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Review

Current strategies in diagnostics and therapeutics against novel coronavirus disease (COVID-19)

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The epidemic of COVID-19 spread quickly through China and engulfed all of the countries across the globe. Several advances have been made in understanding the novel coronavirus's pathophysiology and in the development of newer diagnostics with pinpoint accuracy. Several newer therapeutic methods have either been accepted or are awaiting acceptance. In many countries, vaccination programs have been rolled out. Despite all these efforts, coronavirus still exists, though with lesser propensity. Multiple new forms of the novel coronavirus unexpectedly appeared in various areas of the world, undermining previously existing diagnosis and care protocols. This article highlights our understanding of the novel coronavirus's symptoms in brief, pathogenesis, diagnostics, and therapeutic strategies to contain COVID-19. The clinical findings, including serological, radiological, and other advanced diagnostic strategies, contributed much to control the disease. To date, supportive interventions have been used in tandem with potent antiviral therapies such as remdesivir, lopinavir/ritonavir, or corticosteroids with a level of trust in the care of COVID-19 patients. However, in several areas of the world, vaccination initiatives took place; the vaccines' safety and efficacy to control the outbreak is yet to be identified. This review concludes that improvement in therapies and diagnostics for COVID-19 must continually be explored as new variants constantly emerge.

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INTRODUCTION

More than a year ago, a new form of beta coronavirus appeared in Wuhan Area, China, and spread like a bush fire around the globe (1). None of the country on earth was spared from the devastation of the disease. The human sufferings are unaccountable due to the complete breakdown of the economy and healthcare system.

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The strain was a different form of the coronavirus, and the people did have little to no understanding of the virus. Everything about the virus was unknown to health care workers: the sign and symptoms of the novel coronavirus disease, the mode of transmission, the pathogenesis (2). In the beginning, the whole world lacked adequate facilities to diagnose this unique virus, and for the countries, there was no other option but to cut off the human to human contact and proximity. A complete lockout has been placed into effect in nearly every area of the world. One year has passed on, the virus still exists, the shock and despair might have diminished, but the virus's after-effects are seen everywhere. As of the 24th of March 2021, more than 123 million people got infected, and almost 3 million people lost their lives (3).

Coronaviruses (CoVs) are made up of single-stranded RNA and belong to the *Coronaviridae* group, which infect a number of hosts and cause pathological changes from the common cold to severe/fatal respiratory diseases (4). Up until early January 2021, neither active immunity in the form of vaccines nor potent antiviral medications were available for the treatment of human coronavirus infections. The health care agencies were not having any other options but to follow WHO guidelines; the social distancing and quarantining of patients suspected or confirmed for COVID-19. Remdesivir, lopinavir/ritonavir alone or in conjunction with interferon-β, convalescent plasma, and monoclonal antibodies (mAbs) are the main therapeutic choices used to treat COVID-19 patients (5).

At the beginning of 2021, except in the USA, the novel coronavirus's transmission started declining; the reasons were not clear; the scientist speculated about herd immunity. For almost one year, the world put its entire effort to develop strategies to contain the virus. Most diagnostic techniques have been developed and introduced to the diagnosis of novel coronavirus. Many countries rolled out their vaccines; some were well evaluated and followed the clinical trial guidelines, data of some vaccines were never published. Despite the discrepancies in their results, those vaccines were employed for human use.

Now we have advanced to our approaches in diagnosing and treating this novel coronavirus with a high degree of certainty. Multiple new forms of the novel coronavirus unexpectedly appeared in various areas of the world, undermining previously existing diagnosis and care protocols. These newer variants, the new UK coronavirus type B117 and the South African form (501Y.V2), presented a larger threat to the structures currently in place to manage the virus (6). Will the war footing works across the globe prove futile if these novel mutated strains evade all the recently designed strategies? The question remains unanswered.

This article highlights our latest understanding of the novel coronavirus's symptoms in brief, pathogenesis, diagnostics, and therapeutic strategies to contain COVID-19. These facts and figures may generate some novel ideas which will play a role in getting rid of this deadly coronavirus disease.

SYMPTOMS

The warning sign of COVID-19 infection generally appears after an average of 5.2 days of infections (5). In the case of a deathly outcome, the documented duration between the beginning of COVID-19 symptoms and death is 6 and 41 days, with an average value of 14 days (7). This period is based on the patient's age and immunity level. Fever, cough, and

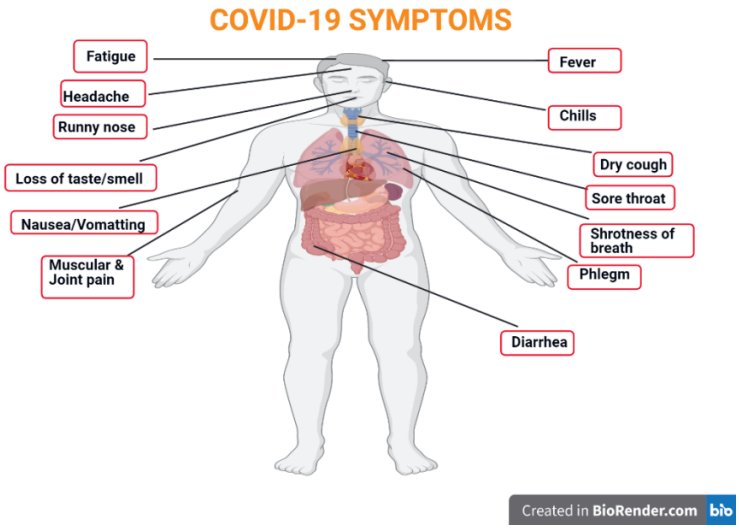


Fig. 1. The virus appears to start with fever accompanied by dry cough and then leads to breathing difficulties after a week and some patients need hospital admission.

weakness or myalgia are the most frequent indications at the start of COVID-19 (Fig. 1), although other symptoms include sputum development, fever, blood-stained bronchial mucus, diarrhea, trouble breathing and loss of smell and taste (8–11).

