

## “A Journey of COVID 19 from Pathogenesis to Therapy”

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### Abstract

The novel Corona virus has come up from China, the first outburst of this Pandemic disease was reported in Wuhan, China in December 2019. Hence it is named as Covid-19. The other forms such as SARS and MERS have already prevailed in the nature, but this Covid-19 is more lethal than the those. In this review the author wants to focus on the epidemiology, pathogenesis & Current treatment scenario with little impact on Ayurveda used during this outbreak. The novel Corona virus is very contagious disease which propagates rapidly via droplets of saliva and other bodily fluids. Currently, confirmation of 2019-nCoV infection is performed at CDC using the CDC real-time RT-PCR assay for 2019-nCoV on respiratory specimens (which can include nasopharyngeal or oropharyngeal aspirates or washes, nasopharyngeal or oropharyngeal swabs, bronchioalveolar lavage, tracheal aspirates, or sputum) and serum. There are some new developing approaches, for example artificial learning (AI), and high throughput screenings can possibly accelerate the revelation of treatment. During this Outburst of Corona Virus, it is necessary & need of time to form collaborations across the world to debacle this outbreak. The Researchers now re-emphasized importance in evolving the broad-spectrum Antiviral Drugs to battle the effects of this COVID-19 Virus. There are many anti-Viral drugs and vaccines which are under clinical trials. The rapid spread of disease permits intense surveillance and isolation protocols to prevent further transmission.

**Keywords:** Pathogenesis, COVID-19, Ayurveda, WHO, Treatment.

### Introduction

Coronavirus; group of related RNA viruses that primarily targets the human respiratory system. Coronaviruses were identified in the mid-1960s and are known to infect humans and a variety of animals (including birds and mammals). Coronaviruses typically cause common cold symptoms, but two beta coronaviruses: SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), may lead to severe pneumonia, respiratory failure, and death [1]. Since 2002, two coronaviruses infecting animals have evolved and caused outbreaks in humans: SARS-CoV (Severe Acute Respiratory Syndrome) identified in southern China in 2003, and MERS-CoV (Middle East Respiratory Syndrome), identified in Saudi Arabia in 2012. Together, they have caused more than 1600 deaths [2].

In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology [3]. On 11 February 2020, The International Committee on Taxonomy of Viruses (ICTV) announced on 11, February 2020 that the virus was named severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) while, on the same day, WHO named the disease as coronavirus disease COVID-19. For communication purposes we will refer the virus as “the virus responsible for COVID-19” or “the COVID-19 virus”. Complete genomic sequences of the COVID-19 virus have been released and different molecular detection protocols developed but not fully validated yet [4]. The infection with a novel beta coronavirus, subsequently named SARS-CoV-2, was reported in people who had been exposed to a seafood market in Wuhan, China, where live animals were sold. Wuhan is the largest city in central China, with a resident population of over fourteen million. The rapid increase in reported cases suggests that community transmission of SARS-CoV-2 had established in the city of Wuhan and nearby regions no later than the end of January. As the rapid molecular diagnostic assay was not available in early January and widespread use was difficult before 23 January 2020, it was difficult to monitor the transmission of SARS-CoV-2 among the community [3]. Since then, there has been rapid spread of the virus, leading to a global pandemic of Covid-19 (named by WHO on Feb 11, 2020) [1].

As reported by WHO dated 19th June 2020, 8,366,417 confirmed cases of COVID-19, including 450,087 deaths so far. Its causative pathogen is a phylogenetic sister to the severe acute respiratory syndrome coronavirus (SARS-CoV) and has been designated as SARS-CoV-2 [2]. However, although SARS-CoV-2 shares 79.6% sequence identity and the same cell receptor with SARS-CoV, the clinical outcome of SARS-CoV-2 not only includes SARS-like viral pneumonia, but also covers milder illness, even asymptomatic infection. In fact, analysis by the China CDC indicated that 80.9% of confirmed COVID-19 cases were characterized as the mild or moderate types—that is, without breathing difficulty and hypoxia [3].

### Different Phases of COVID-19 Disease

Three phases that correspond to different clinical stages of the disease.

#### Stage 1: Asymptomatic state (initial 1–2 days of infection)

After inhalation of SARS-CoV-2 virus in human body, it binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV-2 and SARS-CoV. In vitro data with SARS-CoV indicate that the ciliated cells are primary cells infected in the conducting airways. However, this concept of ciliated cells needs more research to be done because single-cell RNA indicates low level of ACE2 expression in conducting airway cells and no obvious cell type preference. At this first clinical stage the virus can be detected by nasal swabs. But it's very difficult to identify the individuals with stage I because of very low viral burden. The main technique by which detection of corona virus can be done is RT-PCR value and the subsequent infectivity with clinical course. For the RT-PCR cycle number to be useful, the sample collection procedure would have to be standardized. Nasal swabs might be more sensitive than throat swabs.

