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Review Article

Microbiology Section

A Review on COVID-19 Pandemic

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ABSTRACT

Coronavirus associated with Severe Acute Respiratory Syndrome (SARS) has been identified as Coronavirus Disease-2019 (COVID-19) Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), first detected in Wuhan, Hubei province, China, the National Health Commission of China received reports of 27 cases of pneumonia, including seven severe cases of unknown origin, on 30th December 2019. In order to diagnose COVID-19, the virus responsible for the pandemic, SARS-CoV-2, was analysed for its Ribonucleic Acid (RNA). It is possible to detect specific sequences of genes encoding the RNA dependent RNA polymerase (*RdRP*), nucleocapsid (*N*), envelope (*E*), and spike (*S*) proteins of viruses using Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). There are four major groups of drugs recommended by treatment guidelines worldwide: antiviral drugs (eight drugs), antimalarial drugs (two drugs), systemic corticosteroids (five drugs), and immune-based therapy (seven drugs). The recommendations for the treatment with these drugs in all of the guidelines differ depending on the severity of the case and the health conditions of the patient. A successful preventative vaccine is the most important and time-sensitive measure in combating the COVID-19 pandemic. There were 12 SARS-CoV-2 vaccines approved/authorised for full or emergency use in various parts of the world as of 25th February 2021, with more than 200 million doses administered worldwide. Because the disease is still relatively new and healthcare is under considerable pressure, many questions remain unanswered. There is a lack of publications regarding the effectiveness and safety of these drugs in COVID-19 patients. In addition, community members with limited financial resources must still consider the costs associated with some of the proposed treatment regimens.

Keywords: Coronavirus disease-2019, Pneumonia, Vaccine

INTRODUCTION

Acute respiratory disease caused by SARS-CoV-2 caused an explosive catastrophic pandemic which affected almost all part of the world produced significant loss of lives and the worst financial crisis recorded ever, since World War II. SARS-CoV-2 comprises of a nucleocapsid, surrounded by an envelope, measures 120 nm in size; has a helical symmetry [1,2]. Therefore, to diagnose COVID-19, early identification of SARS-CoV-2 infection is important. Also, to develop rapid diagnostic methods in outpatient clinics and regional medical facilities are also important in order to prevent and control the pandemic, besides improving high-throughput accurate diagnostic technology in big laboratories. To find out the origin of the COVID-19 pandemic, one should also consider intelligent medicine as an emerging technology in healthcare [1,3]. In this review, authors have explored the diagnostic information provided by each diagnostic tool and some known shortcomings, as well as the way each diagnostic tool complements the others to provide more comprehensive clinical guidance [1].

A few of the new detection technologies are summarised that have already been adopted or that may find applications in COVID-19, and the kinds of technologies that have been employed in commercial products. The concept of "intelligent medicine" for infectious epidemics is conceived to offer more options for anti-infectious disease management now or in the future [1].

EPIDEMIOLOGY

SARS-CoV-2 originated from China had spread rapidly to affect rest the world over a period of three-four months. First identified in December 2019 in Wuhan, China produced a large cluster of pneumonia cases initially called as the 'Wuhan Virus'. Subsequently-named as the 2019-novel coronavirus (2019-nCoV). On 11th February 2020, World Health Organisation (WHO) announced the official name 'COVID-19' for this new coronavirus disease also renamed the virus as SARS-CoV-2. On 11th March 2020, WHO declared it as a global pandemic and India was one among those countries where the COVID-19 pandemic had a slower growth curve to reach its peak. Globally, as of 15th July 2022, there have been 557,917,904 confirmed cases of COVID-19, including 6,358,899 deaths, reported to WHO. As of 11th July 2022, a total of 12,130,881,147 vaccine doses have been administered. Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2)-coronaviruses have been identified [4].

The WHO was informed by South Africa on November 24, 2021, of a new COVID-19 variant, omicron (B1.1.529). The first detection of omicron (B.1.1.529) occurred on November 11, 2021, in Botswana and on November 14, 2021, in South Africa [5].

TRANSMISSION

Primarily transmitted via respiratory droplets and contact routes.

