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Review Article

Public Health Section

Hype and Hope of Emerging Therapies to Safeguard against COVID-19 Pandemic

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ABSTRACT

The Coronavirus Disease-2019 (COVID-19) is a highly contagious disease presenting with multiple non specific symptoms and caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). Despite its dissemination and worsening trends researchers are still searching for the best treatment option. Timely diagnosis is the key to get more appropriate treatment regimen. Several clinical trials are ongoing to determine the efficacy and safety of existing and new therapies against Coronavirus Disease -2019 (COVID-19). These include corticosteroids, antivirals, monoclonal antibodies, interferon Alpha 2b and other immune modulators. In addition to treatment, efficacious and safe vaccines are required to slow viral transmission and to prevent further morbidity and mortality. The vaccination is useful tool to get control over the virus. Although, mass immunisation campaigns are ongoing in many countries, global coverage is crucial for getting the pandemic under control. This descriptive review collated the information on current diagnostics tools for determination of COVID-19 infection and available preventive and therapeutic strategies based on the ongoing clinical trials data and published literature.

Keywords: Coronavirus disease-2019, Diagnostic tools, Treatment, Vaccines

INTRODUCTION

The Coronavirus Disease -2019 (COVID-19) is an infectious disease which has spread to almost every part of the world. This disease is caused by SARS-CoV-2, belonging to *Coronaviridae* family [1]. The clinical manifestation of disease ranges from asymptomatic case to severely ill patients and deaths. Those who get infected experience mild to moderate symptoms such as cough, dyspnea, fever, bodyache and viral pneumonia and recover without any special cure [2]. Elders and those with underlying medical problems such as cardiovascular disease, chronic respiratory disease, diabetes, and cancer are more in danger to develop serious illnesses [2]. With the increasing number of cases daily, globally multiple drugs are being tested as possible candidates. Researchers are also testing the use of drugs which were found to be effective against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV disease [3]. However, there are currently no specific antivirals or drug combinations introduced for SARS-CoV.

The COVID-19 vaccination is an important tool with multiple possible benefits. An effective vaccine could prevent the infection, reduce progression to severe disease, or block the transmission within a population. However, the vaccine effectiveness depends on multiple factors including the host factors, virus factors (e.g., viral mutations), programmatic factors (e.g., storage and handling of vaccine). The need of the hour is wearing masks, social distancing, getting vaccinated and an early diagnosis of the infection which enables initiating the standard of care at earliest. All the necessary steps taken can reduce the chance of being exposed to the virus and also the chance of infecting the community.

DIAGNOSTIC TOOLS

1. Screening Test

The amplification of the viral genetic material extracted from the saliva or mucus sample is done using Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and is a widely-used method. Isothermal nucleic acid amplification test is another rapid and robust diagnostic method conducted in the field and at the local Point-of-Care (POC) centres without the usage of specialised equipment and trained professionals to interpret the results [4]. Rapid antigen test is carried out to determine the proteins that are present on the virus surface. Since this process is quick, it is more useful to accelerate the testing at all government hospitals, private health facilities, community settings and remote regions [5]. Recently, Indian Council of Medical Research (ICMR) has approved Coviself™ home based self-test kit manufactured by Mylab discovery solutions ltd., Pune [6]. On the other hand, rapid antibodies test is a quantitative test for the detection of SARS-CoV-2 IgG antibodies. Positive test result indicates past exposure. Neutralising antibodies are also measured by Plaque Reduction Neutralisation Test (PRNT), but it is not practical for large scale serodiagnosis [7]. Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) is an FDA-approved diagnostic tool for detection of SARS-CoV-2 E gene and N2 region of the N gene [8]. This test is conducted using nasal or oral swabs like RT-PCR. However, the testing machine is costlier it can run only few samples at a time and requires to run under Biosafety 2 Level (BSL-2) conditions with appropriate biosafety precautions [9].

Artificial Intelligence and voice forensic technologies can search specific patterns in voice, tone and other sounds post COVID-19 infection. The analysis of speech, cough and respiratory segment using smartphones or other machine learning classifiers have shown up to 80% accuracy while distinguishing between healthy and COVID-19 sounds [10,11].