#### Stage 2: Upper airway and conducting airway response (next few days)

The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response. The level of CXCL10 (or some other innate response cytokine) may be predictive of the subsequent clinical course. Viral infected epithelial cells are a major source of beta and lambda interferons. CXCL10 is an interferon responsive gene that has an excellent signal to noise ratio in the alveolar type II cell response to both SARS-CoV and influenza. CXCL10 has also been reported to be useful as disease marker in SARS. Optimizing the innate immune response of host can automatically help in prediction of course action of disease and need for more aggressive monitoring. About 80% of the infected patients from the disease will be having mild and mostly upper and conducting airways restrictions. These individuals may be monitored at home with conservative symptomatic therapy.

#### Stage 3: Hypoxia with progression to Acute Respiratory Distress Syndrome (ARDS)

Unfortunately, about 20% of the infected patients will progress to stage 3 disease and will develop pulmonary infiltrates and some of these will develop very severe disease. The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells. The infected alveolar units tend to be peripheral and subpleural. SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die (Figure 1). It results in release of self-replicating pulmonary toxin from the viral particles. Type II cells are completely lost from lungs and secondary pathway for epithelial regeneration will be triggered. Normally, type II cells are the precursor cells for type I cells. This postulated sequence of events has been shown in the murine model of influenza pneumonia. The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. The aberrant wound healing may lead to more severe scarring and fibrosis than other forms of ARDS. Recovery will require a vigorous innate and acquired immune response and epithelial regeneration. From my perspective, like influenza, administering epithelial growth factors such as KGF might be detrimental and might increase the viral load by producing more ACE2 expressing cells. Elderly individuals are particularly at risk because of their diminished immune response and reduced ability to repair the damaged epithelium. The elderly also has reduced mucociliary clearance, and this may allow the virus to spread to the gas exchange units of the lung more readily [5, 6].

**SARS-CoV-2 GENOME STRUCTURE AND PATHOGENESIS**  
SARS-CoV-2 is an enveloped positive-sense unsegmented single-strand RNA virus that belong to the genus Betacoronavirus. The whole-genome sequences of SARS-CoV-2 isolated from patients living in or visiting Wuhan showed a genome 29 844 to 29 891 nt in size, encoding approximately 9860 aa and lacking the haemagglutinin-esterase gene. The SARS-CoV-2 genome has great sequence similarity (89–96.3%) with two bat coronaviruses, bat-SLCoVZC45 and bat-SL-CoVZXC21, and 79% to 82% with that of human SARS-CoV. The genome contains 14 open reading frames (ORFs) encoding 27 proteins. The longest ORF is located at the 5' terminus encoding for 15 nonstructural proteins collectively involved in virus replication and possibly in immune evasion. The 3' terminus of the genome encodes for structural and accessory proteins. Hypervariable genomic hot spots have been detected in the spike gene and in other ORFs for nonstructural proteins. Interestingly, the unique aspects of SARS-CoV-2 were found in genes of spike glycoprotein, orf8 and orf3b. The spike protein is composed of two subunits, the S1 domain of a single polypeptide containing the receptor-binding domain and the S2 domain, composed of highly conserved polypeptides associated with the envelope. The external subdomain of SARS-CoV-2 spike globular head S1 has only 40% similarity with its counterparts in the bat and human SARS-CoV virion. The outer portion of the external

subdomain responsible for direct contact with the human receptor (//angiotensin-converting enzyme 2, ACE-2) has the most diversity in amino acids. Such variations are believed to have evolved from homologous recombination between a bat coronavirus and another coronavirus of unknown origin. Orf3b is a putative novel protein that seems to play a pivotal role in pathogenesis of SARS-CoV-2, while Orf8 is an accessory protein shorter than its counterparts found in other Beta coronavirus with unknown function [5].

The family of Coronaviridae of Corona virus has subfamily of Coronavirinae and order Nidovirales, and this subfamily includes four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. The genome of CoVs is a single stranded positive sense RNA (+ssRNA) (~30 kb) with 5' cap structure and 3' poly A tail. The genomic RNA is used as template to directly translate polyprotein 1a/1ab (pp1a/pp1ab), which encodes nonstructural proteins (nsps) to form the replication transcription complex (RTC) in a double-membrane vesicles (DMVs). Subsequently, a nested set of subgenomic RNAs (sgRNAs) are synthesized by RTC in a manner of discontinuous transcription. These subgenomic messenger RNAs (mRNAs) possess common 5' leader and 3' terminal sequences. Transcription termination and subsequent acquisition of a leader RNA occurs at transcription regulatory sequences, located between open reading frames (ORFs). These minus strand sgRNAs serve as the templates to produce subgenomic mRNAs.