Novel SARS-CoV-2 virus and older beta coronaviruses worsen effects such as headache, dry cough, and shortness of breath. However, novel SARS-CoV-2 displayed some exclusive clinical features that comprise infecting the lower respiratory tract soon after the upper respiratory tract symptoms like runny nose, sneezing, and sore throat appear (12). Few patients affected by SARS-CoV-2 had digestive issues such as diarrhoea, however, a small percentage of patients reported similar GI discomfort.

PATHOGENESIS AND DIAGNOSIS: CLINICAL MANIFESTATION

A significant number of documented clinical and literature reports offered ample knowledge regarding the pathogenesis process of novel SARS-CoV-2 infection. The virus reaches to lungs, infecting all around the respiratory tract, primarily the mucous membrane of the larynx and nasal cavity. The virus then reaches the supply of peripheral blood from the lungs and then targets the targeting organs expressing ACE2, such as the lungs, the heart, the gastrointestinal tract, the renal system, *etc*. (13, 14). According to new studies, three elements are involved in the entry of novel SARS-CoV-2: the ACE2 receptor, the neuropilin-1 (NRP1) receptor, and the transmembrane protease serine 2 (TMPRSS2) receptor (15). NRP1 and TMPRSS2 serve as co-receptors to allow SARS-CoV-2 to enter the cells and to cause the viral infection. The olfactory epithelium of humans who died from COVID-19 infection has indicated that the novel coronavirus targets more neuropilin-1(NRP1)-producing cells in the nasal cavity. This may be the basis to assume that the loss of smell is

due to the excessive viral entry and infectivity of the olfactory epithelial cells. SARS-CoV-2 was detected in stool most likely that it travels from the lungs through the bloodstream and then from the bloodstream to the gastrointestinal tract (16).

In SARS-CoV-2-infected patients, numerous biochemical changes have been observed. Many biomarkers have been discovered to be a significant parameter for verifying infection with SARS-CoV-2, and those biomarkers suggest the magnitude of the disease. Table I highlights alterations of some biomarkers.

COVID-19 infection is investigated using a range of approaches, including molecular, serological, radiological, and microbiological processes. In molecular diagnosis, detection of the virus is done by viral nucleic acid or RNA sequence amplification utilizing the reverse transcriptase-polymerase chain reaction (RT-PCR) technique (30). When using serological diagnosis, a laboratory can screen for antibodies in patients that have novel coronavirus disease, whereas point-of-care or radiology-based diagnoses rely on the existence of clinical changes in patients that may have or are believed to have novel coronavirus disease (31, 32). Microbiological methods, especially the diagnosis *via* viral culture, rely on SARS-CoV-2 separation on cell lines enhancing virus growth and replication (33).

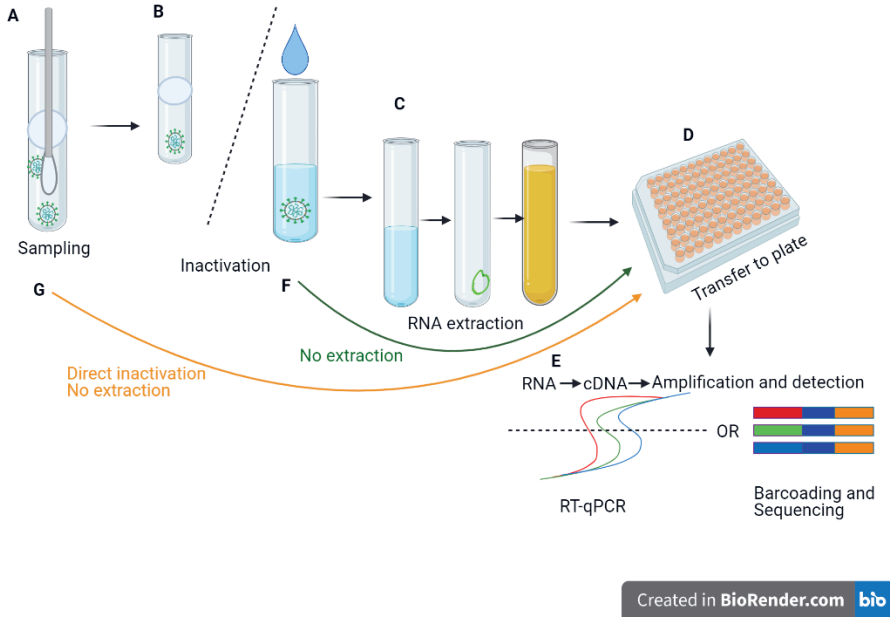


Fig. 2. highlights the SARS-CoV-2 RT-PCR testing procedure: (A) Collection of sample and deposition of viral particles in transport medium. (B) Detergent/chaotropic reagents or heating is used to inactivate the virus. (C) Separation or extraction of RNA is done. In (D) and (E) steps show transfer to PCR-plate in which cDNA synthesis by RT and detection by qPCR happen. The (F) and (G) routes are the direct approaches in which samples are deposited in the transport medium, viral particles are attenuated either through heating or by direct lysis in the detergent-holding buffer. The attenuated samples are then used for the downstream RT-PCR diagnostic reaction. On this theory of molecular detection (reproduced with permission from reference (41)), numerous POC kits and devices operate.