2. Biomarkers Test

Several laboratory parameters are indicative of the SARS-CoV-2 infection in early stage. For example, increased values of liver enzymes, Lactate Dehydrogenase (LDH), muscle enzymes, and C-reactive protein can be detected [12]. The elevated Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) could be the expression of the inflammatory storm. D-dimer value is also increased in COVID-19 cases [13]. Blood lymphocytes are decreased and laboratory alterations of multi-organ imbalance (high amylase, coagulation disorders, etc.,) are also found to be raised [14].

3. Radio-imaging

In view of increasing number of confirmed cases and suspects of COVID-19 Indian Radiological and Imaging Association (IRIA) recommends that chest radiograph can be performed in suspect case if any 'two' of the following are present [15]:

- Fever (without any apparent non respiratory cause)
- Shortness of breath
- Immunocompromised host
- Hypoxia (room air SpO_2 < or equal to 94%)
- Respiratory rate > or equal to 20/min

It shows patchy or diffuse reticular-nodular opacities and consolidation, with basal, peripheral and bilateral predominance in advance stage of the disease. Finally, to quantify the extent of COVID-19 lung involvement, a severity score (Radiographic Assessment of Lung Oedema-RALE) between 0 and 48, ranging from the absence of any pathological sign (score 0) to the complete pathological involvement of lung parenchyma (score 48) will be given [16]. Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes [17].

In chest High Resolution Computed Tomography (HRCT), Ground Glass (GGO) pattern is the most common finding in COVID-19 infections. The severity of the lung involvement on the CT correlates with the severity of the disease. It is performed by scoring the percentages of each of the five lobes that is involved as <5% involvement, 5-25% involvement, 26-49% involvement, 50-75% involvement and >75% involvement. The total Cycle Threshold (CT) score is the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement), when all the five lobes show more than 75% involvement [18]. Ultrasonography (USG) a low cost, radiation free method has potential for rapid assessment of the severe pneumonia/Acute Respiratory Distress Syndrome (ARDS) and to track disease evolution [19].

