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REVIEW PAPER

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Journey so far with COVID 19 – a comprehensive review

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ABSTRACT

Introduction. The occurrence of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged as a global pandemic with huge death tolls. Coronavirus disease 2019 (COVID-19) may progress from minimal infection to serious respiratory failure mandating treatment for a continuum of developed disease condition.

Aim. The purpose of this review is to summarize the findings related to epidemiology, clinical manifestations, modes of transmission, diagnosis and the treatment modalities (both experimental and repurposed) for COVID-19.

Material and methods. Literature were searched using various search engines like PubMed, SCOPUS, EMBASE, J-Gate, Google Scholar to look for review articles, randomized controlled trial results, prospective studies and, retrospective studies done on COVID-19 for the purpose of this comprehensive review.

Analysis of the literature. The transmission seems to be occurring through droplet, fomite and aerosols (rarely). Currently there is no specific/targeted vaccine available. Priority is highly placed to identify possible treatment approaches to circumvention this disease.

Conclusion. Till we find a vaccine, we have to strategize to optimally use the existing evidence of the indirect effects of these various available drugs for therapy and maintain a strict protocol for prevention and we must use triage system to admit only those critically ill or having severe disease.

Keywords. clinical trials, respiratory infection, treatment strategies

Introduction

The trigger of coronavirus disease 2019 (COVID-19) by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has expanded all over the globe culminating in a pandemic. Coronaviruses are morphologically spherical or pleomorphic in nature, with a mean diameter of approximately 80–120 nm having distinct large (20 nm) "club-like" surface extensions, which are the glycosylated spike proteins of the virus.[1] The revelation of a novel human coronavirus, SARS-CoV-2, has now become a global health issue that causes serious human respiratory tract infections. Incubation times between 2-10 days have been identified for human-to-human transmissions, facilitating their spread through droplets, contaminated hands or surfaces.[2] On inanimate surfaces, coronavirus continue to exist for up to 9 days at room temperature while the related survival of the viruses declines at a temperature of 30°C or higher

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and disinfectants like ethanol (62-71%), hydrogen peroxide (0.5%) or sodium hypochlorite (0.1%) can inactivate the virus within 1 minute.[2]

It is pertinent to admonish readers that new data specific for COVID-19 emerge around every hour concerning clinical features, treatment choices and therapeutic outcomes. Optimized support treatment regimen remains the bedrock of intervention, and the clinical effectiveness of subsequent treatments is still being researched upon. So many of the preclinical and clinical data on antiviral therapy are derived from the research studies on other viruses such as severe acute respiratory syndrome-1 coronavirus-1 (SARS-CoV-1), Middle East coronavirus respiratory syndrome (MERS-CoV) and non-coronavirus (Ebola). In addition, the clinical prominence of *in vitro* anti-viral activity remains uncertain given the lack of pharmacokinetic/pharmacodynamic or clinical evidence equating realistic doses to a treatment impact compared to such values. Hence, it needs to be noted that in vitro details should be appropriately evaluated across findings given the possible variation in test methodologies that could affect purported behavior.

Aim

This narrative review summarizes the epidemiology, clinical manifestations, modes of transmission, diagnosis and the treatment modalities (both experimental and repurposed) for COVID-19. It is an attempt that could provide needful references for further research endeavours.

Material and methods

Literature were searched using various search engines like PubMed, SCOPUS, EMBASE, J-Gate, Google Scholar to look for review articles, randomized controlled trial results, prospective studies and, retrospective studies done on COVID-19 for the purpose of this comprehensive review.

Viral structure in nutshell

The virus responsible for COVID-19, SARS-CoV-2, is 125 nm in size which is slightly larger than the influenza, SARS and MERS viruses.[3] It shares the identical morphology of "spike-protein" with other coronaviruses and this spike latch onto human cells, then fuses with the cell membrane through structural change and, this gives entry of the viral genes into the host cell to be copied, producing more viruses.[4] It is known to be a descendant of a bat corona virus, the closest being originated from the Rhinolophus bat which is > 96% homologous with stated one.[3]

The viral membrane consists of four proteins: 1) the spike (S) glycoprotein, 2) a small glycoprotein making up the envelope (E), 3) a glycoprotein forming the membrane (M), and 4) the nucleocapsid (N) protein.[5] The membrane (M) glycoprotein, spanning the membrane bilayer three times, is the most abundant one.[6] A study performed next-generation sequencing from samples of bronchoalveolar lavage fluid and found that the ten 2019-nCoV genome sequences from these nine patients were quite similar, almost in excess of 99.98% for sequence similarity.[7] There was homology (88%) to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 but found to be more distinct from SARS-CoV and MERS-CoV by about 79% and 50%, respectively.[7] Homology modeling prominently demonstrated that 2019-nCoV had a receptor-binding domain architecture close to that of SARS-CoV, given the differences in amino acids at some key residues.[7] The spike (S) glycoproteins consist of two subunits, namely S1 and, S2.[5] Out of these two parts, Part S1 determines host virus range and cellular tropism along with the formation of receptor binding domain while S2 mediates virus fusion and transmitting to host cells.[8] Homotrimers of S proteins make up the spikes on the viral surface which direct the connection with the host receptors.[9] The most important inducer of neutralizing antibody is the spike protein. The dynamics of CoV pathophysiology and virulence, including that of SARS-CoV-2, have ties to the role of non-structural proteins (*nsps)* and structural proteins. There are 16 *nsps* identified so far and they play various roles like IFN signaling inhibition and host innate immune response blockage by promotion of cellular degradation and blockage of translation of host's RNA, protein binding prohibition, cytokine protein expression and viral polyprotein cleavage, contributing to formation of transmembrane scaffold protein and many others.[5] Researches have shown that *nsp* can suppress the innate immune response of the host.[10]