Table I. Main biochemical changes seen in extreme COVID-19 patients

Biomarker(s)	Status	Remarks	Ref.
Lymphocyte	Decreased	Virus directly infect lymphocytes, principally T cells	17–19
Neutrophils	Elevated levels	An early indicator of COVID-19, suggesting extreme respiratory illness and worse results, is blood neutrophils	20, 9
Blood platelet	Decreased	The immune system, which induces thrombocytopenia, kills platelets.	21
Cytokine	Increased	A higher level of cytokines such as IL-6, IL-2, IL-7, TNF-α, interferon-γ was found in moderate to severe COVID-19 patients	22
C-reactive protein (CRP)	Increased	CRP is a good diagnostic tool for detecting COVID 19 in a very early stage	23
D-dimer	Increased	An increased risk of ARDS, ICU entry, and mortality, is linked with increased D-dimer levels	24
Coagulation factors	Increased	The severity and mortality of COVI-19 are related to an increased level of coagulation parameters	25
Electrolyte balance	Decreased	Specifically, hypocalcemia, hypokalemia, hyponatremia, *etc.*, have been observed with severe illness	26
Liver enzymes (aspartate transferase AST, alanine transferase ALT, alkaline phosphatase ALP, gamma-glutamyltransferase GGT, *etc.*)	Elevated	There has been no direct association. This can be attributed to secondary liver damage caused by systemic inflammation, hepatotoxic medicinal administration, *etc.*	27
Creatine kinase (CK)	Increased	The alteration of creatine kinase in COVID-19 may be as a result of kidney dysfunction and cardiac injury, or a direct effect of the SARS-CoV-2, which can also infect cells of the muscle tissue due to the expression of the ACE2 receptor	28
Cardiac troponin	Increased	Indicating cardiac injury	29

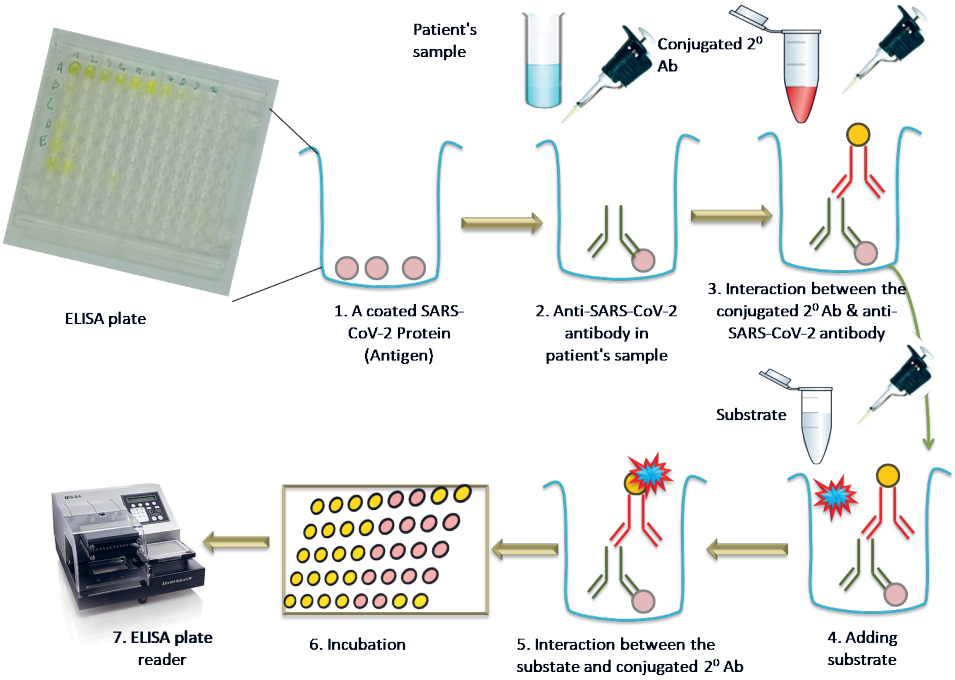


Fig. 3. Various steps of the ELISA technique (reproduced with permission from ref. 46).

Molecular tests (RT-PCR)

The swabs are placed through nasal and or oral routes into the upper airways for the collection of samples. For mechanically ventilated patients, samples are collected through expectorated phlegm and bronchoalveolar lavage from the lower airways. In order to detect the pathogen's genetic content, the sample was amplified in the 4 °C annealing stage using a reverse transcription process. To allow the formation of a double-stranded DNA molecule,

Table II. Different target genes to diagnose the COVID-19 worldwide

Country/ organization	Target gene/s	Country/organization	Target gene/s
CDC USA	Three targets in the N gene	NIH, Thailand	N gene
China	ORF1ab and N gene	Hong Kong	ORF1b-nsp14 and N gene
Germany	RdRP, E and N gene	NIID, Japan	Spike protein
France	Two regions of the RdRP gene	PHA, Canada	RdRp, E and Any3 gene

CDC – Centers for Disease Control and Prevention, NIH – National Institute of Health, NIID – National Institute of Infectious Diseases, PHA – Pulmonary Hypertension Association

a reverse transcription method or a real-time RT-PCR technique can be used from a single--stranded viral RNA molecule (34, 35). Finally, replication of genetic information is used to identify the SARS-CoV-2 genetic code. For the molecular level identification of the COVID-19 pathogen, various countries have introduced different target genes (Table II) (36, 37).

The sensitivity of these measures is moderate; for example, 53.3 percent of COVID-19 documented patients had positive oropharyngeal swab test, whereas 71 percent of patients had positive sputum test (38, 39). After 2–8 days of viral infection, the outcomes of RT-PCR generally show positivity (40).

Serology based diagnosis

When molecular techniques deliver an unsatisfactory result, serological tests come into place by detecting antibodies in the patient's blood (42). At the beginning of a novel coronavirus outbreak, serological techniques were considered a supplementary diagnostic method (43). There are several serological measures widely used in laboratories around the world to diagnose novel coronavirus infections (44).

The enzyme-linked immunosorbent assay (ELISA) is widely used to identify a variety of viruses, such as novel coronaviruses (45). The various phases of the novel SARS-CoV-2 ELISA experiment are represented in Fig. 3 (46). The degree of sensitivity of this examination to IgG or IgM in COVID-19 positive patients is almost 84.3 percent (47).

