

## **SECTION II- CLINICAL FEATURES, DIAGNOSIS AND TREATMENT OF COVID 19**

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## **I. SIGNS AND SYMPTOMS**

The first case of COVID 19 was reported in India on 30<sup>th</sup> January 2020 in Kerala. The clinical features of COVID-19 are varied.

- Ranges from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction.
- The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Thus, they are indistinguishable from other respiratory infections.
- Conjunctivitis has also been described.
- The median time from onset of symptoms to dyspnea was 5 d, hospitalization 7 d and acute respiratory distress syndrome (ARDS) 8 d.

### **A. Progression of Disease**

- In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF $\alpha$  [1]. The need for intensive care admission was in 25–30% of affected patients in published series.

### **B. Complications and Adverse Outcomes:**

- Acute lung injury, ARDS, shock and acute kidney injury.
- Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50–75% of fatal cases).

### **C. Recovery**

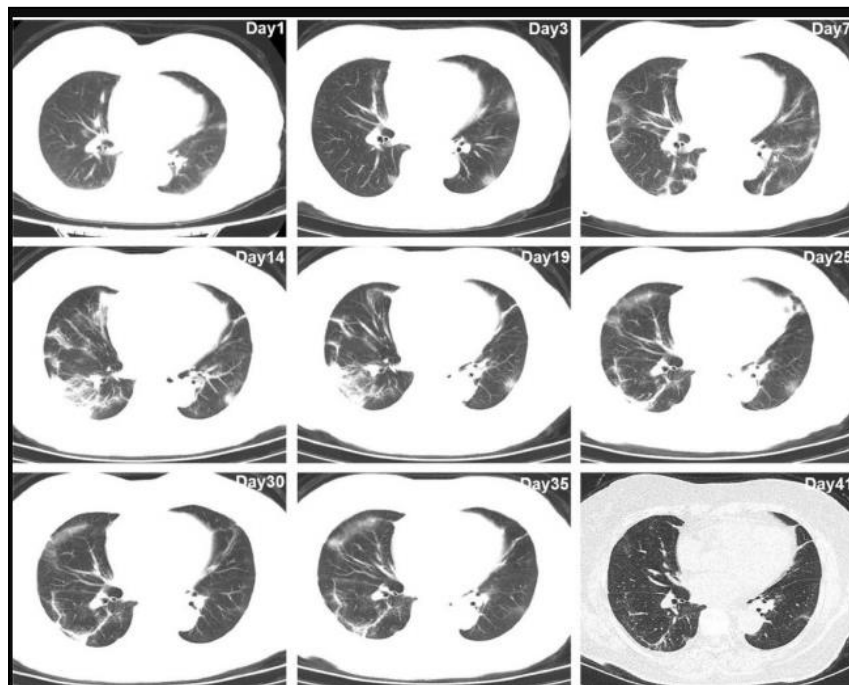
Recovery starts in the 2nd or 3rd wk.

### **D. Fatality**

Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range between 2 and 3% [2].

## II. RADIOGRAPHIC FEATURES

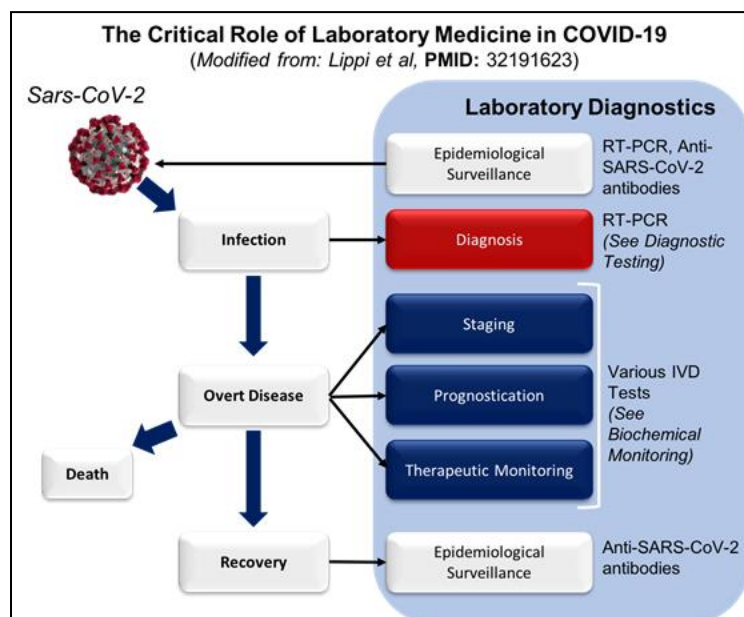
- In general, the radiographic features of coronaviruses are similar to those found in community-acquired pneumonia caused by other organisms [3].
- Chest computed tomography (CT) scan is an important tool to diagnose this pneumonia. Several typical imaging features are frequently observed in COVID-19 pneumonia, including predominant ground-glass opacity (65%), consolidations (50%), smooth or irregular interlobular septal thickening (35%), air bronchogram (47%), and thickening of the adjacent pleura (32%), with predominantly peripheral and lower lobe involvement [4].
- Combining chest CT imaging features with clinical symptom and laboratory tests could facilitate early diagnosis of COVID-19 pneumonia.