Droplet and aerosol transmission: Occurs when a person is in close contact (within one meter) with an infected person. Occurs through coughing, sneezing or very close personal. Use of mask can prevent droplet transmission. Spread of the infected droplet nuclei beyond one meter-not documented yet. Specific settings in which aerosol-generating procedures are performed (e.g. endotracheal intubation), aerosol transmission of the COVID-19 virus may be possible. Use of N95 respirator-important to prevent this type of transmission.

Contact transmission: COVID-19 virus can spread directly via contact with infected people, or indirectly. In direct or indirect contact, the virus can only be transmitted by touching the contaminated surfaces and those who already infected. Frequent hand hygiene following potential contact exposure is crucial to prevent this type of transmission.

Presymptomatic transmission: Defined as the transmission of the COVID-19 virus from a person who is infected and shedding the virus but has not yet developed symptoms. Observed in people within one to three days before the onset of their symptom [4].

Vertical transmission: The high expression of Angiotensin Converting Enzyme-2 (ACE-2) receptors in the human maternal-foetal interphase may allow COVID-19 to be transmitted vertically. People suffered with COVID-19 in pregnancy are at high-risk for complications that can affect the pregnancy and the developing embryo. For example, COVID-19 during pregnancy increases the risk of delivering a preterm (earlier than 37 weeks) and/or a stillborn infant. When comparing pregnant women in pre-Delta period aged 15-44 (January 1, 2020-June 26, 2021) with those in the Delta period (June 27, 2021-December 25, 2021), it was observed that,

- The risk of admission to an Intensive Care Unit (ICU) was 41% higher in the Delta period.
- The risk of invasive ventilation or Extracorporeal Membrane Oxygenation (ECMO) was 83% higher in the Delta period.
- The risk of death in the Delta period was 3.3 times the risk in the pre-Delta period.

The emergence of the Delta variant in June of 2021 in pregnant people was associated with severe outcomes including a rise in ICU admissions, an increase in required medical interventions such as invasive ventilation and ECMO, and an increased mortality that was previously seen in the pre-Delta period (January 1, 2020-June 26, 2021).

DIAGNOSIS OF COVID-19

Clinical symptoms: COVID-19 patients have reported mild to severe symptoms ranging from flu-like symptoms to other severe illnesses. There may be 2-14 days between exposure to the virus and the onset of symptoms. COVID-19 may be present in people with these symptoms [5]. Most common symptoms are fever, cough, tiredness, loss of taste or smell. Less common symptoms are sore throat, headache, aches and pains, diarrhoea, a rash on skin, or discolouration of fingers or toes, red or irritated eyes. Serious symptoms are difficulty breathing or shortness of breath, loss of speech or mobility, or confusion, chest pain. If patient presents with serious symptoms, seek medical attention immediately. Before visiting the doctor, always call ahead. Mild symptoms should be managed at home by people who are otherwise healthy. An infection with the virus typically takes five to six days to manifest its symptoms, but it can take up to 14 days [5].

LABORATORY DIAGNOSIS

Non specific Laboratory test: Test for COVID-19 cases include Complete Blood Count (CBC),C-reactive Protein (CRP), Random Blood Sugar Test (RBS), Haemoglobin A1C (HbA1C), D-Dimer, Lactate Dehydrogenase (LDH), Serum Ferritin, High-Resolution Computed Tomography (HRCT) Chest on day five of symptom onset tests related to pre-existing illness Repeat CBC/Liver Function Test (LFT)/Renal Function Test (RFT)/Electrolytes/CRP/D-Dimer every 72 hours case based: Procalcitonin, Interleukin-6 (IL6), AQT Panel, Arteria Blood Gas (ABG) [6,7].

Monitoring: Clinical: Haemodynamic, work of breathing, change in O_2 requirement, Serial: chest X-Ray (CXR)/HRCT if worsening, Lab: CRP, D-Dimer 48-72 hourly, CBC, Electrolytes, Kidney function test KFT, LFT 24-48 hourly, IL6 if patient deteriorating [6,7].