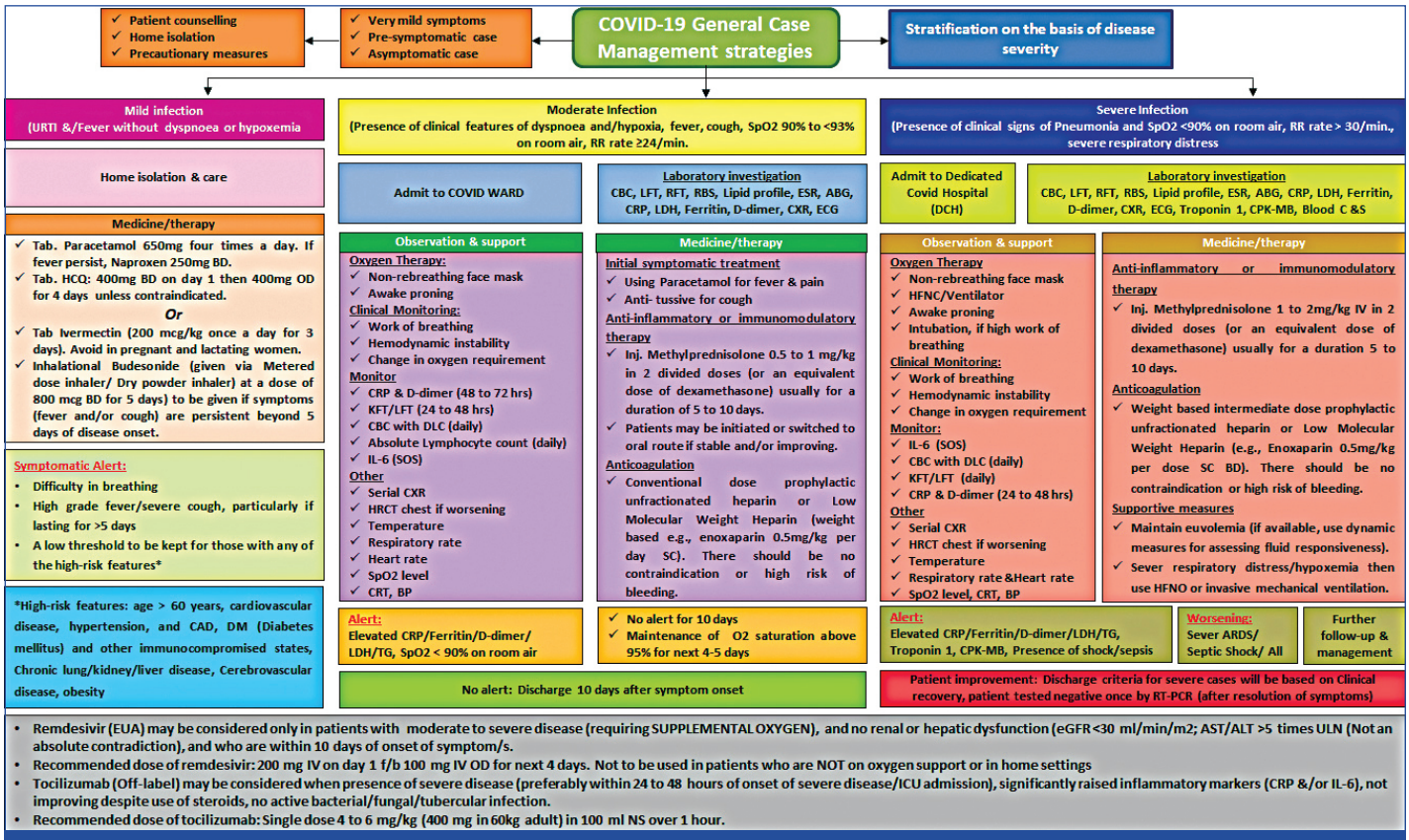
PHARMACEUTICAL TREATMENT OPTIONS

The mass vaccination program is ongoing in many countries but it is a time-consuming process. Current, SARS-CoV-2 treatment protocol is based on development of signs and symptoms, to the COVID-19 infected individual. However, the oxygen therapy is the first option that addresses the respiratory difficulties developed. In cases of respiratory failure which could be refractory to Oxygen therapy, Non Invasive (NIV) and Invasive Mechanical Ventilation (IMV) might be essential. Apart from this, the intensive care unit is necessary to deal with the complicated forms of the disease. [Table/Fig-1] indicates the general COVID-19 management strategies which are followed in the hospital premises [20,21].

1. Antiviral Drugs

Remdesivir is the most promising antiviral drug in the treatment of SARS-CoV-2 infection. It works by targeting viral Ribonucleic Acid (RNA)-dependent RNA polymerase (RdRp) while evading proofreading by viral exo-ribonuclease 17 that result in premature termination of viral RNA transcription [22]. Remdesivir has initially shown its superiority against placebo in recovering the hospitalised patients suffering from the mild to severe COVID-19 disease [23,24]. However, World Health Organization (WHO) solidarity study conducted across 40 countries and prospective trial performed in India found that remdesivir therapy is not useful in improving clinical outcome and length of hospital stay of patients [25,26]. Nausea, vomiting, rectal haemorrhage, and hepatic toxicity are some of the uncertain adverse effects of this drug [27].

Same as remdesivir, another drug favipiravir act as an inhibitor of the RNA-dependent RNA polymerase and reduce the efficacy of viral replication [28]. This drug has received approval for emergency use in mild to moderate COVID-19 infections in Italy, Japan, Russia, Ukraine, Uzbekistan, Moldova, Kazakhstan, Turkey, Bangladesh, UAE and India last year during the pandemic [29]. In the clinical studies conducted in China, favipiravir has shown superior recovery rate compared to umifenovir and shorter viral clearance time than lopinavir/ritonavir, respectively [30,31]. Recent prospective, randomised phase-3 clinical trial of oral favipiravir plus supportive care versus supportive care alone in 18-75 years adults with mild to moderate coronavirus disease in India also suggest significant improvement in time to clinical cure [32]. As of 21st of May, 2021; there are 23 studies registered on website clinical trials.gov; which



[Table/Fig-1]: General COVID-19 management strategies.

are in active recruiting phase for assessment of this drug in COVID-19 management.

