INTERNATIONAL PULMONOLOGIST'S CONSENSUS ON
COVID-19

2nd Edition

Chief Editor

Dr. Tinku Joseph (India)
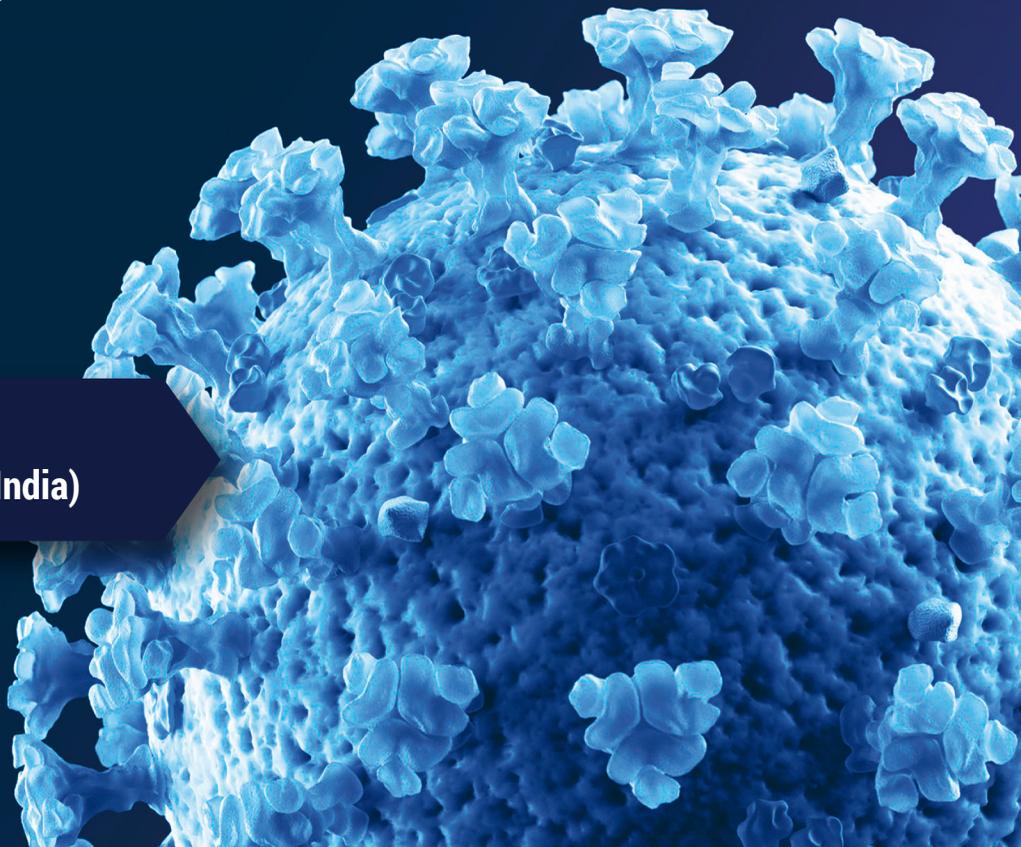
Editors Note

The novel Corona virus disease (COVID-19) has been spreading at a rapid rate across the world, which made World health organization (WHO) to declare it as a pandemic disease. A lot is still unknown about this virus. In view of this Pulmonologist's from different nations affected by this disease joined hands to frame an E-book titled "International Pulmonologist's consensus on COVID-19, which focused on various preventive and treatment strategies. The first edition of E-book was officially published on March 14th 2020 and it was accepted by health care professionals across the world. Inspite of the collective efforts from all human beings we are still finding it difficult to contain the spread of this disease.

