally, if a confirmed COVID-19 individual needs hospitalization, they must be put in a single space with negative air pressure – at least six switches of air in every hour. The depleted air must be filtered by high-efficiency particulate air (HEPA), and health workers entering the room should use personal protective equipment (PPE) such as gloves, gowns, disposable N95. It is important to raise public

awareness to understand and recognize unusual symptoms such as chronic cough or shortness of breath, so that they can seek medical attention to detect the virus early on. When large-scale group transmission emerges, social events should be mitigated, temporary school closures, home isolation and close monitoring of the symptomatic patient should be advocated [24].

TREATMENT OPTIONS

Below discussed are a group of drugs with their mechanism of action that are extensively researched upon for the treatment of the stated disease. Much of the existing evidence for pharmacological interventions are derived from drugs employed during the pandemic of SARS-CoV or MERS-CoV or from in vitro studies [25]. There is lack of proof stating the fact that antibiotic prophylaxis can resist bacterial super infection. The bulk of the data available come from descriptive research and common knowledge.

Following section discusses the frontline drugs that are investigated to be used as potential therapies for the circumvention of COVID-19 in the near future (Table 1) [26-31].
Listed below are the various drugs which have undergone trials for their use in COVID-19 infection.

Hydroxychloroquine

An observational study conducted in New York City on 1376 patients revealed that administration of hydroxychloroquine was not associated with increased risk of intubation or death (composite end point) [32]. A meta-analysis which included a total of 23 studies, of which 3 were randomized controlled trials (all from China) [33-35], affirmed the evidence was weak and conflicting considering the benefit and harms of using chloroquine or hydroxychloroquine in treating COVID-19 patients [36]. The studies have shown that this drug is not useful in the treatment of COVID-19 infection.

Hydroxychloroquine with Azithromycin

Results of an open-label, non-randomized clinical trial in France coordinated by The Mediterranee Infection University Hospital Institute has stated that there is significant reduction in viral load/disappearance in patients with COVID-19 on hydroxychloroquine and azithromycin [37]. More studies are required to know if this combination therapy would be useful in treating the disease.

Remdesivir

In a multinational double-blind, randomized, placebo-controlled trial on 1063 adult patients who were hospitalized with lower respiratory tract involvement of COVID-19 infection, intravenous remdesivir (200mg loading dose on day 1, followed by 100mg daily for up to 9 more days)was found to be superior to placebo in shortening the time to recovery (median,11days vs. 15 days; rate ratio of recovery,1.32; 95% confidence interval[CI],1.12 to 1.55; $p<0.001$). However, the Kaplan-Meier mortality by 14 days in the remdesivir and placebo group was 7.1% and 11.9% respectively without any significance [38]. In one more multinational study involving 53 patients, where remdesivir was given on compassionate-use basis to patients with severe COVID-19 infection (oxygen saturation of 94% or less on breathing ambient air/needing oxygen support), clinical improvement was seen in 68% of the patients [39]. A randomized,

open-label, phase 3 trial funded by Gilead Sciences was conducted on 397 patients (multinational) with severe COVID-19 infection who underwent randomization in a 1:1 ratio and received intravenous remdesivir for either 5 or 10 days. This trial did not show any significant difference in a 5-day course/10-day course of remdesivir in patients who did not require mechanical ventilation [40]. On more randomised, double-blind, placebo-controlled, multicentric trial was conducted in China on 237 patients with severe COVID-19 infection. Patients underwent randomization in a 2:1 ratio to receive intravenous remdesivir or same volume of placebo for 10 days. However, concomitant use of interferon, lopinavir-ritonavir, and corticosteroids were permitted. It concluded that the time to improvement as well as the duration of invasive mechanical ventilation was not significant in both the groups [41]. Remdesivir has been found to be effective in the treatment of severe COVID-19 infection and could be considered as the therapy of choice in treating such a disease.