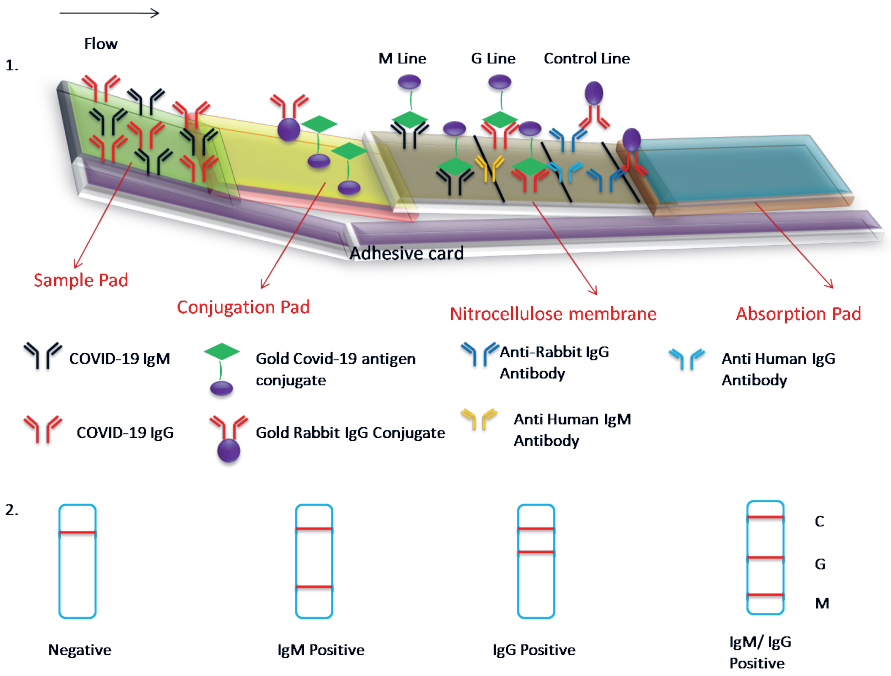


Fig. 4. Steps in lateral flow immunoassay (LFIA)-based COVID-19 diagnosis (reproduced with permission from ref. 50).

For the identification of novel coronavirus, a tweaked form of luminescent ELISA is used in the chemiluminescent immunoassay (CLIA). Chemiluminescent immunoassay is used to determine the quantity of antibodies such as IgG, IgM, and IgA (48). Patient samples may be mixed with virus-specific proteins using this process. The development of the antigen-antibody complex is then observed by the attachment of another secondary antibody, which undergoes a particular chemical reaction to create illumination. The sum of light released is then measured for the calculation of the number of antibodies found in the COVID-19 sample (44). The degree of sensitivity of CLIA is almost 97.8 % in the COVID-19 positive patients (47).

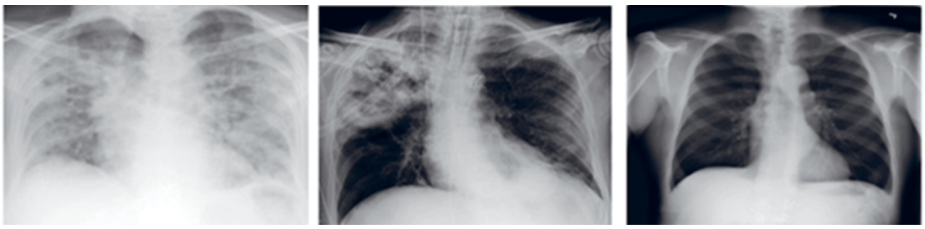
In Point of Care (POC) immunodiagnostics, rapid diagnostic tests (RDTs) are gaining popularity due to their compact, simple, and portable nature (44, 49). RDTs utilize the lateral flow immunoassay (LFIA) technique which uses colour lines to assess if samples of saliva, nasal swabs, and/or blood for viruses are positive or negative (Fig. 4) (50).

Two distinct lines are present in a lateral flow immunoassay where a membrane containing gold-nanoparticle-labeled antibodies (Au-Ab) and trap antibodies are present (44). As the sample of the patient is placed on the membrane, it moves across the membrane by capillary motion. The viral antigens bind and shape a complex with Au-Ab. This complex then moves forward and is caught by the capture antibodies in the second line, resulting in the formation of coloured lines on the surface, verifying the tests (44, 50).

Diagnosis based on radiology

Chest X-ray. – Chest x-rays normally do not display noticeable alterations in the early stages of the illness. When the infection develops, bilateral multifocal alveolar opacities are discovered, and pleural effusion is often seen in the latter stages (51).

Computed tomography. – High-resolution computed tomography (HRCT) is particularly sensitive and, also in the early stages of the illness, is the preferable technique for COVID-19 pneumonia diagnosis. The most prominent attributes are multifocal bilateral 'ground-glass' areas consistent with convergence and patchy peripheral distribution, with the lower lobes becoming more involved. In certain patients, a 'reverse halo sign' is also seen, which is known as a focal region of patchy opacities surrounded by a consolidation peripheral ring. Other observations include pleural effusion, calcification, cavitation, and lymphadenopathy (52).



a) b) c)

Fig. 5. a) The COVID-19 infected chest, b) pneumonia infected chest, c) normal chest (reproduced with permission from ref. 51).

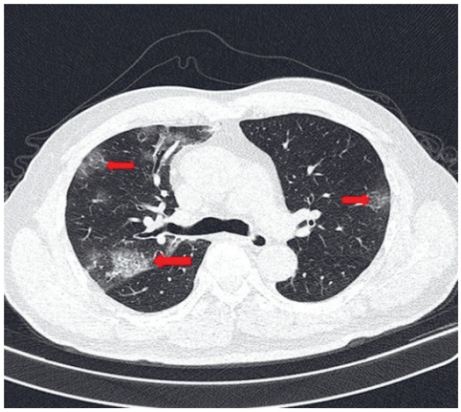


Fig. 6. The inter-lobular septal thickening, multiple ground-glass opacities, and an insane pattern in the two lung lobes (reproduced with permission from ref. 52), comparisons were illustrated in the HRCT scan.