Ribavirin, a guanine analogue has its activity against other nCoVs and makes it a candidate for COVID-19 treatment. The drug had been earlier tested against MERS-CoV infection. There it has been reported to increase survival of patients compared to other treatments [33,34]. The combination of ribavirin and lopinavir-ritonavir with interferon-β-1b led to a significant shortening in the duration of viral shedding [35]. Other studies reported that, ribavirin has failed to improve the clinical outcome or viral clearance in the treatment of MERS [36,37]. A systemic analysis, of more than 25 ribavirin studies for the treatment of SARS disease, revealed no conclusive results for efficacy [38]. Similarly, a retrospective cohort study was conducted to study the effect of ribavirin therapy against severe COVID-19. In this study, 44 patients receiving intravenous ribavirin were analysed against 71 patients in control group. Patients in treatment group did not show improvement in mortality rate and time to recovery compared to control arm [39]. At the same time, it also demonstrates the possibility of severe dose dependent haematologic disorders and liver toxicity [38].

The HIV protease inhibitors such as lopinavir and ritonavir are being used as a combination of HIV remedial drugs [40]. The evidence also suggests that, these drugs also have inhibitory effects against 3-chymotrypsin-like protease of MERS and SARS disease [41-43]. Whereas, a randomised control clinical trial of these drugs versus standard of care in 199 patients hospitalised with severe COVID-19 reported no benefits beyond standard of care and fails to decrease mortality rate [44]. Moreover, A systematic review of randomised clinical trials of lopinavir-ritonavir for assessment of its efficacy and safety does not observed improvement in virological cure, radiological findings, mortality in COVID-19 patients [45].

Oseltamivir, a neuraminidase inhibitor approved for the treatment of influenza was included as a regimen for the treatment of COVID-19 in early stage of pandemic [46]. A survival analysis of 1190 adults in retrospective cohort study indicated that, administration of oseltamivir reduces the risk of severe disease and is associated with slowing down the disease progression [47]. However, in a retrospective case series of 79 adults with COVID-19 infection, early use of oseltamivir had no effect on COVID-19 and did not effectively slow the progression of the disease [48]. Umifenovir (also known as Arbidol) is promising repurposed antiviral agent with a unique mechanism of action targeting the S protein or Angiotensin-Converting Enzyme 2 (ACE2) interaction and inhibiting membrane fusion of the viral envelope [49]. In randomised, controlled study, Hydroxychloroquine (HCQ) followed by Arbidol compared to HCQ followed by Lopinavir/ritonavir, significantly contributes to clinical and laboratory improvements, including oxygen saturation, Intensive Care Unit (ICU) admissions, duration of hospitalisation, chest CT involvements, WBC, and ESR but study warranted more research [50]. A systematic review and metal analysis of 12 studies conducted in 1052 COVID-19 patients found that, umifenovir was safe for administration but does not significantly reduces the hospital length of stay, symptoms or disease progression [51].

2. Anthelmintic

Ivermectin an anti-parasitic agent has also shown antiviral activities against SARS-CoV-2 [52]. A single dose is found to effect ~5000-fold reduction in Corona virus at 48 hours in in-vitro study [53]. A double blind, randomised, placebo contorolled clinical study of Ivermectin conducted in Cali, Coombia, in mild COVID-19 476 adult patients, did not observed improvement in illness [54]. Similarly, other placebo controlled clinical study was conducted in Bihar, India. In this study, 55 patients administered with the ivermectin 12 mg on day 1 and day 2 of admission, does not show difference in primary outcome compared to 57 patients those who have received the placebo [55]. Conversely, the case control study conducted in All India Institute of Medical Sciences, Bhubaneswar, India whereas two-dose ivermectin prophylaxis at a dose of 300 mcg/kg in a gap of 72 hours among healthcare workers indicated 73% reduction in SARS-CoV-2 infection for the following month [56].