Favipiravir

A prospective, randomized, controlled, open-label multicentre trial was conducted in 3 hospitals of China involving 240 adult patients with COVID-19 infection. Patients were randomized in 1:1 ratio and received Favipiravir (1600mg, twice first day followed by 600mg, twice daily, for the following days) or Umifenovir (200mg, three times daily) plus standard care for 7 days. Differences in clinical recovery at day 7 were observed in patients with moderate infections (71.4% favipiravir and 55.9% Arbidol, P = .019). No significant differences were observed in the severe or severe and moderate (combined) arms [42]. An observational study was done in Japan on 2,158 cases where favipiravir was given on compassionate-use basis. Rates of clinical improvement at 14 days in mild, moderate and severe cases were 87.8%, 84.5% and 60.3%, respectively with rates of clinical worsening being 5.9%, 8.8% and 25.2%, respectively [43]. The open-label randomized, multicenter clinical trial was conducted on 150 patients across India to evaluate the efficacy by Glenmark Pharmaceuticals. They found that 69.8% of patients in the favipiravir treatment arm of the study achieved clinical cure by day four vs. 44.9% of participants achieving the measure by the same point in the control arm [44]. Hence this could be a potential drug to treat mild-moderate cases of COVID-19 infection.

Convalescent plasma (CP)

A pilot study was conducted in 3 different hospitals of Wuhan, China on 10 patients. Patients with severe COVID-19 infection were selected for the study. All patients received antiviral therapy with supportive care. A single dose of inactivated CP (200 mL) with neutralizing activity of >1:640 titres was transfused to the patients within 4 hours. The case fatality rate 0% and SARS-CoV-2 RNA reduced to undetectable levels in three patients on day 2, three patients on day 3 and one patient on day 6 after CP therapy [45]. A systematic review from various sources on CP therapy in severe COVID-19 infection was done which included five studies. The major findings were reduced mortality in critically ill patients, increase in neutralizing antibody titres and disappearance of SARS-CoV-2 RNA, and improvement in clinical symptoms [46]. Multicenter clinical study was done on 189 patients with documented hypoxia which included 115 patients in the plasma therapy group and 74 patients in the control group. There were more discharges

in plasma therapy group compared to the control group i.e. 98.2% vs 78.7% respectively. The need for intubation was significantly lower in the plasma therapy group compared to the control group i.e. 7% vs 20% respectively providing a strong evidence to treat COVID-19 patients with convalescent plasma therapy [47].

Tocilizumab

A retrospective observational cohort study in 544 adults from Italy with severe COVID-19 pneumonia was done. One group received standard care (antivirals and supportive therapy) and the other group received tocilizumab along with standard care. Of the patients who required mechanical ventilation, the mortality rate was 20% in standard care group compared to 7% in patients who received tocilizumab ($p<0.0001$). There was also reduced risk of invasive mechanical ventilation in tocilizumab group (adjusted hazard ratio 0.61, 95% CI 0.40-0.92; $p=0.02$) [48]. Phase II, single-arm, open-label, prospective, blinded, clinical trial with tocilizumab as the sole agent has already started in Mexico in which 200 participants are expected to take part [49]. The randomized, double-blind COVACTA trial conducted in patients with severe COVID-19 pneumonia did not meet its primary end points, including a difference in patient mortality at week 4 [50]. Hence, we cannot really comment about its efficacy in treating severe COVID-19 infection though it is being used in some countries to treat cytokine storm.

Dexamethasone

The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is a randomized, controlled, open-label, adaptive, platform trial which compares various possible treatments with usual care in hospitalized COVID-19 patients. Preliminary results of the study for the comparison of dexamethasone 6 mg given once daily for up to ten days vs. usual care alone are out. The primary outcome of the study was 28-day mortality. 2104 patients, who were randomly allocated, received dexamethasone and compared with 4321 patients who received usual care. The mortality within 28 days was 21.6% in patients who received dexamethasone compared to 24.6% in those who received usual care (age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; $P<0.001$). Dexamethasone reduced deaths by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; $p=0.002$), by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; $p<0.001$), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; $p=0.14$). Hence, dexamethasone was useful in reducing the 28-day mortality among those receiving oxygen or invasive mechanical ventilation at randomization [51]. Prospective randomized controlled trials are going on in China regarding the safety and efficacy of glucocorticoids (methylprednisolone) for the treatment of COVID-19 pneumonia.