Diagnosis through histopathological changes

Usually, microscopic findings have low sensitivity and are associated with individuals who are less symptomatic or not symptomatic (44). The post mortem findings of an elderly COVID-19 patient revealed a variety of lung complications, including inflammation in the lungs, pneumocyte hyperplasia, ground-glass opacities in chest x-rays, and lymphocytic focal inflammation, among others (53). These features were close to those identified with previously reported SARS and MERS infections (54, 55). Lung consolidation, pleurisy, pericarditis, and pulmonary edema in the affected lung are some of the most noticeable macro-findings (44). In comparison to normal healthy lungs, COVID-19 patients' lungs had an elevated weight (56).

Newer techniques

CRISPR in the diagnosis of SARS-CoV-2. – The coronavirus preventive antiviral CRISPR, which is a Cas 13-based process, was created as a therapeutic tool, but drug authorities around the world are yet to sanction human clinical trials. The CRISPR-based DETECTR assay offers positive and negative COVID-19 outcomes with 95 and 100 percent accurate predictions, respectively (57).

Algorithm-based coronavirus detection. – An algorithmic technique that focuses on random access instead of batch-wise testing for easy diagnosis of the disease is Hologic Panther Fusion (PF) screening (58, 59). Some Iranian experts are recommending one of the techniques to diagnose and provide appropriate care for children suffering from COVID-19 (44, 60). Following the analysis of patient symptoms, their response to treatments, and surveillance data obtained from their country, this technique was devised and in use in many countries (44). When comparing PF assay with Laboratory Developed Test (LTD), PF was 98.3 % in agreement with LTD (61).

LAMP-based detection of SARS-CoV-2. – The technique utilizes the spectrophotometric method to detect the virus. This technique was found to be equally sensitive to the existing RT-qPCR molecular screenings for viral identification (62). Jinzhao Song recommended that the LAMP technique could be improved by combining two stages of amplification in a single tube utilizing recombinase polymerase amplification (RPA) (63). He further recommended using the LAMP to build a POC testing system for user-friendly diagnosis. On combining with paper-based technology, these devices had remarkable features in their ability to be tagged with an advanced cellphone on which quarantined and self-isolated individuals can obtain highly responsive, accurate, and rapid results on their own (64). The findings of paper-based tests may be uploaded to the cloud internet and made accessible to physicians for immediate updates about an individual's health condition, as well as forwarded to the government (65). As a result, rushing to the hospital for a checkup is reduced, and the risks of spreading the virus are significantly decreased (66). When combined with surveillance data, tests that measure the potential of antibody responses to novel coronavirus infection are critical for the production of vaccines and contribute to the estimation of the number of patients that should be screened for a suspected infection (67). The existing scenario necessitates the implementation of lessons gained through the previous coronavirus outbreak in order to address the latest COVID-19 pandemic with a more systematic approach (44, 68).

THERAPEUTIC STRATEGIES

When the COVID-19 pandemic ramifications become evident, pharmaceutical companies immediately seek to either develop new drugs or repurpose medications to manage this menace. A host of effective drug development projects is ongoing in Europe, America, China, and other parts of the world. Pharmaceutical firms such as GlaxoSmithKline, Pfizer, Sanofi, Moderna, AstraZeneca, and Gilead Sciences are designing the majority of treatment options, keeping in mind the various aspects of the disease. The Gilead remdesivir clinical trial, which was performed in partnership with the Chinese Authority, produced mixed results; however, another clinical trial data showed the drug's potential to decrease hospitalization stay and mortality of the COVID-19 patients (69).

The following strategies have been developed so far to contain COVID-19 infection: (*i*) virus-neutralizing agents, (*ii*) ACE2-receptor blockers, (*iii*) TMPRSS2 inhibitor, (*iv*) NRP-1 inhibitor, (*v*) cytokines release inhibitors, (*vi*) protease inhibitors, (*vii*) RNA-dependent RNA polymerase inhibitor, (*viii*) use of antibiotics, (*ix*) use of antimalarial drugs, (*x*) miscellaneous agents.

The strategies that successfully fight the virus are shown in Fig. 7. A brief overview of the widely discussed drugs has been separately outlined and all the available drugs and therapeutics that can be used in the different conditions and stages of novel SARS-CoV-2 infection have been listed in Table III.

Mild symptomatic COVID-19 patients, suspected or confirmed cases (with light fever, fatigue without dyspnoea), should be excluded in quarantine and palliative care is recommended (71). Fever is usually treated with paracetamol or anti-inflammatory non-steroidal medicines, and no additional medication is recommended at this stage (71). In addition, the use of conventional Chinese medicine to control patient conditions is also encouraged

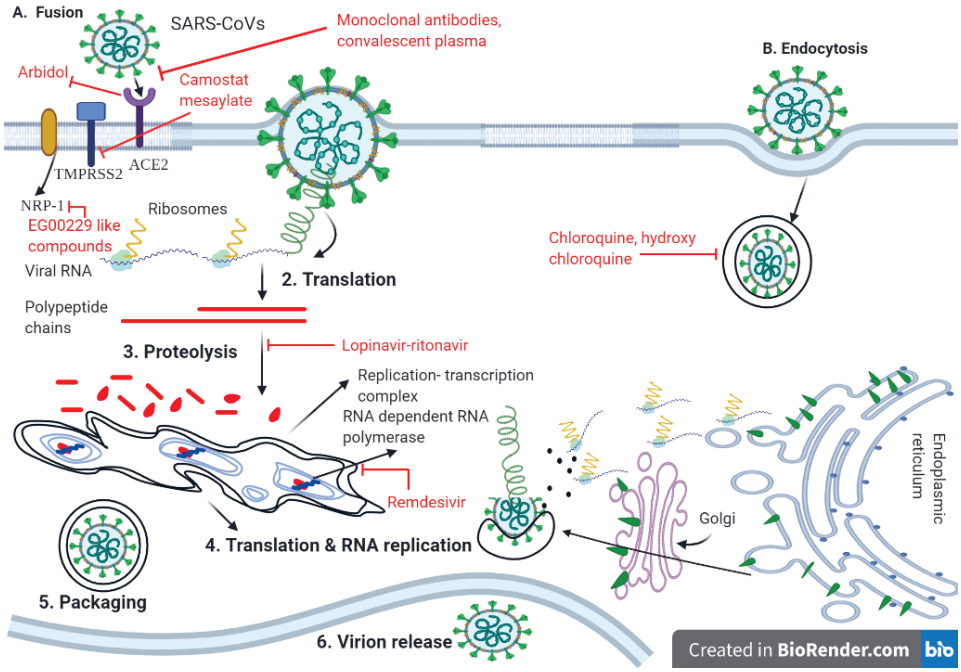


Fig. 7. The figure highlights different strategies to contain the SARS-COV-2 infection (reproduce with permission from ref. 70).