The genome and subgenomes of a typical CoV contain at least six ORFs. The first ORFs (ORF1a/b), about two thirds of the whole genome length, encode 16 nsps (nsp1-16), except Gamma coronavirus that lacks nsp1. There is a -1 frameshift between ORF1a and ORF1b, leading to production of two polypeptides:

pp1a and pp1ab. These polypeptides are processed by virally encoded chymotrypsin like protease (3CLpro) or main protease (Mpro) and one or two papain-like proteases into 16 nsps. Other ORFs on the one third of the genome near the 3' terminus encodes at least four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Besides these four main structural proteins, different CoVs encode special structural and accessory proteins, such as HE protein, 3a/b protein, and 4a/b protein. All the structural and accessory proteins are translated from the sgRNAs of CoVs.

The genome sequence alignment of CoVs shows 58% identity on the nsp coding region and 43% identity on the structural protein coding region among different CoVs, with 54% at the whole genome level, suggesting the nsps are more conserved and the structural proteins are more diverse in need of adaptation to new hosts. Since the mutation rates in the replication of RNA viruses are much higher than that of DNA viruses, the genomes of RNA viruses are usually less than 10 kb in length. However, the CoV genome is much larger, with roughly 30kb in length, the largest known RNA viruses. The maintenance of such a large genome of CoVs may be related to the special features of the CoV RTC, which contains several RNA processing enzymes such as the 3'-5' exoribonuclease of nsp14. The 3'-5' exoribonuclease is unique to CoVs among all RNA viruses, probably providing a proofreading function of the RTC. Sequence analysis shows that the 2019 nCoV possesses a typical genome structure of CoV and belongs to the cluster of betacoronaviruses that includes Bat SARS like (SL)-ZC45, Bat- SL ZXC21, SARS- CoV, and MERS- CoV. Based on the phylogenetic tree of CoVs, 2019 nCoV is more closely related to bat- SL-CoV ZC45 and bat-SL-CoV ZXC21 and more distantly related to SARS-CoV [6].

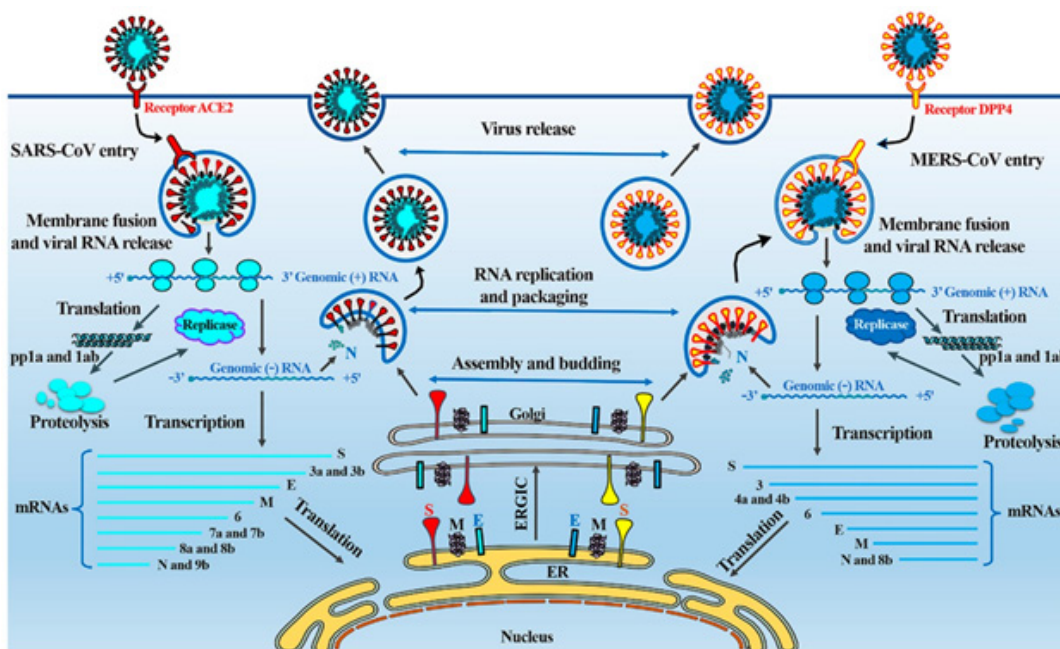


Figure 1: Genotype of COVID 19 Virus



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## COVID- 19 PHENOTYPES

Based on detailed observation of several cases and discussions with colleagues treating these patients, we hypothesize that the different COVID-19 patterns found at presentation in the emergency department depend on the interaction between three factors: 1) the severity of the infection, the host response, physiological reserve and comorbidities; 2) the ventilatory responsiveness of the patient to hypoxemia; 3) the time elapsed between the onset of the disease and the observation in the hospital. The interaction between these factors leads to the development of a time-related disease spectrum within two primary “phenotypes”: Type L, characterized by Low elastance (i.e., high compliance), Low ventilation to perfusion ratio, Low lung weight and Low recruitability and Type H, characterized by High elastance, High right-to-left shunt, High lung weight and High recruitability.