Anticoagulation

There is growing evidence that COVID-19 causes thrombus formation due to the damage of endothelium. A retrospective multicenter cohort study from China analysed 191 patients with COVID-19 infection. They

found coagulopathy in 50% of the 54 non-surviving patients, compared to 7% of 137 surviving patients ($p<0.0001$) [52]. A recent study done on 184 ICU patients with COVID-19 pneumonia showed the presence of pulmonary embolism (CT pulmonary angiogram proven) in 27% of the cases necessitating the use of anticoagulants in severely ill patients. These patients also had no evidence of DIC [53]. Therefore, it is recommended to start anticoagulation in moderate-severe COVID-19 patients and also in patients with elevated D-dimer levels.

Vaccines

Vaccines typically demand years of research and testing prior to clinical usage; however, scientists are highly engaged to produce a safe and efficient coronavirus vaccine in the coming year. Vaccine may be the safest, most efficacious way to prevent COVID-19 infection and bring the current progressing pandemic under control [54].

As of 21st February 2021, the draft landscape summary of World Health Organization states that there are 64 vaccine candidates in clinical evaluation stage [55]. 179 vaccine candidates are in preclinical evaluation stage.

We briefly describe published trials of vaccine candidates who are in stage 3 and those which are approved for clinical use. The vaccines for which published data is not available but have reached phase 3 and the ones that are approved for use are mentioned in Table 2 [55].

University of Oxford/AstraZeneca vaccine - It is chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19). Phase 3 trials of this vaccine candidate are at advanced stage. Results of phase 1/2 trials involving 1077 adults are published [56]. The adverse effects were mild and were reduced with prophylactic paracetamol. Humoral response peaked by day 28. Cellular T-cell response is induced by day 14. Results of phase 3 trials is an Interim data from Phase 3 trial in the UK, Brazil and South Africa which as shown an overall efficacy of 70% with vaccine efficacy at 62.1% in a group of participants receiving two standard doses and 90% in a group receiving one half dose followed by a standard dose [57] . Presently it is approved for use in any country.

CanSino Biological Inc. /Beijing Institute of Biotechnology vaccine -. In phase 2, it was found that single dose schedule of vaccine is enough for healthy adults. However older people have significantly lower immune response. Additional doses may be needed for them. Phase 3 trials are being conducted [58].

Gamaleya Research Institute vaccine (Sputnik V) - It is a vaccine with two different adenoviral vectors (recombinant Ad26 [rAd26] and recombinant Ad5 [rAd5]), both carrying the gene for SARS-CoV-2 spike glycoprotein (rAd26-S and rAd5-S). Small phase 1 and 2 human trials with 38 volunteers have been conducted. Vaccine has been proved safe and efficacious in these small trials [59]. Phase 3 trials were conducted in Russia involving 21977 participants. Vaccine efficacy was reported to be 91.6% and it is approved for use [60].

Wuhan Institute of Biological Products/Sinopharm vaccine - It is inactivated whole virus vaccine. Two placebo controlled randomized Phase 1 (96 participants), phase 2 (224 participants) were conducted. The vaccine demonstrated good immunogenicity by detecting neutralizing antibody response by day 14. Adverse effects were mild. Phase 3 trials were conducted [61]. The vaccine is approved for use.