Specific Test

RT PCR Test: A COVID-19 diagnosis is based primarily on epidemiological data, clinical symptoms, as well as some adjuvant technologies, such as nucleic acid detection and immunological testing. In addition, in order to ensure personnel safety, SARS-CoV-2 isolation requires high-throughput equipment (biosafety level-2) [8]. In order to diagnose COVID-19, the virus responsible for the pandemic, SARS-CoV-2, is analysed for its RNA. It is possible to detect specific sequences of genes encoding the *RdRP, N, E,* and *S* proteins of viruses using RT-PCR [8].

Heating methods that do not require extraction, such as those that lyse viral particles to release RNA for subsequent analysis, are more convenient and suitable for point-of-care testing [9].

The genes encoding *N, E*, and *S* proteins, open reading frame 1ab (*Orf1ab*), and *RdRP* are targets for the detection of SARS-CoV-2. It is important to choose the targets carefully, since the *E* gene is highly conserved throughout all beta coronaviruses while the *N* gene is cross-reactive with other coronaviruses. SARS-CoV-2 can be distinguished from SARS-CoV by analyzing its *RdRP* gene. The *S* gene is also useful for distinguishing SARS-CoV-2 from other coronaviruses because of its high divergence [10].

Cycle Threshold (CT) values less than 40 are considered positive for SARS-COV, while CT values of 40 or more are considered negative for SARS-COV [11].

It is recommended that commercial RT-PCR-based tests be used under Biosafety Level 2 conditions, under notification of Drug Controller General of India (DCGI) and Ministry of Health and Family Welfare (MoH and FW), with appropriate biosafety precautions. Indian Council of Medical Research (ICMR) also validates commercial testing kits (RT-PCR, CRISPR, NAAT, Rapid antigen, IgG ELISA etc.) before they are used in mass testing. The tests are validated at the National Institute of Virology (NIV), Pune, and at 14 other ICMR-approved validation centers [12].

CLINICAL MANAGEMENT

Clinical Severity of COVID-19 [13]

Mild disease: Iinfluenza-Like Illness (ILI): Patients with uncomplicated upper respiratory tract infection with mild symptoms (fever, cough, sore throat, nasal congestion, malaise, headache without evidence of breathlessness or hypoxia).

Moderate disease: Pneumonia with no signs of severe disease-dyspnoea, fever and cough hypoxia, SpO_2 <94%, respiratory rate ≥24 per minute.

Severe disease: Called as severe acute respiratory illness (SARI).

Severe pneumonia: Clinical signs of pneumonia plus one of the following sign of severe respiratory distress: (i) Respiratory rate >30/min or (ii) SpO_2 <90%.

Acute Respiratory Distress Syndrome (ARDS): Symptoms: Onset of new or worsening respiratory symptoms within one week. **Chest imaging:** Shows bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules decreased PaO_2/FiO_2 (normal value ~500): ARDS can be classified into-mild (<300), moderate (<200), and severe (<100); (when Positive End Expiratory Pressure (PEEP) or Continuous Positive Airway Pressure (CPAP) is maintained at ≥5 cm H_2O).

Sepsis: Acute life-threatening multiorgan dysfunction: Clinically diagnosed by Sequential Organ Failure Assessment (SOFA) score.

Septic shock: Persisting hypotension despite volume resuscitation, requiring vasopressors to maintain mean arterial pressure ≥65 mm Hg and serum lactate level >18 mg/dL [Table/Fig-1] shows clinical management in Mahatma Gandhi University of Medical Sciences, Jaipur, Rajasthan, India [6,14].

VACCINATION

SARS-CoV-2 vaccines are targeting the viral S glycoprotein. The coronavirus was also the target for the development of vaccines against other coronaviruses, and attempts were made in the past to develop vaccines against SARS and MERS based on S glycoproteins [15]. In viral replication, the S glycoprotein is responsible for binding to the ACE-2 receptor on the host cell, as well as fusion of the host cell membrane with the viral membrane. Therefore, it is believed that vaccines based on S glycoproteins should elicit antibodies that block viral genome attachment and uncoating from receptors [16]. The S glycoprotein's immunogenicity and ability to bind to the ACE2 receptor are not affected by the presence or absence of other viral glycoproteins, making it a strong candidate for vaccine development [17]. There is also consideration of developing a 'pan-CoV' vaccine

