



DIAGNOSTICS TEST AND RECENT ADVANCE TREATMENT FOR COVID-19

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Abstract: Coronaviruses are a group of enveloped viruses with nonsegmented, single-stranded, and positive-sense RNA genomes. Apart from infecting a variety of economically important vertebrates (such as pigs and chickens), six coronaviruses have been known to infect human hosts and cause respiratory diseases.

SARS -CoV-2 first emerged in China in December 2019 and rapidly spread worldwide. No vaccine or approved drug is available to eradicate the virus, however, some drugs that are indicated for other afflictions seems to be potentially beneficial to treat the infection albeit without unequivocal evidence. Two kinds of tests are available for COVID-19: viral tests and antibody tests. A viral test tells you if you have a current infection. An antibody test tells you if you had a previous infection. Treatment outcomes from their applied drugs during treatment of COVID-19 patients, 4 report laboratory tests, one report animal trial and other recommendations based on the treatment process and clinical outcomes of other diseases such as malaria, ebola, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). SARS and MERS were associated mainly with nosocomial spread, whereas SARS-CoV-2 is much more widely transmitted in the community. The data and recommendations are categorized in 4 classes a) anti-viral and anti-inflammatory drugs, b) anti-malaria drugs, c) traditional Chinese drugs and d) other treatment/drugs.

Keywords: Coronavirus, SARS Cov-2, COVID-19, Treatment, Diagnosis.

INTRODUCTION:-

COVID-19 is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 is now a pandemic affecting many countries globally. WHO declared COVID-19 as a public health emergency of international concern (PHEIC) on January 30, 2020 and a pandemic on March 11, 2020. Although China was the epicenter of the pandemic in the beginning, Europe was declared as the new epicenter on March 13, 2020 as the number of cases and deaths in Europe exceeded that of China. ³However, as the number of COVID-19 cases has increased significantly in the United States recently, it could become the new epicenter of COVID-19, as mentioned by the WHO on March 24, 2020. According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded. ²Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012. CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (corona is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. ¹The subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirales) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages. Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.





Coronaviruses are a large family of viruses which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19. ⁶People can catch COVID-19 from others who have the virus. The disease spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. These droplets are relatively heavy, do not travel far and quickly sink to the ground. People can catch COVID-19 if they breathe in these droplets from a person infected with the virus. This is why it is important to stay at least 1 metre (3 feet) away from others. These droplets can land on objects and surfaces around the person such as tables, doorknobs and handrails. People can become infected by touching these objects or surfaces, then touching their eyes, nose or mouth. This is why it is important to wash your hands regularly with soap and water or clean with alcohol-based hand rub. ^{10,11}The most common symptoms of COVID-19 are fever, dry cough, and tiredness. Some patients may have aches and pains, nasal congestion, sore throat or diarrhea. These symptoms are usually mild and begin gradually. Some people become infected but only have very mild symptoms. Most people (about 80%) recover from the disease without needing hospital treatment. Around 1 out of every 5 people who gets COVID-19 becomes seriously ill and develops difficulty breathing. Older people, and those with underlying medical problems like high blood pressure, heart and lung problems, diabetes, or cancer, are at higher risk of developing serious illness. ¹⁵However anyone





can catch COVID-19 and become seriously ill. Even people with very mild symptoms of COVID-19 can transmit the virus. People of all ages who experience fever, cough and difficulty breathing should seek medical attention.