Janssen Pharmaceutical Companies vaccine - It uses a non-replicating adenovirus 26 based vector vaccine expressing the stabilized pre-fusion spike (S) protein of SARS-CoV-2. A multi-center phase 1/2 randomized, double-blinded, placebo-controlled clinical study was conducted. Early data in preprint showed robust immune response after only one dose. Phase 3 trials involving 43738 participants are ongoing [62]. In topline Phase 3 data from 43,783 participants, J&J has announced their vaccine has shown overall efficacy of 66% with 72% protection against moderate or severe disease in the United States, 66% in Latin America and 57% in South Africa [63]. Final results are awaited

Moderna/NIAID vaccine - It uses mRNA-1273 which encodes the stabilized pre-fusion SARS-CoV-2 spike protein. A phase 1, dose-escalation, open-label trial including 45 healthy adults was conducted. 2 doses were given at 0, 28 days. There were mild to moderate but no major trial limiting adverse effects. Immune response was induced in all [64]. Phase 3 trial involving 30,000 volunteers was conducted in USA demonstrating 94% efficacy and the vaccine is approved for use [65].

BioNTech/Fosun Pharma/Pfizer vaccine - It uses BNT162b1 mRNA vaccine that encodes the trimerized receptor-binding domain (RBD) of the spike glycoprotein of SARS-CoV-2. A placebo-controlled, observer-blinded dose-escalation study (45 participants) was carried out. Adverse effects were mild to moderate. Humoral antibodies were induced after 14 days. Phase 3 trials were conducted involving 43,448 people [66]. It was found to be 95% effective and the vaccine is approved for use [67].

Novavax vaccine - It is a protein subunit vaccine using trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant. A randomized, placebo-controlled, phase 1–2 trial with 131 healthy adults was performed. Adverse effects were mild. It elicited immune responses that exceeded levels in COVID-19 convalescent serum [68]. Phase 3 data from UK trial, the company has announced the vaccine efficacy to be 89.3% and in Phase 2b clinical trial going on in South Africa it was found to be 60% effective. Final results of the trials are still awaited [69].

An ideal vaccine must be safe and should have high efficacy. It should also be able to be readily mass produced inexpensively, be easily transportable with minimal cold chain requirements.
The table 3 depicts treatment protocol of our hospital.

CONCLUSION

The emerging pandemic of COVID-19 is obviously a global public health concern. Under such a complicated scenario, aggressive multifaceted action against COVID-19 should be enforced to trigger the

disease's deceleration process. To reduce the accelerated spread, it is important to encourage social isolation, avoid crowds, and wear masks and gloves, along with wash hands with soap and water. Since asymptomatic patients may transmit the disease, there is a necessity to investigate studies about its transmission. Treating the patients with antiviral medication early in the course of disease could be the key to success and also may reduce mortality. Preventative vaccination is the need of the day that will help prevent potential COV-related complications.

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TABLES:

Table 1. Potential drugs for the treatment of COVID-19

Drug	Medication Class	Developer	Original indications	Rationale for use in COVID-19	References
Remdesivir	Antiviral	Gilead Sciences	Treatment for Ebola and Marburg virus infections	Remdesivir, an intravenous drug inhibiting viral replication, has demonstrated activity against SARS-CoV-2 as shown by in vitro and in vivo results.It was initially established as a therapy for Ebola that eventually proved less successful than other interventions but showed efficacy against other coronaviruses as evidenced in animal studies.	[26]
Hydroxychloroquine (Plaquenil) and chloroquine (Aralen)	Antimalarial	Sanofi (Plaquenil and Aralen); Mylan, Teva, Novartis, Bayer, Rising Pharmaceuticals (generics)	Hydroxychloroquine (HCQ) is recommended for both the prevention of acute malaria attacks attributable to susceptible Plasmodium strains and for suppressive care as well. Chloroquine is recommended for treating uncomplicated malaria and for malaria prophylaxis where resistance to chloroquine is not observed. The drug has also shown efficacy in the treatment of rheumatoid arthritis, systemic lupus erythematosus and porphyria cutanea tarda.	In vitro and in vivo results suggests potential therapeutic efficacy of both HCQ and chloroquine against SARS-CoV-2.	[27]
Convalescent plasma	Immunoglobulin			Research teams have hypothesized the use of convalescent plasma as	[28,29]