Epidemiology

According to the situation report-194 released by the WHO, the entire world appears to have been infected by the virus, but the influx of new outbreak trends has migrated from China to the European countries drastically and finally to encompass the Asian subcontinent also.[11]

According to the WHO situation report-194, a summary of the outbreak in the different zones of the world are presented in Table 1.[11]

Some countries have adopted to test only the seriously infected patients. This has eventually led to a false statistics related to high death rate but it is a fact that the actual burden of the disease can be measured only by mass testing. South Korea took up massive testing from the beginning of the outbreak and has a very low fatality rate and could bend the pandemic curve very early while UK, Italy and France started late and the fatality rates are disastrous now.[12]

Table 1. Summary of total confirmed cases and deaths as per Situation Report-194

Area	Confirmed COVID 19 cases	Deaths due to COVID 19
Global	17396943	675060
Western Pacific region	312771	8388
European region	3357465	212978
South-East Asia region	2072194	44900
Eastern Mediterranean Region	1544994	40019
Region of the Americas	9320330	355217*
African Region	788448	13545

* highest contributing zone towards deaths from COVID 19; WHO, World Health Organisation

The proportion of the elderly population, health care facilities and known co-morbidities also play a key role in assessing the fatality rate as a result of this infection, as the majority of older people with co-morbid conditions suffer from serious disease.[13]

Clinical features

Table 2. Summary of the characteristics of clinical symptoms

Type of clinical symptoms	Characteristics
Mild	Clinical symptoms present but there is no evidence in chest imaging
Moderate	Respiratory problems with fever and positive chest imaging findings
Severe	If any of the criteria is satisfied then that patient is designated to be suffering from severe disease: 1) Oxygen saturation ≤ 93% during resting phase, 2) Shortness of breath (RR ≥ 30 times per minute), 3) Higher than 50% progression of the lesions in a time period of 24-48 hours or, 4) Inspiration oxygen fraction ≤300 mm Hg but this should be adjusted in the plateau region according to the different atmospheric pressure to get the partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2 ratio)[18]
Critically severe	If the patient satisfies any of these criteria: 1) Failure of organ needing ICU admission followed by treatment, 2) Shock or, 3) Respiratory failure with a need for mechanical ventilation

The clinical manifestations of COVID 19 are multifaceted which varies from being asymptomatic to the precipitation of acute respiratory distress syndrome to dysfunction of multiple organs. In general, mild or asymptomatic variety comprises almost 80% of infections, 15% are severe requiring oxygen, and 5% are critical who might require ventilation.[14] The disease might progress to pneumonia, respiratory failure and even death for a sub-group of patients by the end of the first week. This phenomenon has to do with a significant rise in inflammatory cytokines namely IL2, IL7, IL10, TNFα, GCSF.[15] Patients with COVID-19 usually experience the associated symptoms such as mild respiratory problems and fever in a time period of 5 to 6 days on an average after infection.[16]

Table 3. Extra-pulmonary manifestations of COVID-19

System	Manifestations
Hematologic	Low total white blood cell count (Lymphopenia) or even leukocytosis, increased neutrophil count or low platelet count. Elevated CRP, ferritin, Interleukin-6, LDH, D-dimer, fibrinogen, P Time and partial thromboplastin time
Thrombotic	Arterial thrombotic complications: type 1 and 2 MI, ischemic variety of stroke, acute ischemia of limb, and mesenteric ischemia; venous thrombotic complications: deep vein thrombosis and PE; thrombosis related to catheter: thrombosis found in venous and arterial catheters, as well as in extracorporeal circuits
Immune system-related	Cytokine-release syndrome comprising of high-grade fevers, hypotension requiring inotrope support and, multi-organ dysfunction
Cardiovascular	Myocardial ischemia and type 1 and 2 MI; myocarditis; new onset Arrhythmias - sinus tachycardia as well as bradycardia, atrial fibrillation and flutter, QTc prolongation (often associated with use of drugs) resulting in torsades de pointes and even sudden cardiac death, PEA; new onset cardiomyopathy resulting in biventricular or isolated right or left ventricular dysfunction and, even cardiogenic shock
Renal	Acute kidney injury; electrolyte abnormalities such as hyperkalemia and, hypo or hypernatremia; urinary protein and blood loss; metabolic acidosis
Gastrointestinal	Diarrhea, nausea and/or vomiting, abdominal pain; rare cases of mesenteric ischemia and gastrointestinal bleeding and, elevated liver enzymes and low albumin
Endocrinal	Hyperglycemia in a patient of diabetes that might lead to ketoacidosis, stress hyperglycemia (non-diabetic patient); ketosis with no or minimal elevation in blood glucose level
Neurologic and ophthalmologic	Headache, dizziness; anosmia, loss of taste sensation (ageusia), anorexia and feeling of extreme fatigue; ischemic stroke; acute hemorrhagic necrotizing encephalopathy, encephalitis, GBS, and, conjunctivitis