by Chinese health professionals and doctors (72). However, the use of hydroxychloroquine (HCQ) was endorsed by European guidelines in patients with documented COVID-19 (73). In the other severe cases such as COVID-19 pneumonia, COVID-19 ARDS, and septic shock the health caregivers are advised to follow the treatment strategies recommended by the WHO (71).

Therapeutics in use/consideration

RNA-dependent, RNA polymerase inhibitor: Remdesivir. – Remdesivir, produced by Gilead Sciences, a US-based corporation, has traditionally been used to eradicate the Ebola virus (103). The drug is widely being used in the USA and globally against COVID-19 infection (104). The latest study of hospitalized patients specifically shows a dramatically decreased mortality risk (from 11 to 7.1 %) with the usage of remdesivir (105).

Protease inhibitors: Lopinavir/ritonavir. – Many clinical trial reports concluded that the treatment with Lopinavir/ritonavir were inconsistent for severely ill COVID-19 patient (78). In addition, a team of Chinese scientists (ChiCTR2000029308) undertook an open-label randomized control study of serious COVID-19 patients seeking treatment with lopinavir/ritonavir and compared the results with standard care. Their results revealed that there was no therapeutic benefit from lopinavir/ritonavir. In the less severe cases of COVID-19, the possibility of beneficial effects lopinavir/ritonavir is yet to be ascertained (78).

Table III. COVID-19 therapies possibly in use in various parts of the world

Drug	Clinical trial/status	Trial registration No.	Safety parameter	Dose in clinical trial/s	Ref.
Antimalarial Drugs					
Chloroquine	Evaluation of the effectiveness and protection of chloroquine in hospitalized patients with COVID-19 infections/ phase-4	ChiCTR2000029542	Cardiac arrhythmias (*e.g.*, QT prolongation), retinal damage, not safe for people with G6PD deficiency and diabetes	500-mg dose peroral, twice a day, for not more than 10 days	74, 75
Hydroxy-chloroquine	The purpose of the trial is to determine the efficacy and protection of hydroxy-chloroquine in the therapy of COVID-19 pneumonia/phase-3	ChiCTR2000029559 NCT04261517	Same as chloroquine	200 mg peroral thrice a day for 10 days; generally in combination with azithromycin	76, 77
Protease Inhibitors					
Lopinavir/ ritonavir	A controlled, open-label trial to determine the efficacy and protection of lopinavir/ritonavir in patients with moderate COVID-19 pneumonia/ phase-0 (completed)	ChiCTR2000029539	Cardiac arrhythmias (*e.g.*, QT prolongation), Not safe for patients with hepatic disease or hepatitis	Lopinavir: 400 mg peroral twice a day; ritonavir: 100 mg peroral twice a day for 14 days	78, 79
RNA-Dependent RNA Polymerase Inhibitors					
Favipiravir	Efficacy and protection of favipiravir for novel coronavirus-infected pneumonia: multicenter, randomized, open-label, optimistic, parallel-controlled clinical trial/phase-0 (completed)	ChiCTR2000030254	Cardiac arrhythmias (*e.g.*, QT prolongation) Hyperuricemia and diarrhoea	1600 mg *per os* twice one day, followed by 600 mg *per os* twice per day until the cessation of the illness	80–82
Remdesivir	Research to assess the protection and antiviral efficacy of remdesivir (GS-5734^{TM}) in participants with severe COVID-19/phase-3	NCT04292899	Hepatotoxicity	200 mg dose *i.v.* once a day for 1 day followed by 100-mg dose *i.v.* once a day for the next 4–9 days	83–85

Drug	Clinical trial/status	Trial registration No.	Safety parameter	Dose in clinical trial/s	Ref.
Antibiotics					
Azithromycin	Efficiency and protection of azithromycin relative to base therapeutic dosage of hydroxychloroquine in mild to severe COVID-19: A randomized, regulated, double-blind, clinical trial/phase-4	NCT04359316	Cardiac arrhythmias (*e.g.*, QT prolongation)	500 mg peroral for the first day accompanied by 250 mg daily for the upcoming 4 days	86, 87
Cytokine Release Inhibitors					
Tocilizumab	Multicenter, randomized clinical study of the effectiveness and protection of tocilizumab in the management of new coronavirus pneumonia (COVID-19)/ phase-4	ChiCTR2000029765	GI perforation, hepatotoxicity; not safe for patients with thrombocytopenia and neutropenia	4–8 mg kg^{-1} intravenous diluted in normal saline (single dose)	88, 89
Leronlimab	Research to assess the effectiveness and protection of leronlimab in patients with more severe or critical COVID-19/phase-2	NCT04347239	Minimal or no toxicity was observed	Leronlimab 700 mg *per os* weekly	90
Sarilumab	Analysis of the performance and protection of sarilumab in hospital patients with novel COVID-19/phase-2	NCT04315298	The toxicity and safety profile of the drug is yet to come online	Single or multiple intravenous doses	91, 92
Passive Immunity					
COVID-19 convalescent plasma	Convalescent plasma trial in COVID-19 patients/phase-0 (completed)	NCT04356534	Some sporadic anaphylactic shock were observed	Convalescent plasma (400 mL) from the recovered patient can be delivered as 200 mL at 2 hours interval on 2 successive days	93, 94
Corticosteroids					
Methylprednisolone	Efficiency and protection of corticosteroids (methylprednisolone) in COVID-19/ phase-0 (completed)	NCT04273321	Reactivation of hepatitis B virus, herpes virus, tuberculosis	Methylprednisolone 1 mg kg^{-1} per day intra- venously for 7 days	95