3. Antimalarials

Chloroquine and hydroxychloroquine are well known drugs for the prevention and treatment of malaria as well as the treatment of chronic inflammatory diseases including Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) [57]. Small, randomised study conducted in hospitalised adults in China, compared chloroquine with Lopinavir/Ritonavir (LPV/RTV) wherein 10 moderate to severe COVID-19 patients received 500 mg chloroquine and 12 patients received lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days. Chloroquine was associated with shorter time to RT-PCR conversion and quicker recovery of patients than LPV/RTV. However, total number of patients were limited in this study. Also, the median time of treatment initiation post onset of any symptom was shorter in patients treated with chloroquine compared to LPV/RTV [58]. Many clinical trials are registered and active on clinicaltrials.gov but no high-quality evidence exists for the efficacy of chloroquine for treatment of SARS-CoV-2. Hydroxychloroquine is proposed to control the cytokine storm that occurs in critically ill late phase SARS-CoV-2 infected patients [59]. In the systematic review, of 24 clinical studies for assessment of efficacy and safety of Chloroquine and hydroxychloroquine amongst the COVID-19 patients, 100% clinical trial data showed no significant difference in virus clearance or reduction in viral transmission compared to control group. Similarly, nearly 58% patients observed no benefit against achieving primary outcome of efficacy among the observational studies. Moreover, many clinical and observational studies had also reported high incidence of cardiac adverse events of QTc prolongation and/or arrhythmias in treated patients [60]. The patients suffering from retinopathy, deficiency of glucose-6-phosphatase, QTc prolongation in electrocardiograms, history of allergy to hydroxychloroquine, pregnant women or the breastfeeding mothers are contraindicated for receiving hydroxychloroquine therapy too [61].

4. Antibiotics

Azithromycin is known to have good potential in preventing severe respiratory tract infections among pre-school children when it is administrated to patients suffering from viral infection [62]. An open label, randomised, multicenter clinical trial was conducted in Brazil in which patients were randomised in 1:1 ratio to receive oral azithromycin (500 mg once daily for 10 days) plus standard of care (n=214) or standard of care alone. Addition of azithromycin to standard of care does not show any superiority in primary outcomes based on a 6-level ordinal scale that ranged from not hospitalised (1) to death (6) [63]. Azithromycin has been studied in randomised, controlled clinical trial, conducted in hospitalised COVID-19 patients. One group of 2582 patients received 500 mg of azithromycin once daily for 10 day plus standard of care where as other group of 5181 patients were administered with standard of care alone. The mortality rate, time to hospital discharge, risk of disease progression rate was similar in both groups and thus the study found no benefit of azithromycin in hospitalised COVID-19 patients [64]. Another study in UK observed that, the administration of azithromycin in outpatients with ≥65 years of age or ≥50 years with at least one co-morbidity was ineffective in terms of reducing the risk of hospitalisation or recovery time. While 80% and 77% patients were found recovered in azithromycin and standard of care group after 28 days respectively [65]. The use of azithromycin in conjunction with the regimen of hydroxychloroquine might be a promising alternative but the documented evidence is limited. Whereas, the available data for this combination is based on observational, non randomised or other retrospective studies for evaluation of its possible benefit in patients with SARS-CoV-2 infection [66-69].

5. Immunomodulators

Mesenchymal Stem Cells (MSCs) are proven to have an anti-inflammatory action by decreasing pro-inflammatory cytokines and producing paracrine factors to repair tissues. MSCs cannot only restore endothelial permeability but also reduce inflammatory infiltrate [70] and can thus alter the innate and adoptive immune responses in COVID-19 [71]. Different sources of stem cells could be used for different groups of patients. The isolation and availability of clinical grade MSCs under GMP compliant cell processing facilities is a major challenge for a number of countries especially the developing and underdeveloped countries.

Tocilizumab, used in the treatment of RA exacerbation, is a monoclonal antibody developed and customised to inhibit the binding of interleukin-6 to its receptors alleviating cytokine release syndrome which is used in severe COVID-19 infection [72,73]. Two randomised, placebo controlled clinical trials of tocilizumab reported that use of tocilizumab is not associated with prevention of intubation, clinical outcome or mortality rate in hospitalised severe COVID-19 patients [74,75]. Another, COVINTOC trial conducted in India was open label phase 3 study wherein moderate to severe COVID-19 adult patients were randomised to receive tocilizumab 6 mg/kg plus standard care or standard care alone to assess the progression of COVID-19 disease from moderate to severe or sever to death during 28 days follow-up period. This study does not support the routine use of tocilizumab in hospitalised moderate to severe COVID-19 patients [76]. There are few other immunomodulators like sarilumab, canakinumab, ravulizumab, gemtuzumab ozogamycin, namilumab, adalimumab, otilimab etc., which are being studied in various clinical trials for treatment against COVID-19 [77].