MI, myocardial infarction; ESR, ESR erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase; P Time, prothrombin time; PE, pulmonary embolism; PEA, pulseless electrical activity; GBS, Guillain-Barré syndrome

Clinically SARS-CoV-2 infection can be categorized under the following sub-headings based on the symptoms shown by the patients (Table 2).[17]

COVID-19 has shown to affect most of the systems of the body and many extra-pulmonary manifestations are also seen which are given in Table 3 below.[19]

Radiological features

The prevailing CT outcomes included opacification, consolidation, bilateral involvement and peripheral and diffuse distribution.[20] A radiological reterospective study involving patients with RT-PCR confirmed COVID-19 pneumonia admitted to one of two hospitals in Wuhan were subjected to sequential chest CT scans and were further divided into four treatment groups based on the mean of the total involved lung segments: group 1 having 10·5 ± 6·4, 2·8 ± 3·3% involvment, group 2 having 11·1 ± 5·4% involvement, group 3 having 13·0 ±5·7% involvement, and group 4 having 12·1 ±5·9% involvement. Out of the total 849 affected segments, the principal types of abnormalities noted were bilateral (79%) involvement, peripheral (54%) involvement, ill-defined (81%) lesions and ground-glass opacification (65%), which majorly involved the right lower lobes (27%).[21] The study interpreted that COVID-19 pneumonia demonstrates abnormalities in chest CT imaging, also in asymptomatic patients, with rapid change from focal unilateral to diffused bilateral ground-glass opacities which progressed to or co-existed within 1–3 weeks. The pictorial representations of COVID-19 pneumonia were observed to be highly unspecific and were most frequently bilateral with subpleural and peripheral diffusion and varied from ground-glass opacities in milder forms to more extreme consolidations.[22]

Predictors of severity

The results of a retrospective study conducted in children in China stated that lower count of lymphocytes, raised body temperature, and high concentrations of procalcitonin, D-dimer and creatine kinase MB were significantly associated with the presentation of COVID-19 intensity.[23] All the enrolled subjects (children) received interferon-α twice daily via aerosolisation, 14 (39%) received lopinavir – ritonavir syrup twice daily and six (17%) required oxygen inhalation. In the present study, it was observed that age was the predominant factor for the incidence of increased risk of severe illness and related death.[24] In a study by Xiaobo Yang and colleagues done on 32 non-survivors from a group of 52 patients in intensive care unit due to COVID-19, it was found that Cerebrovascular diseases (22%) and diabetes (22%) were the dominant comorbidities.[25]

Another research study involving 1099 COVID-19 patients reported that 23.7% had serious disease with hypertension comorbidities, 16.2% with diabetes mellitus, 5.8% had coronary heart disease while 2.3% suffered from cerebrovascular disease.[26] Similar reports was also published from another study conducted in Wuhan, China showing 91 (48%) patients had some type of comorbidity.[27] This study found that hypertension was the most common (30%) comorbidity and, was followed by diabetes (19%) and coronary heart disease (8%). Immunosuppression was likely to be effective in hyperinflammatory conditions. Re-analysis of results from a phase 3 randomized controlled trial of IL-1 blockade (anakinra) in subjects with sepsis, demonstrated major survival benefits in patients with hyperinflammation without elevated incidence of adverse effects.[28] A research indicated to evaluate all patients with extreme COVID-19 to be screened for hyperinflammation employing laboratory indicators such as elevated levels of ferritin or declining platelet countsor erythrocyte sedimentation rate as well as H-Score (which creates a propensity of secondary haemophagocytic histiocytosis) to classify the sub-group of patients for whom immunosuppression would increase the mortality rate.[29]

Pathogenesis and inflammatory cytokine storm

The process of pathogenesis and initiation of inflammatory cytokine storm are detailed as follow:

Entry and cellular replication

The virus enters into the host cell by a specific protein known as corona virus S protein.[30] In SARS-CoV-2, the envelope spike glycoprotein binds to the cellular receptor, ACE2.[31] The viral RNA genome is transferred into the cytoplasm as the virus enters the cell which is further translated into two polyproteins and structural proteins furthering to replication of the viral genome.[32] The newly shaped envelope of glycoproteins is introduced into the endoplasmic reticulum or Golgi membrane, and the nucleocapsid is developed by the fusion of genomic RNA and nucleocapsid protein. The viral particles then germinate into the intermediate reticulum-Golgi endoplasmic compartment (ERGIC) leading to the fusion of the vesicles containing the virus particles with the plasma membrane leading to the virus release.