### TYPE-L

At the beginning, COVID-19 pneumonia presents with the following characteristics:

- Low elastance: the nearly normal compliance indicates that the amount of gas in the lung is nearly normal.
- Low ventilation to perfusion (VA/Q) ratio: since the gas volume is nearly normal, hypoxemia may be best explained by the loss of regulation of perfusion and by loss of hypoxic vasoconstriction. Accordingly, at this stage, the pulmonary artery pressure, should be near normal.
- Low lung weight: Only ground-glass densities are present on CT scan, primarily located subpleurally and along the lung fissures. Consequently, lung weight is only moderately increased.
- Low lung recruitability: the amount of non-aerated tissue is very low, consequently the recruitability is low [4].

To conceptualize these phenomena, we hypothesize the following sequence of events: the viral infection leads to a modest local subpleural interstitial edema (ground-glass lesions) particularly located at the interfaces between lung structures with different elastic properties, where stress and strain are concentrated [4, 5]. Vasoplegia accounts for severe hypoxemia. The normal response to hypoxemia is to increase minute ventilation, primarily by increasing the tidal volume [6] (up to 15-20 ml/kg), which is associated with a more negative intrathoracic inspiratory pressure. Undetermined factors other than hypoxemia, markedly stimulate, in these patients, the respiratory drive. The near normal compliance, however, explains why some of the patients present without dyspnea as the patient inhales the volume he expects. This increase in minute ventilation leads to a decrease in PaCO<sub>2</sub>.

The Evolution of the Disease: Transitioning Between Phenotypes  
The Type L patients may remain unchanging for a period and then improve or worsen the possible key feature which determines the evolution of the disease - other than the severity of the disease itself, is the depth of the negative intrathoracic pressure associated with the increased tidal volume in spontaneous breathing. Indeed, the combination of a negative inspiratory intrathoracic pressure

and increased lung permeability due to inflammation, results in interstitial lung edema. This phenomenon, initially described by Barach in 1938 and Mascheroni in 1988 both in an experimental setting, has been recently recognized as the leading cause of Patient - Self Inflicted Lung Injury (P-SILI) [9]. Over time, the increased edema increases lung weight, superimposed pressure, and dependent atelectasis. When lung edema reaches a certain magnitude, the gas volume in the lung decreases, and the tidal volumes generated for a given inspiratory pressure decrease [10]. At this stage, dyspnea develops, which in turn leads to worsening P-SILI. The transition from Type L to Type H may be due to the evolution of the COVID-19 pneumonia on one hand and the injury attributable to high-stress ventilation on the other.

### TYPE H

The Type H patient

- High elastance: The decrease of gas volume due to increased edema accounts for the increased lung elastance.
- High right-to-left shunt: This is due to the fraction of cardiac output perfusing the non-aerated tissue which develops in the dependent lung regions due to the increased edema and superimposed pressure.
- High lung weight: Quantitative analysis of the CT scan shows a remarkable increase in lung weight (> 1.5 kg), on the order of magnitude of severe ARDS.
- High lung recruitability: The increased amount of non-aerated tissue is associated, as in severe ARDS, with increased recruitability.

The Type H pattern, 20 – 30% of patients in our series, fully fits the severe ARDS criteria: hypoxemia, bilateral infiltrates, decreased the respiratory system compliance, increased lung weight and potential for recruitment. Figure 1 summarizes the time course we described. In Panel A, we show the CT in spontaneous breathing of a Type L patient at admission and, in Panel B, its transition in Type H after 7 days of noninvasive support. As shown, a similar degree of hypoxemia was associated to different patterns in lung imaging [7].

## IMMUNODISGNOSTIC TESTS FOR COVID-19

Currently, WHO recommends the use of these new point-of-care immunodiagnostic tests only?

## RAPID DIAGNOSTIC TESTS BASED ON ANTIGEN DETECTION

Rapid diagnostic test (RDT) is a type of medical diagnostic test which can be performed easily and at low cost as well as give results in short period of time. This test in case of COVID 19 situation detects the presence of viral proteins (antigens) in a sample from the respiratory tract of a person. If the target antigen is present in enough concentrations in the sample, it will bind to specific antibodies fixed to a paper strip enclosed in a plastic casing and generate a visually detectable signal, typically within 30 minutes. The antigen(s) detected are expressed only when the

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virus is actively replicating; therefore, such tests are best used to identify acute or early infection.