Group A		Group B	Group C
Mild case COVID-19			
Criteria/Definition	Asymptomatic but positive for COVID-19 Upper respiratory tract symptoms and/or fever without shortness of breath or hypoxia HRCT chest suggested suspected contact/ incidentally detected	Symptomatic, without co-morbidity • Fever/chills • Cough • Sore throat, shortness of breath • Malaise, fatigue • Headache • Anosmia/ageusia • Diarrhoea/pain abdomen/nausea, vomiting • Congestion, running nose SpO_2.94%, RR <24/mt, CTSS: 1-8	Symptomatic, with co-morbidity • Obesity • >60 years • DM • HTN/IHD • COPD/CLD • CKD • CVA • Immunocompromised states/drugs causing immunosuppression
Red flag signs Consult Dr/Hospital	1. SpO_2 <94% 2. Resting tachycardia 3. Deoxygenation on 6 minute walk test 4. High-grade fever, severe cough	Same as mild	Same as mild, worsening of pre-existing illness Advised admission if co-morbid conditions present and require treatment
Advise:	Home isolation, physical distancing, indoor mask use, hand hygiene for 15 days Stay in contact with treating physician Monitor temperature, SpO_2 with finger probe No Medication for COVID-19 infection Healthy diet, proper hydration, proning	Tab Meftal forte SOS for fever Syp Reswas 1-2 TSF TDS Tab Fabiflu 1800 mg BD×on Day 1 f/b 800 mg BD×Day 2 to Day 7 Cap Doxycycline 100 mg BD×7 days Cap Pantocid DSR 40 mg OD A/C Tab ZAC-D 1-tab BD MDI Budesonide 800 mcg BD for five days, if symptoms persistent beyond five days of disease onset.	Tab Meftal forte SOS for fever Syp Reswas 2 TSF TDS Tab Fabiflu 1800 mg BD×on Day 1 f/b 800 mg BD×Day 2 to Day 7 Tab Rivolas 10 mg OD Cap Doxycycline 100 mg BD×7 days Cap Pantocid DSR 40 mg OD A/C Tab ZAC-D 1-tab BD MDI Budesonide 800 mcg BD for 5 days, if symptoms persistent beyond 5 days of disease onset Steroids as required Continue medicines for other co-morbidities, if any.
Moderate cases			
Definion/Criteria		Investigatios	Treatment
	Shortness of breath ++ Difficulty breathing ++ RR 24-30/mt SpO2: 90-93% CTSS: 9-15 Extreme fatigue Advise admission	CBC/RBS/LFT/RFT/Electrolytes CRP/D-Dimer/Ferritin/ ECG/ABG/ LDH/Blood C/S, HbA1C, (PT INR, PCT, Trop T, IL6 etc if required) HRCT Chest on admission AQT Panel, ABG (Case based) **Monitoring:** **Clinical:** haemodynamic, work of breathing, change in O2 requirement. **Serial:** CXR/HRCT if worsening. **Lab:** CRP, D Dimer 48-72 hrly, CBC, Electrolytes, KFT, LFT 24-48 hrly, IL6 if patient deteriorating.	Advise admission Oxygen support by nasal prongs or non-rebreathing face mask as required: Target SpO2 92-96%, (In COPD 88-92%) Awake proning, sequential position changes every two hours. Tab Meftal forte SOS for fever Tab Abflo-N 100 mg BD Tab Montair LC HS Syp Reswas 2TSF TDS Tab Fabiflu 1800 mg BD×on Day 1 f/b 800 mg BD×Day 2 to Day 7 OR Inj Remdesivir 200 mg in 100 mL NS IV OD on Day 1 f/b 100 mg in 100 mL NS IV OD for Day 2 to Day 5 (If available and for off label use) Cap Doxycycline 100 mg BD×7 days Tab Predmet 16 mg × 3 days f/b 8 mg × 3 days f/b 4 mg×3 days OR Inj MPS 40 mg IV OD/BD as indicated. (0.5-1 mg/kg in 2 devided doses, usually for 5-10 days. Switch to oral route if patient stable/ improving. Inj Clexane 0.6 mL SC OD/BD according to D-Dimer levels. (Enoxaparin 0.5 mg/kg/day SC). There should be no contraindication or high-risk of bleeding. Tab ZAC-D 1-tab BD MDI Budesonide 800 mcg BD for 5 days, if symptoms persistent beyond 5 days of disease onset Tab Tofacitinib 10 mg BD/ Baricitinib 4 mg OD 2DG Sachet according to weight in 100 mL water BD *Antibody Cocktail Therapy (Casirivimab 120 mg/mL and Imdevimab 120 mg/mL) IV/SC* Add methylene blue in oxygen flowmeter/Nebulization 2 mL 6 hrly
Severe cases			
Definion/Criteria		Investigations	Treatment
	Fever or suspected respiratory infection +one of the below: Shortness of breath +++ Difficulty in breathing +++ Respiratory rate >30/min SpO2:<90% at room air or less than 94% with Oxygen CTSS >15 ARDS/Septic Shock Red flag signs: *Elevations in* • D-Dimer >1000 ng/mL (normal range: <500 ng/ mL),	CBC RBS LFT RFT Electrolytes CRP D-Dimer Ferritin ECG/ABG/LDH/Blood C/S, PT INR, PCT, Trop T, IL6, Blood C/S, TSH, NT ProBNP, S. Lactate, S. Cortisol etc. (if required) HRCT Chest on admission **Monitoring:** **clinical:** haemodynamic, work of breathing/	Admit immediately, Decide ICU requirement Immediate oxygen therapy to reach target SpO2≥90%, NIV/HFNC/Invasive, Use ARDS net protocol for ventilatory management. Consider use of O2/HFNC/NIV/intubation and mechanical ventilation Tab Meftal forte SOS for fever Tab Abflo-N 100 mg BD Tab Montair LC HS Syp Tossex SF 2TSF TDS Inj Remdesivir 200 mg in 100 ml NS IV OD on Day 1 f/b 100 mg in 100 mL NS IV OD for Day2 to Day 5. Inj MPS 40 mg IV BD/TDS according to severity. (1-2 mg/kg in 2 devided doses, usually for 5-10 days). Inj Pantop 40 mg IV OD Inj Clexane 0.6 mL SC OD/BD according to D-Dimer levels. (Enoxaparin 0.5 mg/kg/day SC). There should be no contraindication or high-risk of bleeding.