Antigen presentation

When the virus reaches the cells, it will be presented to the antigen presentation cells (APC), which is the fundamental anti-viral mechanism of immune system in the body. The viral antigens are presented by the major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) followed by recognition by virus-specific cytotoxic T lymphocytes (CTLs).[33] Till date there are no reported evidence supporting the same and some information can be retrieved from the previous research work involving SARS-CoV so MERS-CoV.[33] In SARS-CoV both MHC I and II helps in antigen presentation.[34] HLA polymorphisms correlating to the susceptibility of SARS-CoV are HLA-B*4601, HLA-B*0703, HLA-DR B1*1202.[35]

Role of immunity at humoral and cellular levels

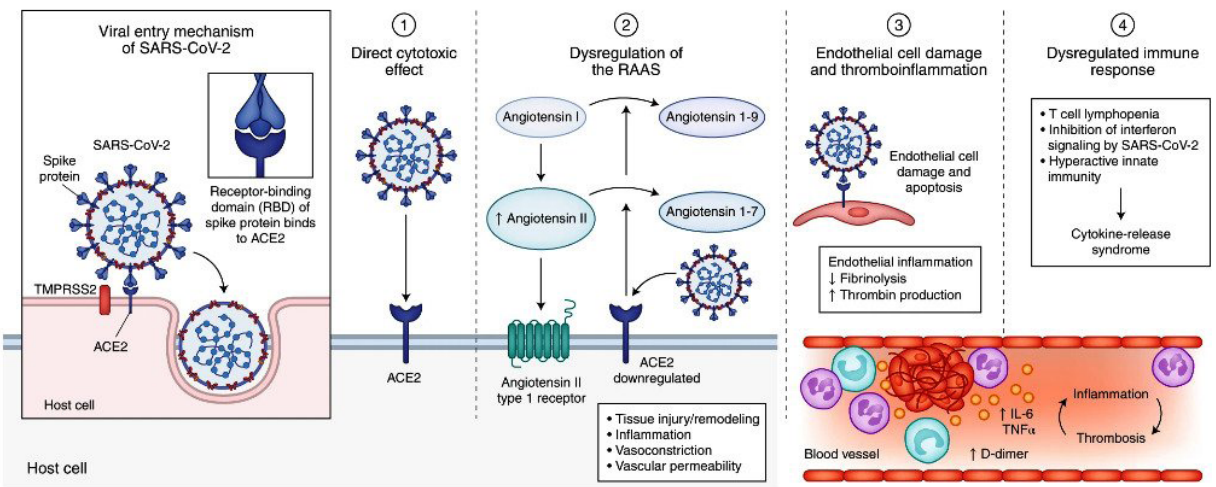
Consequentially, antigen exposure activates the humoral and cellular immunity of the body, which is regulated by the B and T cells unique to viruses. The antibody profiling against SARS-CoV virus has a characteristic trend of IgM and IgG levels, relative to common acute viral infections.[36] At the completion of week 12, the SARS-specific IgM antibodies vanish while the IgG antibody last for a longer duration of time period, suggesting that IgG antibodies would serve a defensive role.[37] Approximately, 1.48% of antibody-secreting cells (ASCs) emerged in the blood at the time of viral clearance on day 7 while on day 8 it peaked to 6.91% in a patient with mild COVID 19 symptoms prompting hospitalisation. At day 7 (1.98 percent), the development of cTFH cells occurred simultaneously in blood, rising on day 8 (3.25 percent) and day 9 (4.46 percent). The above analysis revealed a prominent presence of both ASCs (4.54%) and cTFH cells (7.14%) during convalescence (day 20).[38]

Cytokine storm in COVID 19

Reports suggest acute respiratory distress syndrome (ARDS) to be the most common immunopathological incidence for SARS-CoV-2, SARS-CoV and MERS-CoV infections and high concentrations of cytokines in severely ill patients are a common finding indicating the role of cytokine storm as a core driving factor for deterioration.[39] ARDS leads to damage of lung microvasculature, interstitium, and alveolar space by accumulation of neutrophils and the release of inflammatory cytokines.[40] A hyperinflammatory syndrome called Secondary haemophagocytic lymphohistiocytosis (sHLH) has the hallmark features of fulminant and hypercytokinaemia subsequently leading to fatal multiorgan failure.[41] A cytokine profile similar to sHLH is often identified with prevalence of COVID-19. It is characterized by enhanced interleukin (IL)-2, IL-7, stimulating factor granulocytecolony, inducible protein 10, protein monocyte chemoattractant 1, inflammatory protein 1-α macrophage, and factor-α tumor necrosis. One of the key mechanisms for ARDS is release of significant levels of pro-inflammatory cytokines like interferon-alpha (IFN-a), IL-12, etc. and chemokines like CCL2, CCL3, etc. by immune effector cells.[42,43] The cytokine storm may also lead to ARDS and multiple organ failure, and ultimately lead to death in serious cases of SARS-CoV-2 infection, as evidenced in SARS-CoV and MERS-CoV infection.

Evading the immune response

Due to lack of research data related to SARS-CoV-2, the emergence to extrapolate the available data on



SARS-CoV-2 enters host cells through interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2 (far left). Proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS as a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNFα.