6. Steroids

Corticosteroids have anti-inflammatory, antifibrotic effects and research is ongoing for its use in patients with Acute Respiratory Distress Syndrome (ARDS) and septic shock [78]. Use of corticosteroid has been evaluated in randomised, controlled, open label clinical trial conducted in SARS-CoV-2 patients. A 2104 patients received single daily dose of 6 mg dexamethasone plus standard of care by oral or intravenous route for 10 days, whereas 4321 patients received only standard of care. The result of this study indicated, lowering of 28 days mortality rate with IMV or oxygen support in patients receiving dexamethoasone compared to other group [79]. Systemic review of 60 registered clinical studies also show promising results and recommend the use of methylpredinisolone and dexamethasone in severe COVID-19 patients [80].

7. Convalescent Plasma

Convalescent plasma has also been used as the last resort to improve the survival rate of critically ill patients. The immunoglobulin antibodies in the plasma of patients recovering from viral infection might suppress viremia [81]. The Convalescent Plasma Therapy (CPT) was evaluated in past during H1N1, Ebola2 and SARS-CoV-1 pandemics, however controlled clinical trial data was limited to support its efficacy [82-84]. Government of India, FDA approved off label use of CPT with dose of 4 to 13 mL/kg under emergency use during last year for patients with severe life threatening COVID-19 [85,86]. Even though it looks promising, data from multiple studies including India reported, no significant benefits of CPT in improving clinical outcome, hospital stay or overall mortality in COVID-19 patients treated with convalescent plasma versus standard therapy [87-89]. Conversely, CPT might carry risk of transfusion-associated infections, allergic reactions, Transfusion-Related Acute Lung Injury (TRALI), Transfusion-Associated Circulatory Overload (TACO) and antibody-mediated enhancement and before its use various CPT parameters are required to be taken into consideration like donor selection, antibody quantification, timing of use, and dosing etc., [90]. As such, people are not getting the benefit from CPT, Ministry of Health & family Welfare, Government of India released a revised treatment algorithm on 17-May-2021 in which plasma therapy is dropped [20].

8. Monoclonal Antibodies

The REGN-COV2 is the cocktail of two neutralising IgG1 monoclonal antibodies (mAbs) namely, casirivimab and imdevimab that inhibits the binding of virus to the human ACE2 receptor by attaching and blocking epitopes of S protein of SARS-CoV-2 virus indicating high neutralisation ability in non human primates [91]. Interim analysis of an ongoing phase1/2/3 trial conducted by Regeneron evaluated the safety, tolerability, and efficacy of a single IV infusion of casirivimab and imdevimab against placebo in COVID-19 non-hospitalised patients. The analysis showed that, mAbs reduce the higher viral load in patients who were seronegative at baseline and the primary end point of time-weighted average change from baseline was achieved wherein 2.8% patients treated with casirivimab and imdevimab had COVID-19-related medically attended visits compared to 6.5% in placebo [92]. Also, the preliminary result of a Phase 3 trial of REGN-COV (casirivimab/imdevimab) revealed that a single dose of 1.2 g of casirivimab and imdevimab administered subcutaneously to uninfected house-hold contacts reduced the risk of symptomatic SARS-CoV-2 infection by 72% during the first week and by 81% through day 29 compared with placebo [93].

Bamlanivimab and etesevimab are neutralising monoclonal IgG1 antibodies like REGN-COV2 which binds to S protein of coronavirus [94]. COVID-19 related hospitalisation was 0.9% for bamlanivimab together with etesevimab compared to 5.8% in placebo with significant decrease in viral load from day 3 to day 11 [95]. Initial data from randomised, placebo-controlled phase-III trial conducted by Eli Lilly in 12-17 years old adolescents and 18 years and above adults in 1035 patients randomised 1:1 to receive bamlanivimab together with etesevimab versus placebo demonstrated 70% reduction in COVID-19-related hospitalisations and deaths relative to placebo treatment [96].