How well the tests work depends on several factors, including the time from onset of illness, the concentration of virus in the specimen, the quality of the specimen collected from a person and how it is processed, and the precise formulation of the reagents in the test kits. Based on experience with antigen-based RDTs for other respiratory diseases such as influenza, in which affected patients have comparable concentrations of influenza virus in respiratory samples as seen in COVID-19, the sensitivity of these tests might be expected to vary from 34% to 80%.

Based on this information, half or more of COVID-19 infected patients might be missed by such tests, depending on the group of patients tested. These assumptions urgently require further study to understand whether they are accurate. Additionally, false-positive results – that is, a test showing that a person is infected when they are not – could occur if the antibodies on the test strip also recognize antigens of viruses other than COVID-19, such as from human coronaviruses that cause the common cold. If any of the antigen detection tests that are under development or commercialized demonstrate adequate performance, they could potentially be used as triage tests to rapidly identify patients who are very likely to have COVID-19, reducing or eliminating the need for expensive molecular confirmatory testing.

With the limited data now available, WHO does not currently recommend the use of antigen-detecting rapid diagnostic tests for patient care, although research into their performance and potential diagnostic utility is highly encouraged [8].

## **RAPID DIAGNOSTIC TESTS BASED ON HOST ANTIBODY DETECTION**

Another important test is rapid diagnostic test marketed for COVID-19; a test that detects the presence of antibodies in the blood of people believed to have been infected with COVID-19. Antibodies are produced over days to weeks after infection with the virus. The strength of antibody response depends on several factors, including age, nutritional status, severity of disease, and certain medications or infections like HIV that suppress the immune system. In some people with COVID-19, disease confirmed by molecular testing (e.g. reverse transcription polymerase chain reaction: RT-PCR), weak, late or absent antibody responses have been reported. Studies suggest that most patients develop antibody response only in the second week after onset of symptoms. This means that a diagnosis of COVID-19 infection based on antibody response will often only be possible in the recovery phase, when many of the opportunities for clinical intervention or interruption of disease transmission have already passed. Antibody detection tests targeting COVID-19 may also cross-react with other pathogens, including other human coronaviruses and give false-positive results. Lastly, there has been discussion about whether RDTs detecting antibodies could predict whether an individual

was immune to re-infection with the COVID-19 virus. There is no evidence date to support this.

Tests to detect antibody responses to COVID-19 in the population will be critical to support the development of vaccines, and to add to our understanding of the extent of infection among people who are not identified through active case finding and surveillance efforts, the attack rate in the population, and the infection fatality rate. For clinical diagnosis, however, such tests have limited utility because they cannot quickly diagnose acute infection to inform actions needed to determine the course of treatment. Some clinicians have used these tests for antibody responses to make a presumptive diagnosis of recent COVID-19 disease in cases where molecular testing was negative but where there was a strong epidemiological link to COVID-19 infection and paired blood samples (acute and convalescent) showing rising antibody levels.

Based on current data, WHO does not recommend the use of antibody-detecting rapid diagnostic tests for patient care but encourages the continuation of work to establish their usefulness in disease surveillance and epidemiologic research [8, 9].

## **Next Steps**

- Molecular (e.g. PCR) testing of respiratory tract samples is the recommended method for the identification and laboratory confirmation of COVID-19 cases. COVID-19 molecular diagnostic products are being evaluated for quality and safety through the WHO Prequalification Emergency Use Listing Procedures and through a collaboration with the Foundation for Innovative New Diagnostics (FIND). WHO guidance documents for detection of COVID-19 have been published: WHO Guidance on Laboratory testing for COVID-19 in suspected human cases. In addition, guidance on how testing might be rationalized when lack of reagents or testing capacity necessitates prioritization of certain populations or individuals for testing is also available.
- To inform WHO policy on the use of immunodiagnostic rapid tests for COVID-19, WHO is working with our global laboratory expert network, and closely reviewing the results of laboratory and clinical studies planned and implemented by reference laboratories, academic groups and non-governmental organizations.
- Target product profiles for desired COVID-19 diagnostics to inform research and development efforts are in development.
- WHO will continue to work with research groups, other agencies, and Member States to develop and interpret data that might indicate specific areas where such tests can be useful for clinical management of cases, epidemiologic understanding, and/or infection control [8, 9].

## **STRATEGIES FOR DIAGNOSING SARS- COV-2**

Based on data collected from previous epidemics, like SARS and MERS; we require highly sensitive and specific laboratory diagnostics tests for case identification, contact tracing, animal

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source finding, and efficient and rational containment measures. Precise case identification is essential in order to isolate vulnerable individuals because of COVID 19 pandemic in society. Test decision always be based on clinical and epidemiological factors and associated to an assessment of the likelihood of infection, when availability of tests is limited.