CDC works closely with state and local public health departments, travel industry partners, and others to identify and test people who may be infected with MERS-CoV. CDC conducts several different laboratory tests to detect MERS-CoV infection. In general, these lab tests fall into two categories: Molecular tests, which look for evidence of active infection; and Serology tests, which look for previous infection by detecting antibodies to MERS-CoV.^{13,14} Serology tests are for surveillance or investigational purposes and not for diagnostic purposes. There is no specific treatment for disease caused by a novel coronavirus. However, many of the symptoms can be treated and therefore treatment based on the patient's clinical condition. The antiviral drug remdesivir gained emergency use authorization (EUA) from the FDA on May 1, 2020, based on preliminary data showing a faster time to recovery of hospitalized patients with severe disease. There have been more than 300 clinical trials going on, various antiviral and immunomodulating agents are in various stages of evaluation for COVID-19 in those trials and some of them will be published in the next couple of months. Despite the urgent need to find an effective antiviral treatment for COVID-19 through randomized controlled studies, certain agents are being used all over the world based on either in-vitro or extrapolated evidence or observational studies.^{16,17,18} The most frequently used agents both in Turkey and all over the world including chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir and remdesivir will be reviewed here. Nitazoxanide and ivermectin were also included in this review as they have recently been reported to have an activity against SARS-CoV-2 in vitro and are licensed for the treatment of some other human infections. Hydroxychloroquine and chloroquine have been shown to kill the COVID-19 virus in the laboratory dish. The drugs appear to work through two mechanisms. First, they make it harder for the virus to attach itself to the cell, inhibiting the virus from entering the cell and multiplying within it. Second, if the virus does manage to get inside the cell, the drugs kill it before it can multiply.^{19,20,7} Corticosteroids are not generally recommended for treatment of COVID-19 or any viral pneumonia. [90] The benefit of corticosteroids in septic shock results from tempering the host immune response to bacterial toxin release. The incidence of shock in patients with COVID-19 is relatively low (5% of cases).

EQUIPMENT :-

Table No :- 1
PERSONAL PROTECTIVE
EQUIPMENT (PPE) USED IN TREATMENT OF COVID -19

Sr. No	PPE	SPECIFIC TYPE	CHARACTERISTICS	APPLICATION
1	Disposable medical eye shield		Provides protection from splash, spray, spatter or droplets of blood or other potentially infectious materials.	Health care, biological hazards
2	Face shield		Impact and chemical resistant face shield must be combined with safety glasses or goggles	For use with potential chemical splash or projectiles, apparatus under pressure or vacuum, cryogenics handling
3	Disposable gloves, thin-gauge* (<8 – 10 mils)	Disposable latex glove Disposable nitrile gloves 	Some chemical resistance –consult glove resistance chart, incidental chemical contact only	Working with biological hazards (known or potentially infectious materials including work with animals)
4	Tyvek gown/coveralls		Clothing and skin protection, tear resistant, protection from particulates. Some Tyvek clothing is coated for chemical resistance	Working with biohazards, chemicals, animals or airborne particulates

5	N95 respirator		Protects against dusts, fumes, mists, microorganisms including animal allergens	Dusty environments, working with live animals or potentially infectious materials
6	Thermal cyclers, or PCR machines		The Thermal Cycler (also known as a Thermocycler, PCR Machine or DNA Amplifier) is a laboratory apparatus used to amplify segments of DNA via the Polymerase Chain Reaction (PCR).	PCR is used to monitor and track the spread of infectious disease within an animal or human population. PCR can also be used to detect bacterial and viral DNA in the environment, for example looking at pathogens in water supplies.
	Safety glasses	Non-vented 	Provides protection against the passage of dust, mist, liquid and vapors	Protection from particulates, chemical splash, and mist, liquid and vapors
	Scrubs		Provides a layer of protection for the skin and/or clothing from contact with biological and chemical fluids	Working in clinical, medical and surgical settings as needed

EXPERIMENTAL DEVELOPMENT:-

THERE ARE VARIOUS TEST USED TO DIAGNOSE THE COVID -19

DIAGNOSTICS TESTING FOR COVID-19

Laboratories undertaking testing for COVID-19 virus should adhere strictly to appropriate biosafety practices. virus and includes methods that detect the presence of the virus itself (RT-PCR, isothermal nucleic acid amplification, antigen) and those that detect antibodies produced in response to infection. Detection of antibodies (serological tests) can be used both for diagnosis and for population surveillance. Due to limited testing, as of March 2020 no countries had reliable data on the prevalence of the virus in their population. As of 24 May, countries that publicised their testing data have typically performed many tests equal to 2.6 percent of their population, and no country has tested samples equal to more than 17.3% of its population. There are variations in how much testing has been done across countries. This variability is also likely to be affecting reported case fatality rates, which have probably been overestimated in many countries, due to sampling bias.