Over the past one month a lot has changed in the way we approach COVID-19. In view of this my team of Pulmonologist's regrouped to create a second edition of the E-book and I would like to thank all of them who have contributed immensely in between there busy working hours. Like the first edition, the second one is also made available to everyone at free of cost. Also on behalf of all contributors I would like to dedicate this E-book to every health care worker who has been contributing immensely in the fight against this deadly disease. Let us all join and fight against COVID-19

Dr.Tinku Joseph

Editor in chief
International pulmonologist's consensus on **COVID-19**
Associate Prof. & Interventional Pulmonologist
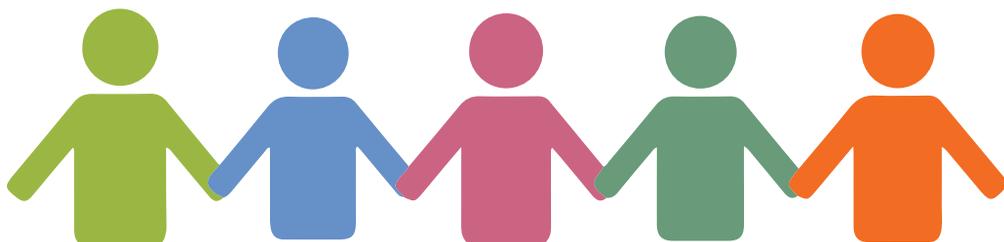Amrita Institute of Medical Sciences, Kochi, Kerala, India

WHAT MAKES A GREAT TEAM?

- Nursing staff
- Medical/Nursing students (Interns/Residents)
- Phlebotomist's
- Respiratory Therapist's
- Radiology & Imaging Technicians
- Pharmacists
- Admission staff
- Physical/occupational/speech therapists
- Coders & Transcriptionists
- Social workers
- Ambulance drivers
- Housekeeping staff
- Ward clerks
- Bronchoscopy & operation theatre staff
- Infection & quality control staff
- Outpatient services
- Dieticians
- Hospital administration staff
- Finance & Accounting team
- Central supply
- Public relations & Marketing team
- Doctors

Together we can. "Never stop. Do your best. Today you are someone's hope and one day someone's hero"

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Contents

1 Introduction

Corona virus comprises of a large family of viruses that are common in human beings as well animals (camels, cattle, cats, and bats). There are seven different strains of corona virus. [1].

- 229E (alpha coronavirus)
- NL63 (alpha coronavirus)
- OC43 (beta coronavirus)
- HKU1 (beta coronavirus)
- MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
- SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
- SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)

Sometimes corona virus from animals infect people and spread further via human to human transmission such as with MERS-CoV, SARS-CoV, and now with this COVID 19 (Corona disease 2019). The virus that causes COVID-19 is designated as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2); previously, referred to as 2019-nCoV.

Towards December 2019, this novel corona virus was identified as a cause of upper and lower respiratory tract infections in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China and then gradually spreading to other parts of the world in pandemic proportions. It has affected almost every continent in this world, except Antarctica. In February 2020, the World Health Organization designated the disease COVID-19, which stands for corona virus disease 2019 [2].

❷ Mode of Transmission

Our understanding of the mode of transmission is currently incomplete. Epidemiologic investigation in Wuhan at the beginning of the outbreak identified an initial association with a seafood market where most patients had worked or visited [2]. The seafood market also sold live rabbits, snakes and other animals. The initial concept was that the virus originated from snakes, however later studies proved that it had more similarity with bats. However, as the outbreak progressed, person-to-person transmission through droplets and fomites became the primary mode of transmission.

Viability of SARS-CoV-2 in aerosols is about 3 hours [5], on plastic and stainless steel for up to 72 hours, on copper up to 4 hours and on cardboard up to 24 hours [6]. The survival for SARS-CoV has been shown to be affected by temperature; a lower environmental temperature favours persistence of virus on surfaces [7]. In a analysis of spread of infection across the globe and its correlation with local environmental conditions it was contemplated that absolute humidity (AH) above 10g/m2 could possible slowdown the transmission of 2019-nCoV [9,10].

Effect of epidemic would depend upon the transmission and the severity of infection. The basic reproduction number (R0 – R naught) is 3 for SARS-CoV-2; which means that 3 new cases are being infected with the virus by the index case [10]. The R0 indicates whether the transmission would be sustained or not; a R0 of less than 1 means that the transmission would die out and a R0 of more than 1 means that it would be sustained.

2A **How does Person-to-person transmission occur?**

Droplet transmission

The virus is released in the respiratory secretions when an infected person coughs, sneezes or talks. These droplets can infect others if they make direct contact with the mucous membranes. Infection can also occur by touching an infected surface and followed by eyes, nose or mouth.