While isolation of the virus itself using electron microscopy would be the most specific diagnostics, it requires biosafety level-3 facilities which are not available in most healthcare institutions. Serum antibody and antigen detection tests would be the easiest and fastest, but have not yet been validated, and there may be cross-reactivity with other coronaviruses, especially SARS-coronavirus. Furthermore, antibodies are not measurable in the initial phase of the infection. Real time reverse transcriptase polymerase chain reaction (RT-PCR) remains the main technique for COVID-19 diagnosis, but chest X-ray, CT scans, and biomarkers (i.e. high CRP, low PCT, low lymphocyte counts, elevated IL6 and IL10) have been also employed by some countries to aid identification or to provide some evidence of more severe disease progression. Therefore, real-time PCR remains the most useful laboratory diagnostic test for COVID-19 worldwide [10].

### **COVID-19 Treatment guidelines:**

There are no drugs or other therapeutics presently licensed or approved by the U.S. Food and Drug Administration (FDA) or WHO for prevention or treatment of COVID-19. While several drug trials and vaccine trails going on in different countries for treatment of pandemic disease, but till now no clinical proof for any medicine or treatment. Current clinical management includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated [11].

### **Antithrombotic Therapy in Patients with COVID-19**

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers. Although the true incidence of thrombosis is unknown, there have been reports of increased incidence of thromboembolic disease associated with COVID-19 in patients in the intensive care unit.

A new section titled Antithrombotic Therapy in Patients with COVID-19 has been added to the guidelines to address many questions related to the role of coagulation markers and thrombolytic, anticoagulant, and antiplatelet agents in those with COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations on the use of antithrombotic agents for the prevention of venous thromboembolic events in hospitalized patients with COVID-19. In addition, the Panel recommends carefully monitoring, evaluating, and treating hospitalized patients with COVID-19 for incident thrombotic events when indicated [12, 13].

### **Antiviral drugs for treatment of COVID 19:**

Several companies from all over the world also working on use of antiviral drugs for treatment of patients of COVID 19, some of these antiviral drugs are already in use against other illnesses. Mostly drugs being developed or tested for COVID-19 comes under class of antivirals. Because, these would target the virus in people who already have an infection [14-18].

### **Remdesivir:**

This drug is developed a decade ago, but this drug failed in clinical trials against Ebola in 2014. This drug when used in case of MERS showed that the drug blocked the virus from replicating. Now, the drug is being tested in COVID 19 patients and clinical trials going on around the world. On the basis of preliminary clinical trial data, the Panel recommends the investigational antiviral agent remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease, defined as SpO<sub>2</sub> ≤94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (BI). Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients, Remdesivir is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication. Remdesivir has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the topline data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705) and from the Gilead-sponsored open-label trial that evaluated different durations of Remdesivir (NCT04292899), it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of patients hospitalized with severe COVID-19.

### **Kaletra**

Kaletra is a combination of two drugs i.e lopinavir and ritonavir; both the drugs work against HIV. Clinical trials are being done to check their effectiveness in treatment of SARS-CoV-2. One small study published May 4 in the Journal Med by Cell Press found that lopinavir/ritonavir did not improve outcomes in people with mild or moderate COVID-19 compared to those receiving standard care. Another study, published May 7 in the New England Journal of Medicine, found that the drug combination was not effective for people with severe COVID-19. But another study published in The Lancet in May 2020 found that people who were given lopinavir/ritonavir along with two other drugs ribavirin and interferon beta-1b took less time to clear the virus from their body. Data collected from this study showed the efficacy and safety of combined interferon beta-1b, lopinavir–ritonavir, and ribavirin for treating patients with COVID-19. Study done by design multicenter randomized open-label phase 2 trial in patients with COVID-19, showed that a triple combination of an injectable interferon (interferon beta-1b), oral protease inhibitor (lopinavir–ritonavir), and an oral nucleoside analogue (ribavirin), when given within 7



days of symptom onset, is effective in suppressing the shedding of SARS-CoV-2, not just in a nasopharyngeal swab, but in all clinical specimens, compared with lopinavir–ritonavir alone. Moreover, the significant reductions in duration of RT-PCR positivity and viral load were associated with clinical improvement. Most of the patients treated with the triple combination were found to be RT-PCR negative in all specimens by day 8. The side-effects were generally mild and self-limiting [18].

### Other Treatments:

**Chloroquine/Hydroxychloroquine:** Both the chemotherapeutic agents i.e chloroquine and hydroxychloroquine used as antimalarial drugs because they act against erythrocytic forms of the Plasmodium parasites. When drug is absorbed, it ultimately increases the pH of acidic food vacuoles in parasite while it is inside the erythrocyte, which interferes with vesicle function and the development and asexual reproduction of the parasite. Chloroquine (CQ) is used to prevent and treat malaria and amebiasis, while hydroxychloroquine (HCQ), a less toxic metabolite of chloroquine, is used to treat rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and Sjogren’s syndrome. Both medications can cause corneal deposits, posterior subcapsular lens opacity, ciliary body dysfunction, and most important, irregularity in the macular pigmentation in the early phase, a ring of macular pigment dropout in the advanced stage, and peripheral bone spicule formation, vascular attenuation, and optic disc pallor in the end-stage.