### III. LABORATORY FINDINGS

15 labs across India led by National Institute of Virology (NIV) Pune, are leading the testing of COVID19 in India. Centre for Cellular and Molecular Biology (CCMB) are working on genome sequence of COVID 19 in India.

- Laboratory examination revealed that 82.1% of patients were lymphopenic and 36.2% of patients were thrombocytopenic.
- Most patients had normal leukocytes, but leukopenia was observed in 33.7% of patients.
- In addition, most patients demonstrated elevated levels of C-reactive protein, lactate dehydrogenase and creatinine kinase, but a minority of patients had elevated transaminase, abnormal myocardial enzyme spectrum or elevated serum creatinine [5].
- In comparison with bacterial pneumonia, patients with COVID-19 had a lower oxygenation index. Cytokine release syndrome is a vital factor that aggravates disease progression. Higher levels of interleukin (IL)-6 and IL-10, and lower levels of CD4+T and CD8+T have been observed in patients with COVID-19, correlated with the severity of disease [6].



<https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19>

## **Patient Testing References Across Various Countries**

### **I. PCR**

#### **a. Nasal Swab Test – PCR**

##### *i. Details*

1. Achieves quick results
2. Availability has increased significantly in the past several weeks
3. Available in physician offices, testing sites, and hospitals
4. Potential future availability in dental practices in some states, providences, and countries.

##### *ii. Types*

#### **1. LabCorp offers COVID-19 PCR testing (COVID-19 swab test)**

##### **a. Testing performed through a hospital or healthcare provider**

##### **b. Home kit on Pixel by LabCorp™ website**

i. This type of COVID-19 test is for individuals who have COVID-19 symptoms or meet the testing criteria established by the CDC.

ii. LabCorp launched a COVID-19 test on March 5, 2020, for ordering by authorized healthcare providers anywhere in the U.S.

The at-home COVID-19 test kit to detect an active COVID-19 infection is available through Pixel by LabCorp, a platform where patients can access many routine lab tests, and the required physician order, online. The at-home COVID-19 test kit is available to frontline healthcare workers and first responders who complete an eligibility screening questionnaire. Visit Pixel by LabCorp™ to learn more.

##### *iii. Expense – usually covered by medical insurance*

#### **b. Salivary Tests – PCR**

i. Oral DNA company– available to medical and dental practitioners in the US. Test sent to lab for result. This is now readily available and is a 2 level test, saliva and minimally invasive nasal swab. They offer 24-hour turn-around time for results. This gives the practitioner flexibility to test 2-3 days before a long dental appointment. This is highly recommended for long appointments.

ii. Rutgers University group RUCDR Infinite Biologics received an EUA (Emergency Use authorization) from the FDA on April 13, 2020. This test does not have any significant

distribution or availability at the time of preparation of this document. The 60 subjects had identical test results with both the salivary and nasal PCR tests.

iii. MicroGen DX test – Available and will ship to patient’s home after account is set up through [www.microgendx.com](http://www.microgendx.com). Fee is \$99 with 24-hour turn around.

## *II. Antibody Testing*

### *a. Fingertick*

i. Available in many physician offices and to dentists in some states. Currently many questions remain regarding low specificity (more false negatives ranging as high as 30% in some tests).

### *b. Venipuncture blood draw*

i. Available in some physician offices. Hospitals in some states are limiting these tests to health care professionals and some essential public employees due to limited lab capabilities on processing tests.

ii. Serology testing, also known as coronavirus antibody tests, can check for different types of antibodies developed after exposure to the SARS-CoV-2 virus which causes COVID-19. The antibodies include: IgG, IgA and IgM. This type of COVID-19 test is for individuals who think they may have previously had COVID-19 but do not currently have symptoms. Note: antibody testing should not be used as the sole basis to diagnose or exclude infection.

iii. The below labs/tests have excellent specificity/sensitivity numbers.