Nucleic acid amplification tests (NAAT) for COVID-19 virus:

Routine confirmation of cases of COVID-19 is based on detection of unique sequences of virus RNA by NAAT such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing when necessary.^{21, 25} The viral genes targeted so far include the N, E, S and RdRP genes. Examples of protocols used may be found here. RNA extraction should be done in a biosafety cabinet in a BSL-2 or equivalent facility. Heat treatment of samples before RNA extraction is not recommended.

Serological Testing :

Serology testing is used to detect **previous infection** (antibodies to MERS-CoV) in people who may have been exposed to the virus. Antibodies are proteins produced by the body's immune system to attack and kill viruses, bacteria, and other microbes during infection.

²⁵The presence of antibodies to MERS-CoV indicates that a person had been previously infected with the virus and developed an immune response. Evidence to date suggests there may be a broader range of MERS disease than was initially thought. For example, public health investigators have identified individuals who are PCR-positive but have no MERS symptoms; we do not know if MERS-CoV can be spread by these people. For this reason, public health scientists are working to learn more about how the virus is transmitted. One way to do this is through voluntary testing of blood samples from people who had close contact with people known to have MERS. CDC has a two-phase approach for serology testing, using two screening tests and one confirmatory test to detect antibodies to MERS-CoV. ELISA, or enzyme-linked immunosorbent assay, is a screening test used to detect the presence and concentration of specific antibodies that bind to a viral protein. CDC tests by ELISA for antibodies against two different MERS-CoV proteins, the nucleocapsid (N) and spike (S). If a clinical sample is determined to be antibody-positive by either ELISA, CDC then uses the microneutralization test to confirm the positive result. The microneutralization assay is a highly specific confirmatory test used to measure neutralizing antibodies, or antibodies that can neutralize virus. This method is considered a gold standard for detection of specific antibodies in serum samples. However, compared with the ELISA, the microneutralization assay is labor-intensive and time-consuming, requiring at least 5 days before results are available. If a clinical sample is positive by either ELISA, and positive by microneutralization, the specimen is determined to be confirmed positive.

Viral sequencing :

In addition to providing confirmation of the presence of the virus, regular sequencing of a percentage of specimens from clinical cases can be useful to monitor for viral genome mutations that might affect the performance of medical countermeasures, including diagnostic tests. Virus whole genome sequencing can also inform molecular epidemiology studies. Many public-access databases for deposition of genetic sequence data are available, including GISAID, which is intended to protect the rights of the submitting party.

Viral culture :

Virus isolation is not recommended as a routine diagnostic procedure.

Antigen Test:

On 8 May 2020, the FDA granted the first Emergency Use Authorization for a COVID-19 antigen test: "Sofia 2 SARS Antigen FIA" by Quidel Corp. It is a lateral flow test which uses monoclonal antibodies to detect the virus's nucleocapsid (N) protein. The result of the test is read out by the company's Sofia 2 device using immunofluorescence. The test, simpler and cheaper but less accurate than available PCR tests, can be used in laboratories or in patient care settings and gives results in 15 minutes. A negative test result may occur if the level of antigen in a sample is below the detection limit of the test and should be confirmed with an RT-PCR test.

Antibody Test:

Antibody tests have a low positive predictive value (PPV) when the prevalence in the population of people with antibodies is low. For example, suppose there is a population in which 5% of the people have at some point been infected and so should test positive for antibodies. Select 100 people at random and administer an antibody test that has a specificity of 95%, meaning that 5 people who are actually negative will be expected to test positive. Since 5% of the people actually do have antibodies those five people will also test positive giving us 10 people testing positive, with an incorrect result being returned for half of them. So even though the specificity of the test is high, the PPV of the test in this population is only 50%, [205] and a person would receive as much assurance that he is actually positive by flipping a coin.