These drugs received emergency use authorization from the FDA at the end of March for treatment of COVID 19. At the time of the FDA authorization in March, manufacturer Novartis donated about 30 million doses of hydroxychloroquine and one million doses of chloroquine to the nation’s Strategic National Stockpile. In late May, the World Health Organization announced that it was halting its clinical trials of hydroxychloroquine due to safety concerns. Around the same time, officials in France, Belgium, and Italy also stopped the use of hydroxychloroquine for COVID-19 treatment due to safety concerns. In early May, the authors of an observational study in the New England Journal of Medicine also reported that patients who had been given hydroxychloroquine didn’t benefit. The medication didn’t harm the participants who took it, but the drug also didn’t lessen their need for ventilators or reduce their risk of death. Another data from trusted sources in JAMA published in May also found that hydroxychloroquine, with or without the antibiotic azithromycin, didn’t help people with COVID-19.

According to recent updates from FDA on 15th June 2020, based on various scientific data and ongoing analysis, FDA revoked the emergency use authorization (EUA) to use both the drugs hydroxychloroquine and chloroquine to treat COVID 19 patients when any clinical trial data is unavailable. FDA decide this thought only because of recent data collected from large, randomized clinical trial study on hospitalized patients. Data showing that these medicines are not having any benefit for

decreasing the likelihood of death or any speeding recovery. This outcome was consistent with one more new data that suggested dosing for these medicines are unlikely to kill or inhibit the virus that causes COVID 19. Each of the drug regimens of chloroquine or hydroxychloroquine alone or in combination with a macrolide was associated with an increased hazard for clinically significant occurrence of ventricular arrhythmias and increased risk of in-hospital death with COVID-19 [17].

### Monoclonal Antibodies

Monoclonal antibodies (mAb or moAb) are antibodies that are made by identical immune cells that are all clones of a unique parent cell. Monoclonal antibodies can have monovalent affinity, in that they bind to the same epitope (the part of an antigen that is recognized by the antibody). These drugs trigger the immune system to attack the virus. Vir Biotechnology has isolated antibodies from people who survived SARS. The company is working with Chinese firm WuXi Biologics to test them as a treatment for COVID-19. AbCellera has isolated 500 unique antibodies from a person who recovered from COVID-19 and is set to start testing them [18].

### Blood Plasma Transfers

This therapy of blood plasma transfers is used to protect or treat humans with some evidence for benefit against rabies, hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Most patients who recover from COVID-19 illness develop some level of circulating neutralizing antibodies to various SARS-CoV-2 proteins 2-3 weeks following infection, detectable by ELISA or other quantitative assays. This has been demonstrated in at least two cohorts of rhesus macaques infected with SARS-CoV-2 who generated antibody responses and could not be re-infected with the virus weeks to months later. Many patients improved clinically and cleared the virus, however the role of the convalescent plasma treatment in these patients is unclear, because all patients received at least one additional therapy, including antivirals, antibiotics or antifungals, and corticosteroids. In May 2020, FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. Along the same lines, the FDA has announced a process for medical facilities to conduct trials on an experimental treatment that uses blood plasma from people who have recovered from COVID-19. In early June, researchers reported that 19 of 25 people with COVID-19 who were treated with convalescent plasma transfusions at Houston Methodist Hospital in Texas had improved. Eleven of those patients have been released from the hospital [18].

### Stem Cells

Atresys began a phase II/III clinical trial that will examine whether

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the company's stem cell treatment could potentially benefit people with acute respiratory distress syndrome (ARDS). This condition occurs in some people with severe COVID-19.

Mesoblast has also developed a potential stem cell treatment for ARDS. The company is enrolling people with moderate to severe ARDS into Phase II/III clinical trial in the United States [16].

### **Immune Suppressants**

In some people with COVID-19, the immune system goes into overdrive, releasing large amounts of small proteins called cytokines. Scientists think this "cytokine storm" may be the reason certain people develop ARDS and need to be put on a ventilator.

Several immune suppressants are being tested in clinical trials to see whether the drugs can quell the cytokine storm and reduce the severity of ARDS.

These include baricitinib, a drug for rheumatoid arthritis; CM 4620-I, a drug for pancreatic cancer; and IL-6 Inhibitors. The FDA has also approved a device that filters cytokines out of the blood of patients.

### **Corticosteroids**

**For Critically Ill Patients with COVID-19:** The Panel recommends against the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without acute respiratory distress syndrome (ARDS) (AIII). For mechanically ventilated patients with ARDS, there is insufficient evidence to recommend for or against the use of systemic corticosteroids (CI). For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (i.e., shock reversal) over no corticosteroids (BII).