Fig. 1. COVID-19 pathogenesis in a nutshell

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SARS-CoV and MERS-CoV is highly needful. The pattern recognition receptors (PRRs) can identify the evolutionarily preserved microbial structures called pathogen-associated molecular patterns (PAMPs). Nonetheless, SARS-CoV and MERS-CoV may induce the development of double-membrane vesicles that lack PRRs and further replicate in these vesicles, thus preventing the detection of their dsRNA by host.[44] The antigen presentation could be suitably affected by the coronavirus as exemplified by gene expression in relation to down regulation of antigen presentation following MERS-CoV infection.[45] The process of virus attachment and proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 are beautifully depicted in Figure 1.[25]

Transmission

The fact that this virus attaches to the human cell surface receptors called angiotensin-converting enzyme 2 (ACE2) 10 to 20 times more than the previous SARS virus in 2002, might have increased the spreading potential of SARS-CoV-2 from person to person than the earlier virus.[4] The cause of increased transmissibility of this virus has been reported by Korber et al. to be highly linked to the mutation seen in the amino acid sequence of the spike protein D614G.[46] The key framework for the transmission of the disease was perceived to be transmission from animal to human, given the case of the initial straight forward contact with the Huanan Seafood Wholesale Market, Wuhan. Still, there was no connection between this responsiveness phase and subsequent events. Mode of transmission was also suspected to be from human to human, and that the most prevalent cause of COVID-19 transmission are the symptomatic individuals.[47,48] The probability of transmission seems infrequent before symptoms occur but it cannot be excluded.[49] Data shows that the best way to control this outbreak is "self-isolation".[50] Transmission through coughing and sneezing is presumed to occur by respiratory droplets. Infections of the respiratory tract can be transmitted by various sized droplets. When the particles of the droplets exceeds5-10 μm in diameter are termed as droplet particles when they are < 5 μm in diameter, they are called droplet nuclei.[51]

Airborne transmission is distinct from droplet transmission as it corresponds to the inclusion of microbes within droplet nuclei, which has the ability to stay in the air for long periods of time, and can be transmitted over distances greater than 1 metre.[52] Reports suggest that infection with COVID-19 can cause intestinal infection and the virus can be found in the feces as shown by one Chinese study which cultured COVID-19 virus from a specimen of stool.[53]

Diagnosis

Diagnosis of SARS-COV-2 infection is generally done by a combination of molecular, serological and radiological findings in a patient having typical symptoms described above or by a combination of molecular testing with radiological help in asymptomatic individuals.[33] Amongst the nucleic acid detection technologies, Real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing are the most widely used for COVID-19.[33, 54] As the latter approach is expensive and burdensome, hence RT-qPCR is primarily used for viral RNA detection.[55] The validity of use of real time RT-PCR test has been questioned by a study from Wuhan, China, as they found high false negative results with this method only and suggested to include clinical features and radiological parameters to be taken into consideration for diagnosis.[56] The samples used for SARS-CoV were nasopharyngeal aspirate, throat swab, urine and stool and almost similar specimens were used for SARS-CoV-2 but bronchoalveolar lavage, endotracheal aspirate and tissue from biopsy or autopsy including from lung have also been approved by WHO for SARS-CoV-2.[57, 58] Studies suggest that the viral RNA yield varies from patient to patient depending on the day of collection after symptom onset, site of collection, technical errors associated with sample collections and the methods applied for detection.[59] A nasopharyngeal swab gives a better yield than an oropharyngeal swab collection but the yield is always highest with the bronchoalveolar lavage collection.[60, 61] While considering serological assays like IgM and IgG for diagnosing SARS-COV-2 infection, we must remember that IgM is notoriously non-specific and both takes almost 2 week time to reach highest levels.[60, 62] Neither RT-PCR,

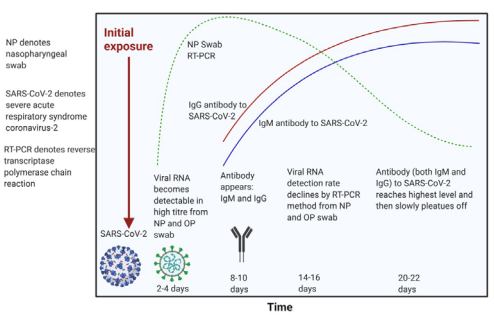

Fig. 2. Timing of applicability of various diagnostic tests for SARS-CoV-2
Adapted from Biorender.com ®

nor computed tomography (CT) thorax should be used solely for COVID-19 diagnosis purpose since both have their own limitations and imaging facilities can be used to aid diagnosis of early and missed, suspicious, symptomatic cases when RT-PCR might come as false nega-