9. Janus Kinase (JAK) Inhibitors

Baricitinib is a selective and reversible Janus Kinase 1 (JAK1) and 2 (JAK2) inhibitor [97]. Its in vitro assessment was found to have an effect on cytokines signaling pathway which resulted in hyperinflammation and severe COVID-19 disease [98]. A baricitinib plus remdesivir versus remdesivir alone in randomised, double blind clinical trial was found to be effective in reducing the recovery period and improving the clinical outcome of hospitalised COVID-19 patients indicating superiority of the combination [99]. However, data is not available on effect of these drugs on different SARS-CoV-2 variants.

Another selective inhibitor of JAK 1 and 2 ruxolitinib did not show significant improvement compared to standard of care treatment in prospective, randomised, comparator phase 2 clinical study, but chest CT was found significantly improved in many patients [100].

AYURVEDIC, SIDDHA, UNANI AND HOMEOPATHY FORMULATIONS

Alternative medicine system includes Ayurveda, Siddha, Unanis and Homeopathy medicines are used as complimentary therapy for treatment of any disease. The Government of India has proposed various measures which could help to boost the immunity level against COVID-19 such as practicing yoga daily; drinking warm water throughout the day; judicious use of turmeric, coriander, and garlic (avoid excessive use); nasal application of sesame oil or ghee; oil pulling (oral rinse with oil); steam inhalation; and the use of clove powder for relief from sore throat [101]. A prospective, randomised, control clinical trial of ayurvedic regimen; *Dasamoolkaduthrayam Kashaya* and *Guluchyadi Kwatham* in tablet form with standard of care versus standard of care alone showed improvement in breathlessness and reduces hospital stay in mild to

moderate COVID-19 patients [102]. More than 67 trials including Ayurveda, naturopathy, unani, siddha and homeopathy have been registered on clinical trials registry of India [103]. Ayurveda and integrative medicines have potential for prophylactic, preventive and symptomatic management of COVID-19 disease. However, it is requiring to be explored more in clinical studies.

VITAMINS AND SUPPLEMENTS

In addition to the vitamin supplements (especially Vitamin C and D in recommended dosage); minerals; trace elements such as iron, selenium, and zinc; and flavonoids has been recommended for the clinical management of COVID-19 [104]. A randomised, open label, pilot clinical trial conducted in COVID-19 hospitalised patients reported positive result. Only 1 out of 50 patients (2%) receiving oral calciferol and standard of care got admitted to ICU unit compared to 13 out of 26 (50%) who received standard of care alone [105]. In contrast, clinical trial of single oral 2,00,000-unit dose of cholecalciferol in comparison with placebo observed, no significant difference in hospital stay, mortality rate and ICU admission in hospitalised adults with moderate to severe COVID-19 disease [106]. Zinc was also evaluated in randomised clinical trial conducted at three major university hospitals in Egypt. In this study, 191 COVID-19 patients either received dose of 220 mg zinc sulfate and HCQ or HCQ alone, along with standard of care twice daily. A 79.2% patients in zinc group and 77.9% patients in HCQ group recovered after 28 days with no significant difference in both treatment arms [107].

BIOLOGICALS (VACCINES)

Regulatory authorities across the globe are moving fast to deliver the biggest ever vaccination programme to battle COVID-19. Currently, more than a dozen vaccines are being approved globally to fight the disease [108]. More than 1.15 billion doses are distributed worldwide out of which 273 million people are fully vaccinated, covering 3.5% of the global population [109]. Many COVID-19 vaccines have been approved in last six months [Table/Fig-2] [108,110-123]. The data on duration of protection and long-term side effects is limited. Hence, the research is going on to confirm that COVID-19 vaccines are remains safe for all who receive them. The new virus variants are spreading fast resulting in successive deadly waves of infection. The Immunological Correlates of Protection (IPC) are not established in humans. It is important to established IPC and knows the effect of current licensed vaccines or other developing vaccines on new variants. Most of the current vaccines approved globally are useful in adults. Although, fewer children are infected because of COVID-19 compared to adults, risk of getting the infection and spreading