**For Hospitalized, Non-Critically Ill Patients with COVID-19:** The Panel recommends against the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients, unless they are in the intensive care unit (AIII).

**For Patients on Chronic Corticosteroids:** Oral corticosteroid therapy used prior to COVID-19 diagnosis for another underlying condition (e.g., primary or secondary adrenal insufficiency, diseases) should not be discontinued (AIII). On a case-by-case basis, supplemental or stress-dose steroids may be indicated (AIII). Inhaled corticosteroids used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 (AIII) [18].

### **HMG-CoA Reductase Inhibitors (Statins):**

Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications (AIII). The Panel recommends against the use of statins for the treatment of COVID-19 outside of the setting of a clinical trial (AIII).

### **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):**

Persons with COVID-19 who are taking NSAIDs for a co-morbid condition should continue therapy as previously directed by their physician (AIII). The Panel recommends that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 (AIII).

### **Next Steps for treatment**

1. The World Health Organization (WHO) welcomes the initial clinical trial results from the United Kingdom (UK) that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with WHO. The benefit was only seen in patients seriously ill with COVID-19 and was not observed in patients with milder disease [19].
2. Eli Lilly and Co could have a drug specifically designed to treat COVID-19 authorized for use as early as September if all goes well with either of two antibody therapies it is testing. Lilly is also doing preclinical studies of a third antibody treatment for the illness caused by the COVID 19 that could enter human clinical trials in the coming weeks.
3. Ayurveda, a traditional system of medicine, originated in India more than 3000 years ago. The term Ayurveda is derived from the Sanskrit words ayur (life) and veda (science or knowledge). The classic Ayurveda text Charaka Samhita, mentioned about epidemic management and defines immunity as the ability to preventing and arresting the progression of disease for maintaining homeostasis. The Ayurveda pays larger emphasis on building strength of mind and body to cope with various stressors, including infection. Like innate and acquired immunity, the Ayurveda concept of immunity (Bala or strength) is classified as natural (Sahaja), chronobiologic (Kalaja), and acquired (Yuktikrut). In Ayurveda several treatment options are available for enhancing immunity against respiratory illnesses, these include certain immunomodulators (known as Rasayana), local and systemic interventions. Local prophylaxis measures such as herbal decoctions, consumptions of hot water, gargling with medicated water, and steam inhalation described in Ayurveda for respiratory illnesses. The prophylactic and therapeutic potential of traditional and complementary medicine systems such as Ayurveda and Yoga can be proven effective prophylaxis and adjuvant therapy of COVID-19. Ashwagandha, Yashtimadhu, Guduchi + Pippali and a poly herbal formulation (AYUSH-64) cleared for trial in battle against Covid-19. The government will conduct a randomized controlled clinical trial to assess the efficacy of Ayurvedic drug Ashwagandha as a preventive intervention among healthcare professionals and high-risk coronavirus population in comparison with hydroxychloroquine. The Interdisciplinary Ayush R&D Task Force has formulated and designed clinical research protocols for prophylactic studies and add-on interventions in Covid-19 positive cases thorough



review and consultative process of experts of high repute from different organisations across the country for studying four different interventions viz. Ashwagandha, Yashtimadhu (Mulethi), Guduchi +Pippali (Giloy) and a poly herbal formulation (AYUSH-64). As the field of alternative medicine gains immense popularity in the wake of COVID-19, the ancient practice of Ayurveda with India as its land of origin can don the role of quiet yet powerful armed forces in the fight against the coronavirus, according to a seasoned Clinical Assistant Professor of Medicine from Weill Cornell Medical College in New York [20].

4. Council of Scientific and Industrial Research (CSIR) constituent lab CSIR-Central Drug Research Institute (CDRI), Lucknow has received permission for carrying out Phase III randomised, trial of efficacy, safety and tolerability of antiviral drug Umifenovir. This drug has a good safety profile and acts by preventing entry of virus into human cells and by priming the immune system. Umifenovir is mainly used for treatment of influenza and is available in China and Russia and has recently come into prominence due to its potential use for Covid19 patients. Researchers on low-dose dexamethasone steroid treatment was a part of the RECOVERY (Randomised Evaluation of COVid-19 therapy) trial that was testing the efficacy of a wide-range of drugs and therapies for COVID-19, the report said [21].

## Conclusion

This article main objective to understand the genotype and phenotype of COVID 19 and the treatment available for COVID 19 till date and how we can prevent from this coronavirus. All over the world various clinical trials are going on various drugs as well as on vaccines to combat from this disease. We all together can join hands and try to prevent from this pandemic disease by taking precautions according to WHO as well as following some guidelines of Ayurveda to increase our immunity to fight against this disease. Safety is not expensive, it's Priceless.

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