Table 4. Summary of treatments under trial and approved on emergency basis

Drug generic name	Class of drug	Possible mechanism of action	Trial type with number of participants (n)	Trial No.	Reference
Hydroxychloroquine; Chloroquine	Anti-malarial	Viral enzyme pathway inhibition including viral DNA and RNA polymerase, glycosylation of viral proteins and its assembly, transport of new virus particles followed by their release. Other mechanisms can also include cellular receptor inhibition of ACE2, cell membrane acidification inhibiting virus fusion, and immunomodulation of cytokine release.	Adaptive, randomised open clinical trial Phase 2, International Multi-site, Bayesian Adaptive, RCT (double-Blind, Placebo Controlled) (n=55000)	NCT04315948 NCT04333732	58,67
Azithromycin	Antibacterial	Down regulation of inflammatory responses with reduction in the elevated production of cytokines correlated with viral infections in the respiratory tract; furthermore, their direct impact on viral clearance is unknown. Mechanisms might also involve immune-modulation comprising of reduction of development of reactive oxygen species and neutrophil chemotaxis, acceleration of apoptosis of neutrophil and disruption of nuclear transcription factor activation as well as hypersecretion of mucus.	Randomized, placebo control, parallel arm trial (phase 4). N=40. Randomized, placebo controlled in mild to moderate COVID-19 patients. N=2271.	NCT04359316 NCT04332107	68,69,70
Azithromycin + chloroquine/ hydroxychloroquine		As stated above in the respective sections.	Randomized, open label, parallel assignment trial. N=750. Randomized, quadruple masked, parallel assignment trial. N=140	NCT04370782 NCT04374552	
Anakinra	Interleukin-1 receptor antagonist	Inhibition of IL-1β and IL-1α from binding which thereby blocks signal transduction pathway.	Randomized, triple masked, parallel assignment trial. N=30. (Phase = 3) Non-randomized, sequential assignment open label, Phase 2 trial. N=90.	NCT04362111 NCT04148430	71
Remdesivir (GS5734)	Inhibitor of RNA-dependent RNA polymerases	The compound undergoes a metabolic pathway, which stimulates the nucleoside triphosphate metabolite to inhibit viral RNA polymerases.	Phase 3 RCT (double-Blind, Placebo Controlled), Multicenter Study (n=308). Phase 3 RCT (double-Blind, Placebo Controlled), Multicenter Study (n= 453) Phase 2 Multicenter, Adaptive, RCT (double--Blind, Placebo Controlled) (n=440)	NCT04252664 NCT04257656 NCT04280705	64,72

Glucocorticoids	Steroids	Patients with refractory shock or an acute respiratory distress syndrome could be usually prescribed; however corticosteroid treatment for viral pneumonia is not suggested.	Randomized, open label parallel group trial (phase 2). N=478. Observational, retrospective, case-control study. N=50. Randomized, open label trial (phase 2, 3) with Lopinavir-Ritonavir combination, Hydroxychloroquine, Corticosteroids, Azithromycin, Convalescent plasma, Synthetic neutralizing antibodies or Tocilizumab. N=15000.	NCT04416399 NCT04445506 NCT04381936	[73]
Tocilizumab	Human, monoclonal antibody inhibiting the interleukin-6 (IL-6) pathway	Enhanced IL-6 is a characteristic inflammatory hallmark noted in the serum of patients with acute respiratory distress related to incidence of COVID-19. Tocilizumab acts by inhibiting IL-6-mediated signaling pathway (competitive binding to IL-6 receptors).	Non-randomized, single group assignment, open label phase 2 trial. N=32. Randomized, double blinded, placebo controlled phase 3 trial. N=300.	NCT04331795 NCT04412772	[74]
Baricitinib	Janus kinase (JAK) inhibition	Inhibition of intracellular enzymes,JAKs, which are responsible for transmitting cytokine signals or receptor growth factor interactions involving hematopoiesis and immune cell function.	Randomized, double blinded, placebo controlled, phase 3 trial. N=600. Single arm, open label, single site, adaptive phase 2/3 trial. N=80.	NCT04421027 NCT04340232	[75,76]
Lopinavir/ ritonavir combination	HIV Protease Inhibitor	Inhibition of Mpro, a key enzyme for coronavirus replication.	Adaptive, randomised open clinical trial (n=3200)	NCT04315948	[77,78]
Favipiravir	Anti-viral	Favipinavir acts by selectively inhibiting the RdRP of influenza virus. It is reported to be approved in China for COVID 19.	Randomized, phase 2, double blinded, placebo controlled, trial. N=120. Proof-of-Concept, randomized, phase 2 open label study. N=50.	NCT04346628 NCT04358549	[65,79,80]
Inhaled GMCSF	Recombinant humanized granulocyte-macrophage colony stimulating factor	Acts by targeting both leukopenia and innate immune cell sensitivity that can play a factor in the treating patients at high risk.	Randomized, phase 2, open label study. N=60. Randomized, prospective, open label, phase 4 trial. N=80.	NCT04411680 NCT04326920	[81]