	• CRP >100 mg/L (normal range: <8.0 ng/L), • LDH>245 units/L (normal range: 110 to 210 units/L), • Troponin >2× the upper limit of normal, • Ferritin >500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L), • CPK >2× the upper limit of normal (normal range: 40 to 150 units/L) *Decrease in* • Absolute lymphocyte count<800/microL (normal rangefor age >21 years : 1800 to7700	pressures on ventilar, change in O2 requirement. **Serial:** CXR/HRCT if worsening. **Lab:** CRP, D Dimer 24-48 hrly, CBC, KFT, LFT 24 hrly, IL6 if patient deteriorating. Admit	Tab ZAC-D 1-tab BD Budesonide nebulisation 8 hourly Nebulisation with 2mL methylene blue in 8 mL NS TDS Maintain euvolemia, manage sepsis/septic shock as per existing protocol/local antibiogram, General ICU care as per protocol. Continue medicines for other co-morbidities, if any, Necessary references to be done *Reserved Medicines:* Add methylene blue in oxygen flowmeter Tab Tofacitinib 10 mg BD/Baricitinib 4 mg OD 2DG Sachet according to weight in 100 ml water BD (Patient should be kept NBM 3 hours prior to 2DG and 30 minutes after administration of 2DG) Antibody Cocktail Therapy (Casirivimab 120 mg/mL and Imdevimab 120 mg/mL) IV/SC Broad spectrum antibiotics as per case and co-morbid illness Add Antifungals in diabetics and other immunocompromised patients upfront after seven days of steroids therapy or if indicated earlier

[Table/Fig-1]: COVID-19 clinical management in MGUMST, Jaipur (update: 2022) [6,14].
HRCT: High-resolution computed tomography; RR: Respiratory rate; CTSS: Computed tomography severity score; DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischaemic heart disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CVA: Cerebrovascular accident; CBC: Complete blood count; RBS: Random blood sugar; LFT: Liver function test; RFT: Renal function test; LDH: Lactate dehydrogenase