Molecular Test:

Molecular tests are used to diagnose active infection (presence of MERS-CoV) in people who are thought to be infected with MERS-CoV based on their clinical symptoms and having links to places where MERS has been reported. Real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays are molecular tests that can be used to detect viral RNA in clinical samples. ²¹CDC's current case definition for laboratory confirmation of MERS-CoV infection requires either a positive rRT-PCR result for at least two specific genomic targets, or a single positive target with sequencing of a second target. Most state laboratories in the United States are approved to test for MERS-CoV by using an rRT-PCR assay developed by CDC. This test is done under authority of an Emergency Use Authorization because there are no FDA-cleared/approved tests available for this purpose in the United States. The success of rRT-PCR testing depends on several factors, including the experience and expertise of laboratory personnel, laboratory environment (e.g., avoidance of contamination), and the type and condition of specimens being tested. For this rRT-PCR assay, CDC recommends collecting multiple specimens, including lower (bronchoalveolar lavage, sputum and tracheal aspirates) and upper (e.g., nasopharyngeal and oropharyngeal swabs) respiratory samples, serum, and stool specimens.

CDC considers a person under investigation to be negative for active MERS-CoV infection following one negative rRT-PCR test on the recommended specimens. Since a single negative result does not completely rule out MERS-CoV infection, in some circumstances additional specimens may be tested.

CDC considers a known MERS patient to be negative for active MERS-CoV infection following two consecutive negative rRT-PCR tests on all specimens.

Swab Test –

In this case, a special swab is used to take a sample from your nose or throat



Fig: Demonstration of a nasopharyngeal swab for COVID-19 testing



Fig: Demonstration of a throat swab for COVID-19 testing

Sputum Test –

Sputum is thick mucus that gets accumulated in the lungs and comes out with a cough. During this test, you're required to cough up sputum in a special cup or a swab is used to take a sample from your nose.

TREATMENT FOR COVID 19:-**1)Interleukin inhibitors:-**

Interleukin (IL) inhibitors may ameliorate severe damage to lung tissue caused by cytokine release in patients with serious COVID-19 infections. Several studies have indicated a “cytokine storm” with release of IL-6, IL-1, IL-12, and IL-18, along with tumor necrosis factor alpha (TNF α) and other inflammatory mediators. The increased pulmonary inflammatory response may result in increased alveolar-capillary gas exchange, making oxygenation difficult in patients with severe illness. On March 16, 2020, Sanofi and Regeneron announced initiation of a phase 2/3 trial of the IL-6 inhibitor sarilumab (Kevzara). The United States-based component of the trial will be initiated in New York. The multicenter, double-blind, phase 2/3 trial has an adaptive design with two parts and is anticipated to enroll up to 400 patients. The first part will recruit patients with severe COVID-19 infection across approximately 16 US sites, and will evaluate the effect of sarilumab on fever and the need for supplemental oxygen. The second, larger, part of the trial will evaluate improvement in longer-term outcomes, including preventing death and reducing the need for mechanical ventilation, supplemental oxygen, and/or hospitalization. Based on the phase 2 trial analysis, the ongoing phase 3 design was modified on April 27, 2020, to include only higher-dose sarilumab (400 mg) or placebo in critical patients (ie, requiring mechanical ventilation or high-flow oxygenation or ICU admission). In the preliminary phase 2 analysis, sarilumab had no notable benefit on clinical outcomes when combining the severe (ie, required oxygen supplementation) and critical groups versus placebo. However, there were negative trends for most outcomes in the severe group, while there were positive trends for all outcomes in the critical group. Phase 2 data for critical patients in the 400-mg group (n=145) compared with placebo (n=77), respectively, included the following:

Change from baseline C-reactive protein level: -79% versus -21%

Died: 23% versus 27%

Remained on ventilator: 9% versus 27%

Clinical improvement: 59% versus 41%

Off oxygenation: 58% versus 41%

Discharged: 53% versus 41%

2)Corticosteroid:-

Corticosteroids are not generally recommended for treatment of COVID-19 or any viral pneumonia. The benefit of corticosteroids in septic shock results from tempering the host immune response to bacterial toxin release. The incidence of shock in patients with COVID-19 is relatively low (5% of cases). It is more likely to produce cardiogenic shock from increased work of the heart need to distribute oxygenated blood supply and thoracic pressure from ventilation. Corticosteroids can induce harm through immunosuppressant effects during the treatment of infection and have failed to provide a benefit in other viral epidemics, such as respiratory syncytial virus (RSV) infection, influenza infection, SARS, and MERS.

Early guidelines for management of critically ill adults with COVID-19 specify when to use low-dose corticosteroids and when to refrain from using corticosteroids. The recommendations depend on the precise clinical situation (eg, refractory shock, mechanically ventilated patients with ARDS); however, these particular recommendations are based on evidence listed as weak.

3)Convalescent plasma

The FDA is facilitating access to convalescent plasma, antibody-rich products that are collected from eligible donors who have recovered from COVID-19. Convalescent plasma has not yet been shown to be effective in COVID-19. The FDA states that it is important to determine its safety and efficacy via clinical trials before routinely administering convalescent plasma to patients with COVID-19.

The FDA has posted information for investigators wishing to study convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of single patient emergency Investigational New Drug (IND) applications for individual patients. The FDA also is actively engaging with researchers to discuss the possibility of collaboration on the development of a master protocol for the use of convalescent plasma, with the goal of reducing duplicative efforts.

The use of convalescent plasma has a long history in the treatment of infectious diseases. Writing in the Journal of Clinical Investigation Casadevall and Pirofski proposed using it as a treatment for COVID-19, and Bloch et al laid out a conceptual framework for implementation. To date, two small case series have been published. These series reported improvement in oxygenation, sequential organ failure assessment (SOFA) scores, and eventual ventilator weaning in some patients. The timelines of improvement varied from days to weeks. Caution is advised, as these were not controlled trials and other pharmacologic methods (antivirals) were used in some patients.

4) Statins

In addition to the cholesterol-lowering abilities of HMG-CoA(3-hydroxy-3-methyl-glutaryl-coenzymeA) reductase inhibitors (statins), they also decrease the inflammatory processes of atherosclerosis. Because of this, questions have arisen whether statins may be beneficial to reduce inflammation associated with COVID-19.

This question has been posed before with studies of patients taking statins who have acute viral infections. Virani] provides a brief summary of information regarding observational and randomized controlled trials (RCTs) of statins and viral infections. Some, but not all, observational studies suggest that cardiovascular outcomes were reduced in patients taking statins who were hospitalized with influenza and/or pneumonia. RCTs of statins as anti-inflammatory agents for viral infections are limited, and results have been mixed. An important

factor that Virani points out regarding COVID-19 is that no harm was associated with statin therapy in previous trials of statins and viral infections, emphasizing that patients should adhere to their statin regimen.

5) Nitric oxide

Published findings from the 2004 SARS-CoV infection suggest the potential role of inhaled nitric oxide (iNO; Mallinckrodt Pharmaceuticals, plc) as a supportive measure for treating infection in patients with pulmonary complications. Treatment with iNO reversed pulmonary hypertension, improved severe hypoxia, and shortened the length of ventilatory support compared with matched control patients with SARS.