Mesenchymal stem cell (MSC); Derived Mesenchymal stem cell (DMSC)	Stem cells	Preventing the stormy release of cytokines by the immune system and encouraging endogenous repair through stem cell reparations.	Randomized, prospective, open label, phase 2 trial. N=20. Randomized, parallel assignment, single masked, phase 1 study. N=20.	NCT04444271 NCT04346368	[82]
Convalescent Plasma therapy	Plasma	Plasma obtained from patients recovering from COVID-19 may harbor SARS-CoV-2 antibodies. Clinical studies are underway to assess the use of COVID-19 convalescent plasma in treating patients with severe or infections due to COVID-19; however it is not anticipated for infection prevention.	Randomized, open label, phase 2, multi-centre trial. N=278. Randomized, prospective, single-institution, single-arm, phase 1/2 study. N=67.	NCT04345523 NCT04438694	[83]
Sarilumab	Human, monoclonal antibody	Inhibition of the interleukin-6 (IL-6) pathway	Randomized, open label, phase 2, pilot study. N=30.	NCT04357808	[84]
Nitric oxide Inhalation	Inhalation	Acts as a targeted pulmonary vasodilator that is employed in refractory hypoxemia as a rescue treatment because of the precipitation of acute respiratory distress syndrome (ARDS). Even, in-vitro and clinical results shows that nitric oxide gas (iNO) inhaled has antiviral activity against other coronaviral strains.	Randomized, parallel assignment, triple masked, phase 2 study. N=260.	NCT04338828	[85]
Losartan potassium	Angiotensin receptor blocker	It was shown that losartan-treated mice after acid-induced acute lung injury (with the addition of SARS-CoV spike protein) had substantially reduced lung injury and pulmonary oedema relative to placebo-treated mice. Reports suggests an improvement in lung injury in patients with SARS-CoV infection	Open label, phase 1 trial. N=50. RCT, placebo controlled, phase 2 trial. N=200.	NCT04335123 NCT04312009	[86]
Aviptadil	Synthetic version of Vasoactive Intestinal Polypeptide (VIP)	Aviptadil is a vasodilator which reduces blood pressure, when intravenously administered. This can significantly reduce inflammatory mechanisms by functioning on the white blood cells implicated in granulomal formation.	RCT, placebo controlled, phase 1 trial. N=80. Randomized, placebo-controlled, phase 2 trial. N=144.	NCT04536350 NCT04311697	[87]
CD24Fc	Non-antiviral Immunomodulator	It is a biological which acts by preventing TLR activation and also involved in activating Siglec signalling.	Randomized, placebo-controlled, double-blinded, multicentre phase 3 study. N=241.	NCT04317040	[88]

RCT, randomized controlled trial

tive but CT aids in diagnosis by generating the typical findings seen in COVID-19 pneumonia like peripheral, subpleural ground-glass opacities, often in the lower lobes.[59] The cycle threshold (Ct) value of RT-PCR can help in detecting patients who are infectious and who are not, since one study found that a Ct value of more than or equal to 34 seems to be non-infective.[62] The stages of appearance and waning of viral RNA material and antibodies are depicted in figure 2.[63]

Treatment

There is currently no clinically approved, appropriate vaccine available for the treatment of COVID-19. Few drugs have been approved recently depending on the disease severity like remdesivir, favipiravir, and, dexamethasone.[64,65,66] The most effective management technique remains supportive care, including oxygen therapy, fluid control and use of wide spectrum antibiotics to mitigate secondary bacterial infections. Several therapeutic interventions are still under evaluation, and further research is anticipated. The details of available treatment modalities which are mostly on basis of compassionate use in emergency condition and trial purposes are illustrated in Table 4.

Potential vaccines

There is comprehensive work in the advancement of vaccine development for COVID 19 as it is believed to be the only viable effective prevention technique like all other viral epidemics to improve the community's herd immunity and thereby limit the spread. According to the WHO draft (dated 20 March 2020), there were 2 vaccines in the clinical evaluation phase (Phase 1-ChiCTR2000030906; Phase 1-NCT04283461) with 42 more candidate vaccines in the pipeline of pre-clinical research evaluation.[89] The various constituents that can be used for vaccine development are depicted in figure 3.

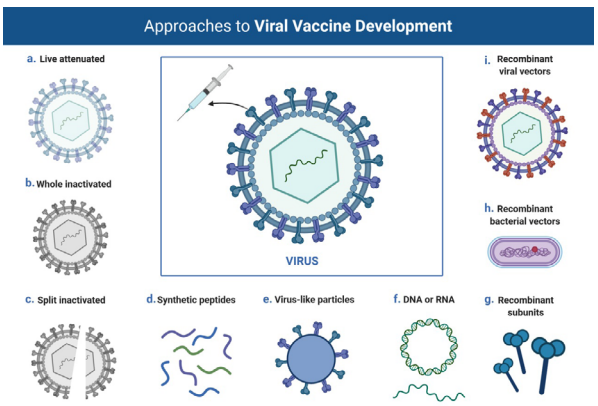

Fig. 3. Concept of potential SARS-CoV-2 vaccine development
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Table 5. Vaccine candidates with sponsor names and trial phase

Candidate	Sponsor	Trial phase
AZD1222	The University of Oxford; AstraZeneca; IQVIA	Phase 2/3
BBV152 Covid vaccine (Covaxin)*	Bharat Biotech International Limited (BBIL); National Institute of Virology	Phase 2/3
Inactivated vaccine	Institute of Biological Products (Wuhan); National Pharmaceutical Group (Sinopharm)	Phase 3
CoronaVac	Sinovac	Phase 3
mRNA-1273	Moderna	Phase 3
BNT162	Pfizer, BioNTech	Phase 2/3
Gam-COVID-Vac	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Phase 1/2, 3
Ad26COVS1	Janssen Pharmaceutical Companies	Phase 1/2, 3
Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M.	Novavax	Phase 1/2, 2b, 3
Ad5-nCoV	CanSino Biologics	Phase 2
Adjuvant recombinant vaccine candidate	Anhui Zhifei Longcom Biopharmaceutical, IMCAS	Phase 2
BBIBP-CorV	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	Phase 1/2
GX-19	Genexine	Phase 1/2
ZyCoV-D	Zydus Cadila	Phase 1/2
Self-amplifying RNA vaccine	Imperial College London	Phase 1/2