Drug	Clinical trial/status	Trial registration No.	Safety parameter	Dose in clinical trial/s	Ref.
Dexamethasone	In COVID-19 dexamethasone linked ARDS: Multicenter, randomized clinical study/phase-3	NCT04395105	Reactivation of hepatitis B virus, herpes virus, tuberculosis	16 mg intravenous for the first 5 days was accompanied with 8 mg intravenous over the next 5 days	96
ACE-2 Receptor Antagonist					
Arbidol	Clinical research of arbidol hydrochloride tablets for the prevention of pneumonia induced by COVID-19/ phase-4	NCT04260594	No seriously side-effects	Two tablets peroral three times a day for 10–14 days	97, 98
Neuropilin-1 (NRP-1) Receptor Antagonist					
EG00229-like compounds	Computer-based recognition and confirmation of interactions between neuropilin receptor 1 and SARS-CoV-2 Spike protein	Not applicable	Data not available	Data not available	99
Miscellaneous Agents					
Enoxaparin	A randomized anticoagulation study (enoxaparin) COVID-19 approach/ phase-3	NCT04359277	Usual side-effect but rare	Every 12 hours, 1 mg kg^{-1} subcutaneously	100
Thalidomide	Efficiency and protection of thalidomide in adjuvant therapy of mild COVID-19 pneumonia/phase-2	NCT04273529	Other less threatening side-effects are: constipation, dizziness and malaise	100 mg *per os* every night for 14 days	101
Fingolimod	Fingolimod for the care of COVID-19/ Phase-2	NCT04280588	Usual side-effects	0.5 mg *per os* every day for 3 days in a row	102

TMPRSS2 blocker: Camostat mesylate. – Camostat mesylate is a powerful protease inhibitor. Previously, the medication was used for a number of therapeutic purposes, including flu and pancreatic inflammatory disorders. The drug also causes the breakdown of the TMPRSS2 co-receptor and therefore, blocks the virus entry into host cells. The serine protease TMPRSS2 interacts with the novel coronavirus spike (S) enzyme to cause the virus to reach the host cell (106). There are no clinical trial reports for this intriguing medication against novel coronavirus infection.

ACE2-Inhibitor: Arbidol (umifenovir). – It is suspected that arbidol (umifenovir) prevents endocytosis of SARS-CoV-2 inside the host cell. Arbidol is reportedly involved in multiple clinical trials against COVID-19 for this cause (107). Along with the NIH, the Chinese clinical research organisations are both running efficacy studies on arbidol, either alone or in conjunction with the protease inhibitor favipiravir (NCT04260594, ChiCTR2000030254).

Human recombinant soluble ACE2: APN01. – Parenteral administration of human recombinant soluble ACE2 binds with the SARS-CoV-2 spike protein, results in suppression of cellular endocytosis (108). This will, in fact, cause a marked decline in damage to lung cells.

A human recombinant ACE2 (APN01) was engineered and shown to contribute to a substantial reduction in AN-II-mediated lung injury and IL-6 levels based on these positive results. The evidence was adequate to justify a clinical trial with RhACE2. Apeiron Biologics is also sponsoring clinical research on the effectiveness and protection of APN01, currently in phase II (NCT04335136).

Adjuvant therapy

Anticoagulant therapy. – Endothelial disturbance during the novel coronavirus infection induces thromboembolism, which is a rare and lethal complication in critically ill patients. Multiple reports showed that anticoagulants perform well in reducing serious complications in critically ill COVID-19 patients (25, 109).

Vitamin C supplementation. – In 2019, Fowler *et al*. focused on the usage of vitamin C vs. placebo in ARDS septic patients, and they found that any inflammatory markers or organ failure score did not boost the vitamin C infusion (110). Many current clinical studies confirm the effects of vitamin C in the treatment of COVID-19 (NCT04682574, NCT04335084).

Anecdotal treatment

Hydroxychloroquine. – Antimalarial medication hydroxychloroquine has demonstrated substantial effectiveness, including HIV-1, Type A, and Type B influenza efficacy. Its antiviral effect on SARS-CoV-2 is based on the effective blockage of viral penetration by obstructing the glycosylation of the ACE-2 receptor (111). It has also been shown that alkalinization of the organelle prevents the development of mature endosomes that shield the virus from immune cells and replication (112). Even though many clinical trials were conducted, the findings were not promising. So far the drug is no more in clinical use.

Ivermectin. – Antiviral behavior was also demonstrated by this wide spectrum antiparasitic agent. It was speculated that the antiviral activity of ivermectin against COVID-19 was achieved from importin-a/b12 obstruction (113). The drug displayed effectiveness in

an improvement in dyspnea and oxygen saturation and a reduction in time of recovery was observed (NCT04668469).

Teicoplanin. – This glycopeptide antibiotic has demonstrated antiviral properties against Ebola, MERS, SARS, and HIV-1. Teicoplanin is known to interact with endosome development by alkalization. S-protein breaking by cathepsin in the late endosome is blocked, which in turn inhibits viral RNA from being released out of the cells (114). Baron *et al.* demonstrated that the cathepsin L sequence is also found in the S-protein of novel SARS-CoV-2 and, therefore, causes the virus to enter the cells. It was also reported that in the event of early detection of novel coronavirus disease 19, teicoplanin is probably a good choice of treatment (115).

Humanized monoclonal antibodies: Tocilizumab, bevacizumab, sarilumab. – Monoclonal antibodies (mAbs) normally modify the host organism's immune system response, *i.e.* a drop in plasma IL-6 levels, which is frequently higher in severe cases of SARS-CoV-2 patients (116). Table III presents the status of tocilizumab, bevacizumab, and sarilumab. However, to decrease the cytokine storm, health care providers around the world often use these drugs.