S. No.	Name of vaccine	Manufacturer/WHO EUL holder	Plate form
1	BNT162b2/COMIRNATY Tozinameran (INN)	BioNTech Manufacturing GmbH	Nucleoside modified mRNA
2	AZD1222 Vaxzevria	AstraZeneca, AB	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.
3	Covishield (ChAdOx1_nCoV-19)	Serum Institute of India Pvt. Ltd.	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.
4	Ad26.COV2. S	Janssen–Cilag International NV	Recombinant, replication incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) Spike (S) protein
5	mRNA-1273	Moderna Biotech	mRNA-based vaccine encapsulated in lipid nanoparticle (LNP)
6	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	Beijing Institute of Biological Products Co., Ltd. (BIBP)	Inactivated, produced in Vero cells
7	COVID-19 Vaccine (Vero Cell), Inactivated/ CoronavacTM	Sinovac Life Sciences Co., Ltd. Sinovac Life Sciences Co., Ltd.	Inactivated, produced in Vero cells
8	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)/COVAXIN	Bharat Biotech, India	Whole-Virion Inactivated Vero Cell
9	NVX-CoV2373/Covovax	Bharat Biotech, India	Recombinant nanoparticle prefusion spike protein formulated with Matrix-M™ adjuvant
10	NVX-CoV2373/Nuvaxovid	Novavax	Recombinant nanoparticle prefusion spike protein formulated with Matrix-M™ adjuvant
11	Sputnik V	Russian direct investment fund	Human Adenovirus Vector-based Covid-19 vaccine
12	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Sinopharm/WIBP2	Inactivated, produced in Vero cells
13	Ad5-nCoV	Cansinobio	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)
14	CoV2 preS dTM-AS03 vaccine	SANOFI	Recombinant, adjuvanted
15	SCB-2019	Clover Biopharmaceuticals	Novel recombinant SARS-CoV-2 Spike (S)-Trimer fusion protein
16	Recombinant Novel Coronavirus Vaccine (CHO Cell)	Zhifei Longcom,China	Recombinant, protein subunit
17	CovIran® vaccine	Shifa Pharmed-Barkat	Inactivated, produced in Vero cells
18	Abdala	CIGB	Protien subunit
19	Corbevax	Biological	RBD antigen of SARS CoV-2 (COVID-19)
20	GBP510	SK Biopharma	Recombinant, protein subunit
21	Recombinant COVID-19 vaccine	WestVac Biopharma	Recombinant SARS-CoV-2 S-RBD protein

[Table/Fig-2]: COVID-19 Vaccine [20-31].

due to the genetic homogeneity among coronaviruses. There is evidence that the S glycoproteins of SARS-CoV-1 and SARS-CoV-2 contain different residues; as a result, antibodies produced against SARS-CoV-1 may not be effective against SARS-CoV-2 [18].

The COVID-19 vaccine is currently approved for full use by six countries and authorised for limited use by another six [19]. Details on each of the approved/authorised vaccines are provided in [Table/Fig-2] [20-31]. The vaccines are inactivated, recombinant adenovirus vaccines (human and nonhuman), and novel mRNA vaccines. There has been considerable evidence that many of these vaccines offer significant protection against severe COVID-19 (often up to 100%), and to a lesser degree, symptomatic COVID-19. The side effects of these vaccines are generally mild to moderate and acute [20-31]. However, there is no data on their long-term efficacy or effectiveness in preventing transmission (sterilising immunity).

CONCLUSION(S)

The COVID-19 pandemic is becoming more severe, with an increase in infections and deaths. The pandemic prompts the use of off-label or consideration of pharmacologic treatments throughout the world. Various drugs were recommended for treating patients with COVID-19 infection.

In most of the guidelines, these drug classes were mentioned, either with compressions on their use or with restrictions for their use only in clinical trials. Generally, there is a big difference between these guidelines. These included indications for using drugs, types of drugs, dosage regimen, period of treatment, and safety of use among different patient groups. The recommendations for the treatment with these drugs in all of the guidelines differ depending on the severity of the case and the health conditions of the patient.

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