6) Hydroxychloroquine

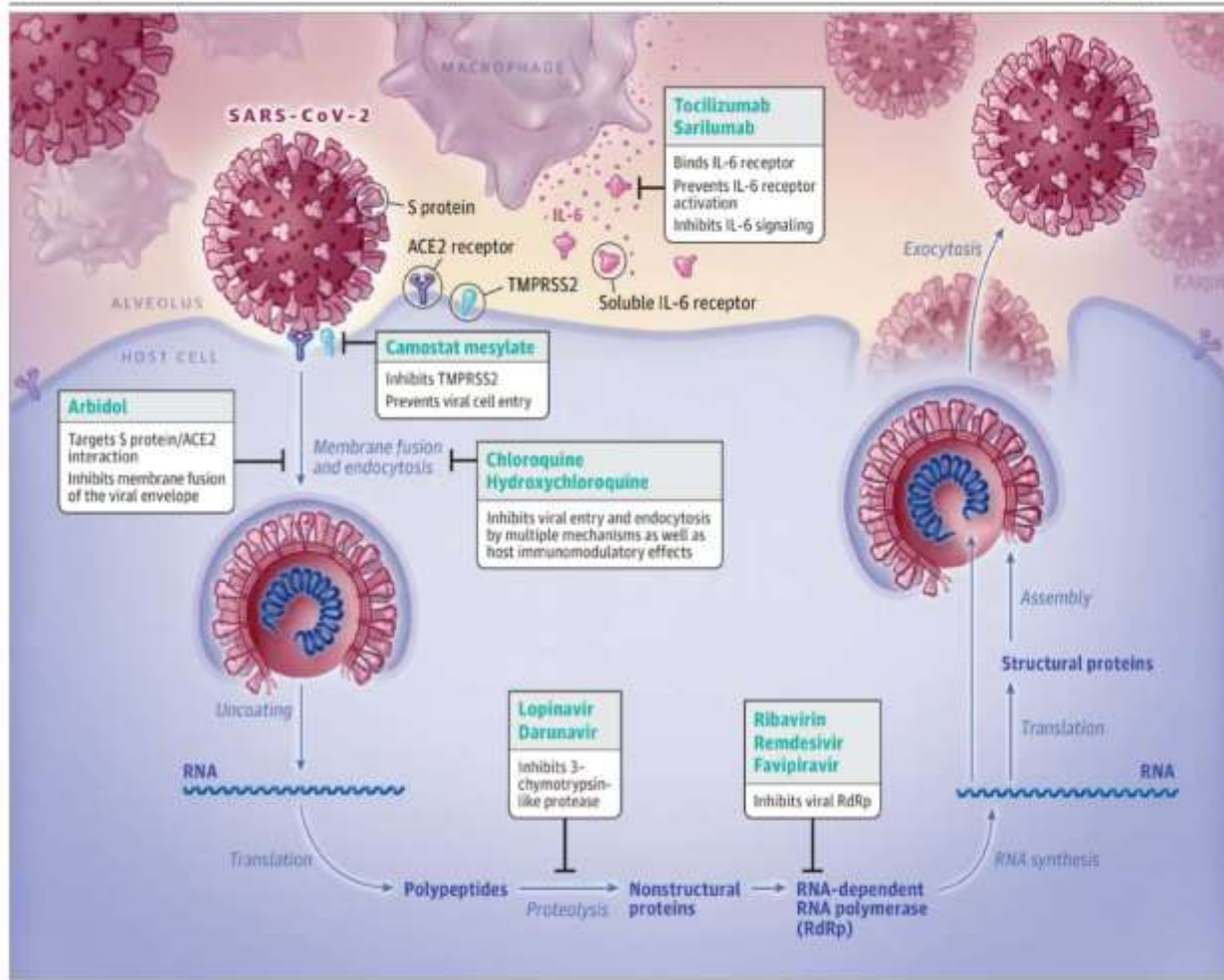
Hydroxychloroquine is an antimalarial drug. It treats malaria by killing the parasites that cause the disease. It isn't fully understood how this drug works to treat lupus erythematosus or rheumatoid arthritis. Hydroxychloroquine (Plaquenil) and its sister drug chloroquine (Aralen) are under investigation for treatment of the COVID-19 coronavirus disease

SARS-CoV-2: Virology and Drug Targets

SARS-CoV-2, a single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein.³ Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles.⁴⁻⁶ These viral lifecycle steps provide potential targets for drug therapy (Figure). Promising drug targets include nonstructural proteins (eg, 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs).



Figure. Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Potential Drug Targets



Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease.