Name of vaccine	Country of origin	Developer/Manufacturer	Vaccine characteristics	Reference
BNT162b2	United States	Pfizer/BioNTech	Nucleoside-modified messenger RNA expressed in lipid nanoparticles encoding the spike (S) protein. The lipid particles allow the transfer of the RNA into host cells, resulting in the SARS-CoV-2 S antigens' expression.	[110-112]
mRNA-1273	United States	Moderna	Lipid nanoparticle encapsulating nucleoside-modified messenger RNA encoding the perfusion stabilized spike (S) protein. The S-2P antigen present on its surface allows entrance into the host cell and resulting in the expression of the SARS-CoV-2 S antigens.	[111,112]
Vaxzevria Covishield	United Kingdom	AstraZeneca Serum Institute of India Pvt., Ltd.,	Replication-deficient chimpanzee adenovirus vector and the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus.	[113]
Sputnik V	Russia	Gamaleya Research Institute	Heterologous rAd26 and rAd5 viral vector vaccine containing the gene that encodes the full-length spike protein (S) of SARS-CoV-2 to stimulate an immune response.	[114]
Sputnik Light	Russia	Gamaleya Research Institute	Recombinant human adenovirus serotype number 26 (rAd26)) of Sputnik V containing vaccine	[115]
Janssen	Netherlands, United States	Janssen Biotech Inc.	Non replicating, viral vector-based vaccine containing the genetic code for the SARS-CoV-2 antigen (spike protein), triggering an immune response to mimic what would occur during a natural infection, thereby helping to protect against a future infection.	[116,117]
Sinovac-CoronaVac	China	Sinovac Biotech	The candidate was produced by β-propiolactone-activation of the CN2 strain of SARS-CoV-2 isolated from the bronchoalveolar lavage of a hospitalised patient. It is inactivated virus alum-adjuvanted candidate vaccine activating immune system.	[118,119]
BBIBP-CorV	China	Beijing Institute of Biological Products	Developed by β-propiolactone-mediated inactivation of the 19nCoV-CDC-Tan-HB02 strain SARS-CoV-2 that was replicated in Vero cells and adjuvanted with aluminium hydroxide. Aluminium hydroxide activates the NLRP3 receptor subunit of the inflammasome and promotes the secretion of high-levels of inflammasome-derived IL-1β and IL-18, thus activating proinflammatory mechanisms of the immune system.	[119,120]
EpiVacCorona	Russia	Vektor State Research Center of Virology and Biotechnology	It contains chemically synthesised peptide antigens of SARS-CoV-2 proteins, conjugated to a carrier protein and adsorbed on an aluminum-containing adjuvant (aluminum hydroxide)	[121]
Covaxin	India	Bharat Biotech	It is developed using whole-virion inactivated vero cell derived platform technology. It included vaccine adjuvants, which are added to the vaccine to increase and boost its immunogenicity.	[122]
Convidicea	China	CanSino Biologics	Genetically engineered vaccine candidate with the replication-defective adenovirus type 5 as the vector to express SARS-CoV-2 spike protein.	[123]
CoviVac	Russia	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Inactivated vaccine	[108]
WIBP-CorV	China	Wuhan Institute of Biological Products	Inactivated vaccine	[108]
ZF2001	China, Uzbekistan	Anhui Zhifei Longcom Biopharmaceutical	Recombinant vaccine	[108]
QazVac	Kazakhstan	Research Institute for Biological Safety Problems	Inactivated vaccine	[108]

[Table/Fig-2]: COVID-19 vaccine candidates approved for use (as on 9th June 2021) [108,110-123].
RNA: Ribonucleic acid; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

it to others is high. Hence, CDC recommends two doses of Pfizer-BioNTech given 21 days apart in 12 years and older children [124]. In view of, risk of infection at any age, the evaluation of vaccines in adolescent and children is going on [125,126].

CONCLUSION(S)

In the current scenario, patients admitted to hospital with COVID-19 infection might present with multiple symptoms. Development of new potent anti-COVID-19 agent could take 5-10 years which is not a feasible option in this pandemic situation. Hence, repurposing of widely acting antivirals and other drugs seems a relevant option. These drugs are easily available with known pharmacokinetics and pharmacodynamics properties. It is for sure that, overcoming COVID-19 will include a combination of measures including the medicinal therapies currently under investigation. Additionally, the worldwide endeavor to create a safe and effective COVID-19 vaccine is bearing fruit. A handful of vaccines now have been authorised around the globe. The race for safe and effective vaccine to combat the multiple variants is still on. Nevertheless, the main treatments like mechanical ventilation, ICU admission, symptomatic and supportive care are still recommended for severe cases.

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