1. Vibrant American – a national lab that has accounts with many functional medicine/dental practitioners. Blood draw and consult may be done in practitioner’s office or consult only using tele-medicine when the patient is referred to a lab or phlebotomist for blood draw. The consult fee, in office or tele-medicine, is billed to the patient’s medical insurance and the practitioner accepts assignment of benefits from the insurance

company. No deductibles or copayments are charged to the patient for any COVID-19 procedures per the recent federal mandate.

2. Cole Diagnostics is a lab in Idaho that will ship boxes of 10 test kits to a physician or dental office. A dentist or physician must perform or arrange the blood draw and may set up an account online, within the state guidelines of the practice.

3. Abbott Labs has an antibody test being drawn through Quest and LabCorp (and perhaps other labs), requiring a physician referral.

4. LabCorp announced on April 22, 2020, that COVID-19 serological antibody testing was becoming more broadly available to hospitals, healthcare organizations and through its patient service centers, including LabCorp at Walgreens locations.

5. Quest diagnostics, as of April 30, 2020, is offering antibody testing through physician referral.

6. Other – There are also several telehealth providers that offer access to COVID-19 antibody testing without having to go to a doctor's office or other healthcare provider. LabCorp has provided more information about telemedicine providers that can order tests from LabCorp.

[\[https://www.koiscenter.com/wp-content/uploads/2020/06/16-Patient-Testing-References.pdf\]](https://www.koiscenter.com/wp-content/uploads/2020/06/16-Patient-Testing-References.pdf)

#### **IV. DIAGNOSIS**

Rapid and accurate detection of COVID-19 is crucial to control outbreaks in the community and in hospitals. Current diagnostic tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP). According to current diagnostic criteria founded by the China National Health Commission, laboratory examinations, including nasopharyngeal and oropharyngeal swab tests, have become a standard assessment for diagnosis of COVID-19 infection. Automated solutions for molecular diagnostics can handle large numbers of samples and can be scaled to keep pace with fluctuating demand.

The current laboratory test is time-consuming, and a shortage of commercial kits delays diagnosis. For patients suffering from fever, sore throat, fatigue, coughing or dyspnea that is coupled with recent exposure, COVID-19 infection should be diagnosed with typical chest computerized tomography (CT) characteristics despite negative RT-PCR results. COVID-19 belongs to the Coronaviridae family; therefore, it is not surprising that COVID-19 has imaging findings that are similar to those for SARS-CoV and MERS-CoV.

Typical CT findings included bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and peripheral lung distribution. Lung abnormalities on chest CT scan were most severe approximately 10 days after the initial

onset of symptoms . Chest CT scans can be used to assess the severity of COVID-19. COVID-19 also manifests with chest CT imaging abnormalities in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progressed to or co-existed with consolidations within 1-3 weeks. Combining assessment of imaging features with clinical and laboratory findings could facilitate early diagnosis of COVID-19 pneumonia. [7]

### Specimens To Be Collected From The Symptomatic Patients And Contacts [8]

	Test	Type of sample	Timing
Patient	NAAT	Lower respiratory tract - sputum - aspirate - lavage  Upper respiratory tract - nasopharyngeal and oropharyngeal swabs - nasopharyngeal wash/nasopharyngeal aspirate.  Consider stools, whole blood, urine, and if diseased, material from autopsy.	Collect on presentation. Possibly repeated sampling to monitor clearance. Further research needed to determine effectiveness and reliability of repeated sampling.
Patient	Serology	Serum for serological testing once validated and available.	Paired samples are necessary for confirmation with the initial sample collected in the first week of illness and the second ideally collected 2-4 weeks later (optimal timing for convalescent sample needs to be established).
Contact in health-care centre associated outbreaks or other settings where contacts have symptoms, or where asymptomatic contacts have had high-intensity contact with a COVID-19 case.	NAAT	Nasopharyngeal and oropharyngeal swabs.	Within incubation period of last documented contact.
	Serology	Serum for serological testing once validated and available.	Baseline serum taken as early as possible within incubation period of contact and convalescent serum taken 2-4 weeks after last contact (optimal timing for convalescent sample needs to be established).



## **V. TREATMENT**

There is no current evidence from randomized controlled trials (RCTs) to recommend any specific anti-SARS-CoV-2 treatment for patients with a suspected or confirmed COVID-19 infection. 80% patients recover without needing any treatment. On 23<sup>rd</sup> March, National Task Force, for COVID19 constituted by Indian Council of Medical Research recommended the usage of Hydrochloroquine for high risk patients.