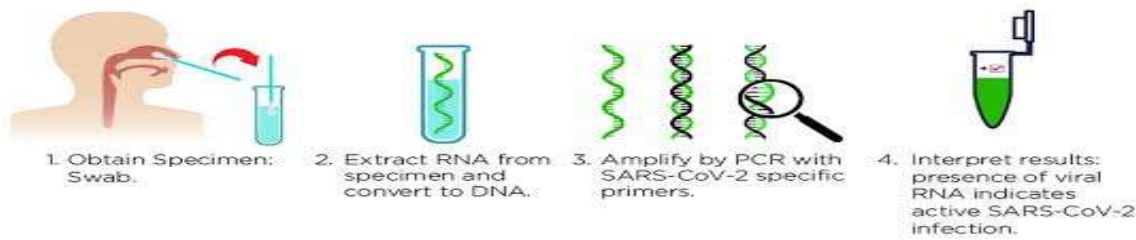
Drugs which are used for treatment of COVID-19

Repurposed Drugs		
No.	Drug	Target
1	Chloroquine Phosphate	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional Immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells
2	Hydroxychloroquine sulphate	Same as Chloroquine
3	Lopinavir/Ritonavir	3CL Protease
4	Umifenovir	S protein/ACE2, membrane fusion inhibitor
Investigational drugs		
No.	Drug	Target
1	Remdesivir	RNA Polymerase inhibitor
2	Flavipiravir	RANA Polymerase inhibitor
Adjuvant therapies		
No.	Drug	Target
1	Tocilizumab	IL-6 inhibition- reduction in cytokine storm

JAMA. doi:10.1001/jama.2020.6019

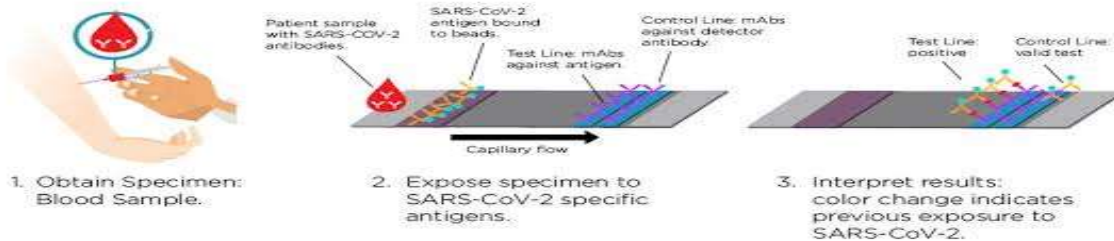
Molecular Tests (Nucleic Acid Detection)

Diagnose active SARS-CoV-2 infections



Antibody Tests (Serology)

Detect immune response to SARS-CoV-2 exposure



RESULT AND DISCUSSION:-

Sr. No.	Tests	Positive test indicates
1	Nucleic Acid Amplification Test (NAAT) for COVID-19	Confirms current SARS-CoV2 Infection
2	Serological Testing	Antibodies to MERS-CoV2, detects previous infection
3	Viral sequencing	Confirms current SARS-CoV2 infection
4	Viral culture	Confirms current SARS-CoV2 infection
5	Antigen Test	Confirms current SARS-CoV2 infection
6	Antibody Test	IgM+ : 3-5 days post onset IgG: Past infection
7		

	Molecular Test	Active infection (presence of MERS-CoV2)
8	Swab test	Infection possible, viral genetic material is present
9	Sputum Test	Infection possible

CONCLUSION:- The accurate diagnosis of people infected with the SARS-CoV-2 is essential to curb the global spread of COVID-19. However, the current RT-PCR based diagnostic assays are not robust, as they are still missing several infected cases. Moreover, they can only be performed in well-equipped central laboratories by highly skilled analysts. Therefore, they are of limited utility and cannot be deployed widely, such as in developing nations, remote locations, and regions with decentralized laboratories. The delay in diagnosing people until after they have passed the disease onto many others is contributing to the continued global spread of COVID-19.

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