Drug	Medication Class	Developer	Original indications	Rationale for use in COVID-19	References
				passive immunotherapy in other coronaviruses such as MERS and in SARS-CoV-2 to neutralize the effects produced by virus.	
Favipiravir	Antiviral	Fujifilm Toyama Chemical (as Avigan) and Zhejiang Hisun Pharmaceutical	Favipiravir is approved in China and Italy to treat COVID-19.	Scientific publications in China have reported favipiravir to be clinically effective against COVID-19.	[30]
Tocilizumab	Interleukin-6 (IL-6) receptor antagonist	Roche	Tocilizumab is indicated for treating moderately to seriously active rheumatoid arthritis in adults with sufficient response from one or more DMARDs, adult giant cell arteritis, active polyarticular juvenile idiopathic arthritis (JIA) in patients (2 years of age or older), systemic JIA in patients 2 years of age or older, CRS in patients 2 years of age or older and CRS induced by chimeric antigen receptor T-cell (CAR-T) treatment.	Research reports has indicated the fact that tocilizumab can be an effective therapy for patients with extreme COVID-19 symptoms.	[31]

Table 2. Potential vaccines to prevent COVID-19 infection

Developer/ manufacturer	Vaccine platform	Type of Candidate vaccine	Number of doses	Timing of doses	Route of administration	Stage of trial
University of Oxford/AstraZeneca	Non-Replicating Viral Vector	ChAdOx1-S	2	0,28 days	IM	Approved
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	1		IM	Approved
Gamaleya Research Institute	Non-Replicating Viral Vector	Adeno-based (rAd26-S+rAd5-S)	2	0,21 days	IM	Approved
Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	Ad26COVS1	1-2	day 0 or day 0,56days	IM	Phase 3
Sinovac	Inactivated	inactivated	2	0,14 days	IM	Approved
Wuhan Institute of Biological Products/Sinopharm	inactivated	inactivated	2	0,14 days or 0,21 days	IM	Approved
Beijing Institute of Biological Products/Sinopharm	inactivated	inactivated	2	0,14 days or 0,21 days	IM	Approved
Moderna/NIAID	RNA	LNP-encapsulated mRNA	2	0,28 days	IM	Approved
BioNTech/Fosun Pharma/Pfizer	RNA	3 LNP-mRNAs	2	0,28 Days	IM	Approved
Novavax	Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	2	0,21 days	IM	Phase 3

Table 3. Treatment protocol of Kasturba Medical College, Manipal

Mild cases	Moderate cases	Severe/Critical cases
Only supportive therapy	**Anticoagulation/Anti-inflammatory** • Inj. Enoxaparin 0.6mg SC once daily • Inj. Dexamethasone 6mg IV once daily x 5-7 days **Antiviral therapy** • Inj. Remdesivir 200mg IV on day 1 followed by 100mg IV daily for 4 days **Convalescent plasma therapy** • 4-13 ml/kg given slowly over not less than 2 hours	**Anticoagulation/Anti-inflammatory** • Inj. Enoxaparin 0.6mg SC twice daily • Inj. Dexamethasone 6mg IV twice daily x 5-7 days **Antiviral therapy** • Inj. Remdesivir 200mg IV on day 1 followed by 100mg IV daily for 4 days **Anti-IL Therapy** • Inj. Tocilizumab 8mg/kg given slowly in 100 ml NS over 1 hour • Inj. Itolizumab 1.6mg/kg dose as IV infusion **Oxygenation** • Oxygen by face mask or non-rebreathing mask at 8-10L/min based on PaO_2/FiO_2 ratio • High flow nasal oxygen (HFNC)/ Non-invasive ventilation • If patient deteriorates, intubation should be considered. **Prone ventilation and Advanced ventilatory strategies** **Antibiotics** • Inj. Ceftriaxone 2gm IV once daily and escalated according to local antibiogram if needed in procalcitonin positive individuals