Treatment is essentially supportive and symptomatic. The first step is to ensure adequate isolation to prevent transmission to other contacts, patients and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. Routine use of antibiotics and antivirals such as oseltamivir should be avoided in confirmed cases. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated.

Mechanical ventilation and even extra corporeal membrane oxygen support may be needed. Renal replacement therapy may be needed in some. Antibiotics and antifungals are required if co-infections are suspected or proven. The role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS[9], [10].

Detailed guidelines for critical care management for COVID-19 have been published by the WHO [11]. There is, as of now, no approved treatment for COVID-19. Antiviral drugs such as ribavirin, lopinavir-ritonavir have been used based on the experience with SARS and MERS. In a historical control study in patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone.[12] The duration of non-invasive ventilation was 4–22 d [median 9 d] and mechanical ventilation for 3–20 d [median 17 d]. There is anecdotal experience with use of remdesvir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19[13]. More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug

available in Russia and China), intravenous immunoglobulin, interferons, chloroquine and plasma of patients recovered from COVID-19.

Various treatment modalities resorted to treat COVID 19 are:

1. Antiviral drugs
2. Chloroquine and Hydrochloroquine
3. Corticosteroids
4. Antibodies
5. Convalescent plasma transfusion
6. Vaccines

The COVID-19 pandemic is a public health emergency of international concern, and all countries need a coordinated international effort to fight COVID-19. The transmission of pneumonia associated with SARS-CoV-2 has not yet been eliminated. In the absence of vaccines and antivirals, isolation and quarantine are achieving remarkable results. It is necessary to strengthen the monitoring of COVID-19 and to develop drugs and vaccines against the COVID-19 infection as soon as possible. [14]

Drugs	Therapy Strategy Categories	Mechanisms of Therapy	Status
Chloroquine phosphate/ hydroxychloroquine	Anti-malaria anti-viral anti-inflammatory	Increasing endosomal pH, interfering with the glycosylation of cellular receptors of SARS-CoV-2, immunomodulator	FDA approved to be used in an emergency situation, implemented in many treatment protocols
Remdesivir	Antiviral drug (Nucleoside analogue)	Interfering with the viral replication	Investigational antiviral, clinical trials are in progress
Baricitinib	Rheumatoid arthritis (RA) drug, AP2-associated protein kinase 1 (AAK1) inhibitor	Interfering with viral entry by inhibiting one of the endocytosis regulators	FDA approved
lopinavir/ritonavir	HIV protease inhibitor	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication	FDA approved
Darunavir	HIV protease inhibitor	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication	FDA approved
Camostat Mesylate	Transmembrane protease, serine 2 (TMPRSS2) inhibitor	Interfering with viral entry	Japan approved
Favipiravir	Nucleoside analog	Binds to the viral RdRp and reduce its reproduction	Investigational
Cepharanthie, Selamectin, and mefloquine hydrochloride	Anti-viral Anti-inflammatory activities	Significantly reduced cytopathic effects of SARS-CoV-2, and decrease the viral load	Investigational
Ivermectin	Anti-parasite	Inhibits SARS-CoV-2 replication in vitro	FDA approved

## VI. PREVENTION

Since at this time there are no approved treatments for this infection, prevention is crucial. Several properties of this virus make prevention difficult namely, non-specific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery.

Isolation of confirmed or suspected cases with mild illness at home is recommended. The ventilation at home should be good with sunlight to allow for destruction of virus. Patients should be asked to wear a simple surgical mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15–20 min. The greatest risk in COVID-19 is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers [12]. It is important to protect

healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission, infection control measures recommended are those for category A agents (cholera, plague). Patients should be placed in separate rooms or cohorted together. Negative pressure rooms are not generally needed. The rooms and surfaces and equipment should undergo regular decontamination preferably with sodium hypochlorite. Healthcare workers should be provided with fit tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol generating procedures such as intubation, suction and tracheostomies. All contacts including healthcare workers should be monitored for development of symptoms of COVID-19. Patients can be discharged from isolation once they are afebrile for at least 3 d and have two consecutive negative molecular tests at 1 d sampling interval.

This recommendation is different from pandemic flu where patients were asked to resume work/school once afebrile for 24 h or by day 7 of illness. Negative molecular tests were not a prerequisite for discharge. At the community level, people should be asked to avoid crowded areas and postpone non-essential travel to places with ongoing transmission. They should be asked to practice cough hygiene by coughing in sleeve/ tissue rather than hands and practice hand hygiene frequently every 15–20 min.

Patients with respiratory symptoms should be asked to use surgical masks. Whether these efforts will lead to slowing of viral spread is not known. A candidate vaccine is under development.

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