IMCAS, Institute of Microbiology of the Chinese Academy of Sciences

For now, a nasal vaccine for COVID 19 has been developed by Bharat Biotech® which has presented to be safe and effective in phase I and phase II of the clinical trials and will be further rendered by introducing gene sequences from SARS-CoV-2 into M2SR (influenza virus self-limiting version) so that the new developed vaccine can also trigger immunity against coronavirus.[90] In

addition, on April 2nd2020, the University of Pittsburgh unveiled a possible SARS-CoV-2 vaccine that can be administered through a fingertip patch which generates SARS-CoV-2-specific antibodies in amounts considered adequate to neutralize the virus.[91] A recent epidemiological research has shed some light on the usage of BCG vaccination to lower down COVID 19 related wellness and risk of death.[92] Few of the vaccines which are in phase 1/2 or phase 3 with their sponsor are listed in Table 5 below which are being adopted from the WHO vaccine landscape.[89]

Existing treatment protocol in adults with COVID-19 as per severity

The treatment protocol varies marginally from one country's guideline to the other, but the essential components of addressing the underlying pathology and critically ill intervention remain unchanged. The summary of existing treatment protocol has been summarized in figure 4.[93, 94]

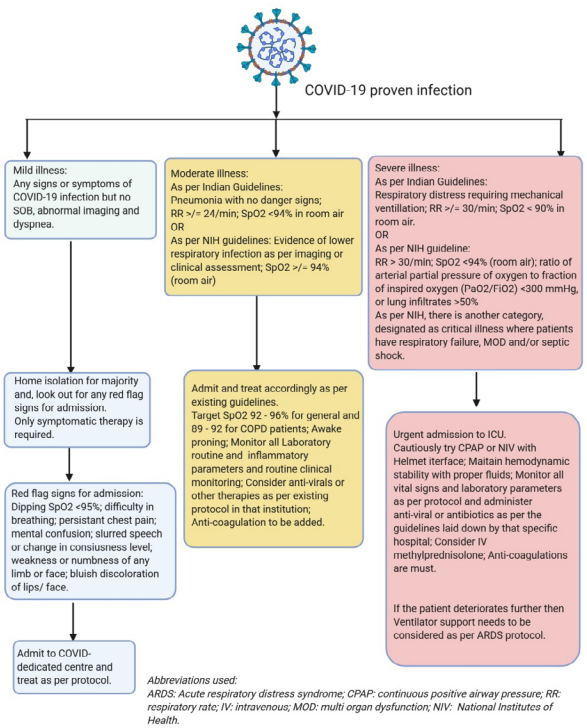

Fig. 4. Summary of treatment protocol as per disease severity
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New learning points from this review

COVID-19 related publications have reached a magnitude of 23000, 5898, and 5393 publications in PubMed, Elsevier, and RG (research gate), respectively, over a few months.[95] Review articles have highlighted the importance of hand-hygiene, travel restrictions, mask use, and physical distancing continuously. Rapid diagnostic assays, effective therapeutic strategies, and prevention through the rapid development of vaccines are the most important step in our battle against this virus.[96, 97] Travels, both international and national, should be restricted only for medical emergency purposes with screening at all levels and self-reporting of the passengers' symptoms. Quarantining of suspected people and their close contacts, increasing public awareness of the non-specific symptoms of the disease, and maintaining proper personal hand hygiene and mitigating social gatherings all have been suggested to play crucial roles in preventing this virus from spreading.[98] This review attempts to summarize the epidemiology, pathogenesis, clinical features, mode of transmission, diagnostic tests with their correct interpretation, available treatment modalities, and on-going vaccine research for COVID-19.

Conclusion

COVID-19 is a pandemic similar to the H1N1 outbreak in 2009 and appropriate action should be taken to curtail the spread of the virus, especially when considering the high-risk population comprising of children, elderly population and the healthcare professionals. The outbreak began in mainland China, with a regional concentration at Wuhan City, Hubei, thereby spreading its arm in rest of the world at an alarming rate with an increased incidence when compared to the epicenter. Clinical research suggest that patients routinely exhibit symptoms consistent with viral pneumonia with the commencement of COVID-19, sore throat, cough, myalgia, fatigue and fever being the common ones. Estimated 80 percent of documented hospitalized patients had mild to moderate form of the stated disease, which happened to involve cases of non-pneumonia and pneumonia, and 13.8 percent of the population presented with serious illness. In such a complex scenario, compelling multifarious intervention against COVID-19 should be imposed to initiate the deceleration phase of the disease. Promoting social isolation, avoiding crowds, wearing mask and gloves along with washing hands with soap and water needs to be advocated to limit the exponential spread. Because asymptomatic patients may spread the disease, studies about its transmission needs to be explored. The current treatment initiatives are geared towards symptomatic diagnosis and oxygen therapy. However, prophylactic vaccination is the need of the hour, which would help to avoid COV-related epidemics or pandemics in the future.

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