Interferon-α. – Interferon-alpha (INF-α) has been proven to be effective in containing SARS-CoV-1, it is predicted that INF-α may control the SARS-CoV-2 also, as both the strains are structurally similar. A clinical trial (ChiCTR2000029387) was performed to affirm the effectiveness of INF-alpha against SARS-CoV-2, together with ribavirin, and the findings were disappointing (117).

Zongji Hospital has funded a clinical trial registered with the NIH to determine the efficacy of INF-5-0072β (NCT04293887) and is currently in early phase I (118).

Corticosteroids. – The use of corticosteroid treatment to recover and/or shorten the duration of hospitalisation for COVID-19 patients has traditionally been problematic owing to lack of clinical evidence (119). However, some trials have suggested its effectiveness, which has prompted NIH to establish recommendations for the use and dosing of dexamethasone in COVID-19 patients. However, these recommendations suggested starting steroids in COVID-19 patients with extra oxygen and artificial ventilation in the novel coronavirus (120).

Passive immunity/convalescent plasma. – Recently, a randomized clinical trial was performed to determine the effects of convalescent plasma in severely ill COVID-19 patients and findings indicated little or no benefits. In addition, the length of the illness did not seem to be reduced by its addition to the normal treatment of COVID-19 (121). There are, however, dangers involved with the administration of immunoglobulins, which is why it can only be used with serious or life-threatening COVID-19, according to the FDA Advisory Board (122).

Vaccines: The most sought after therapeutic

What makes the novel coronavirus so infectious? The answer is simple; this is a new virus, and there is no protection mechanism in our bodies against that virus. Taking precautionary steps and the usage of vaccination are the two most successful methods of alleviating the spread of a pandemic. More notably, the vaccine should be needed to eradicate the high spread capability of COVID-19, which, if not managed, would continue to drive the current pandemic. The most commonly selected target for the development of the COVID-19

Table IV. Vaccines in use or under consideration

Nature of vaccine	Target of vaccine	Principal developer of vaccine	Country	Clinical trial status	Ref.
DNA vaccine (INO-4800)	Spike (S) protein	Inovio Pharmaceuticals	USA	Phase 2/3 NCT04642638	123
Non-replicating virus (AZD1222)	Spike (S) protein	University of Oxford	UK	Phase 2/3 NCT04324606 NCT04400838	124
Whole inactivated virus vaccine	Entire virus	Sinovac Research and Development Co. Ltd.	China and Brazil	Phase 3 NCT04456595	125
mRNA vaccine	Spike (S) protein	Moderna, USA	USA	Phase 3 NCT04470427	126
Recombinant vaccine (adenovirus type-5 vector)	Spike (S) protein	CanSino Biologics	China	Phase 3 NCT04526990	127, 128
Attenuated live vaccine	Entire virus	Serum Institute of India in collaboration with Codagenix	India and USA	Pre-clinical/animal studies	129
Nucleoside-modified messenger RNA BNT162b1&b2	Spike glycoprotein (S)	Pfizer & BioNTech SE	USA	Phase 2/3 NCT04368728	130
Whole-virion inactivated SARS-CoV-2 vaccine BBV152	Spike (S) protein	Bharat Biotech India	India	Phase 1/2 NCT04471519	131
Heterologous recombinant adenovirus (rAd) vaccine Gam-COVID-Vac (Sputnik V)	Spike (S) protein	Gamaleya Research Institute Russia	Russia	Phase 3 NCT04656613	132

vaccine is the spike (S) protein embedded in the SARS-CoV-2 envelope. Different platforms are actively focusing on the creation of COVID-19 vaccines. Globally, significant COVID-19 vaccines in clinical use or different stages of the clinical trial are listed in Table IV.

There are some side-effects reported since the vaccination program started. The researchers are in the opinion that these are minor hiccups. The benefits of taking vaccines outweigh the devastation of the ongoing pandemic. Moreover, the side-effects of these vaccines were not properly documented; therefore, the author did not incorporate the sporadic reports. The author firmly believes that the vaccines will contribute much to the prevention of the disease.

WHAT FUTURE HOLDS?

As of February 2021, treatment for COVID-19 depends on the case's severity. In milder conditions, it is enough to rest at home and take medication to relieve fever. The most severe cases require hospital admission, with therapeutic management that might consist of oxygen supplementation, assisted ventilation, and a complete course of therapeutics. Battling SARS-CoV-2 and the infection it causes is of top importance in health research and therapeutic development. A growing number of research organizations are battling to minimize the effects of the disease and to avoid further spreading of COVID-19 infection. Several organizations, including all big and small pharmaceutical industries, are working on different classes of vaccines. Reports of many vaccines have been published in the most reputed journals and are accessible to everyone. Some undesirable effects, not reported in the published data, were observed in many countries during the vaccination programs. The propensity and infectivity of COVID-19 have been lessened in many parts of the world; however, the USA is still facing the heat and peak of the infection. Getting life back to normal is still a distant dream.

EXECUTIVE SUMMARY

The epidemic of COVID-19 spread quickly through China and engulfed all of the countries across the globe. Several advances have been made in understanding the novel coronavirus's physicochemical properties, the discovery of antiviral drugs and vaccines.

This article highlights our understanding of the novel coronavirus's symptoms in brief, pathogenesis, diagnostics, and therapeutic strategies to contain COVID-19. SARS-COV-2 emerged from bats and is likely to enter some unknown intermediate hosts; binding to high-affinity ACE2 receptors inevitably infects humans. The clinical findings including serological, radiological, and other advanced diagnostic strategies contributed much to control the disease. Supporting procedures in conjunction with powerful antiviral drugs such as remdesivir, lopinavir/ritonavir, or corticosteroids have thus far been used with a degree of confidence in the care of COVID-19 patients. However, in several areas of the world, vaccination initiatives took place; the vaccines' safety and efficacy to control the outbreak is yet to be identified. This review concludes that improved therapies and diagnostics for COVID-19 must continually be explored as new variants are constantly emerging.

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