Droplets typically do not travel more than six feet (about two meters) and do not linger in the air. However, given the current uncertainty regarding transmission mechanisms, airborne precautions are recommended routinely in some countries and in the setting of specific high risk procedures. **Patients are thought to be most contagious when they are symptomatic** [7]. **Some spread might be possible before symptoms appear,** but this is not thought to be a common occurrence [4-6].

Extensive environmental contamination from infected patients has been documented in terms of contamination of air vents, door handles, toilet bowl, sink and on personnel protective equipment [4]. Asymptomatic carriers (super spreaders) have been shown to spread the COVID-19. These are cases that have no symptoms and radiological manifestations, but can transmit the virus to others [14].

Close contact is defined as

a) At least 10 minutes within 6 feet (2 meters) of a patient with confirmed COVID-19 [16], or individuals who was exposed to the COVID-19 patient within 2 meters for more than 1 hour within 2 days before the symptom onset of the patient,

b) Cohabiting family members of the COVID-19 patient or suspected patient (17). Also it is essential to assess the duration of exposure and the clinical symptoms of the patient with COVID-19 [18].

The high viral load during the initial days of the illness suggests that **patients could be most infectious during the first week period,** and it might account for the high transmissibility of SARS-CoV-2 and also high viral load at presentation. Older age groups are associated with high viral loads and thereby severe infection [19].

The mean viral load of severe cases is around 60 times higher than mild case, suggesting that poor clinical outcomes might be associated with viral load [20]. This can probably explain the severe infection in healthcare workers.

Other possible modes of transmission

Formite Spread: It may be possible that a person can get COVID-19 **by touching a surface** or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes, but this is not thought to be the main way the virus spreads.

SARS-CoV-2 RNA has been **detected in stools** and persists for long duration in high concentration even if the patient is asymptomatic, this indicates active replication in the gastrointestinal tract, but till now there are no reports of faecal transmission. [14, 21] Further studies are thus, required to document this mode of transmission.

SARS-CoV has already been demonstrated to **survive in infected water and sewage** for weeks [22]. Thus, this mode of transmission should be actively looked into. Since the demonstration of virus in conjunctival secretions has been noted, the possibility of transmission through ocular surfaces has also been contemplated [23]. Adsorption of virus on airborne dust and particulate matter also needs to be investigated for the possible transmission of virus [24].

Though, anecdotal reports of COVID positivity has been reported in newborns, a case series of 9 pregnant patients from Wuhan, China who delivered in January 2020, did not note a **vertical transmission to their newborns** [25, 26, and 27].

Nosocomial transmission is an important source for infection in healthcare professionals including physicians, nursing and paramedical staff during examination, transport, non-invasive ventilation, intubation and bronchoscopy of COVID patients [28].

The policies that have been used in many countries to break transmission are

- Lockdown of infected areas
- Travel restrictions
- Continuous surveillance and active contact tracing [29].
- Quarantine of close contacts is essential, as they may not have symptoms initially but may develop symptoms later on as the incubation period varies from 5-14 days [30].
- To wear a face mask in public on a mandatory basis

③ Epidemiology

Since the first reports of cases from Wuhan, at the end of 2019, more than 80,000 COVID-19 cases have been reported in China; including all laboratory-confirmed cases as well as clinically diagnosed cases in the Hubei Province. Increasing numbers of cases have also been reported in other countries across all continents except Antarctica.

From the discovery of the disease, up to now, more than 509 154 COVID-19 cases have been reported globally, number of cases that tripled compared to last week, and a total of 23,335 deaths have been reported by WHO. In this moment European Region (Italy, Spain, France, Germany, Switzerland) contain more total confirmed cases outside of China, where the virus first spread. Western Pacific region (China, Republic of Korea, Japan, Malaysia, Australia), Eastern Mediterranean Region (with Iran), region of the Americas have also reported a high number of cases **(Figure 1)** [31].

Figure 1: Countries, territories or areas with reported confirmed cases of **COVID-19, 18th April 2020**
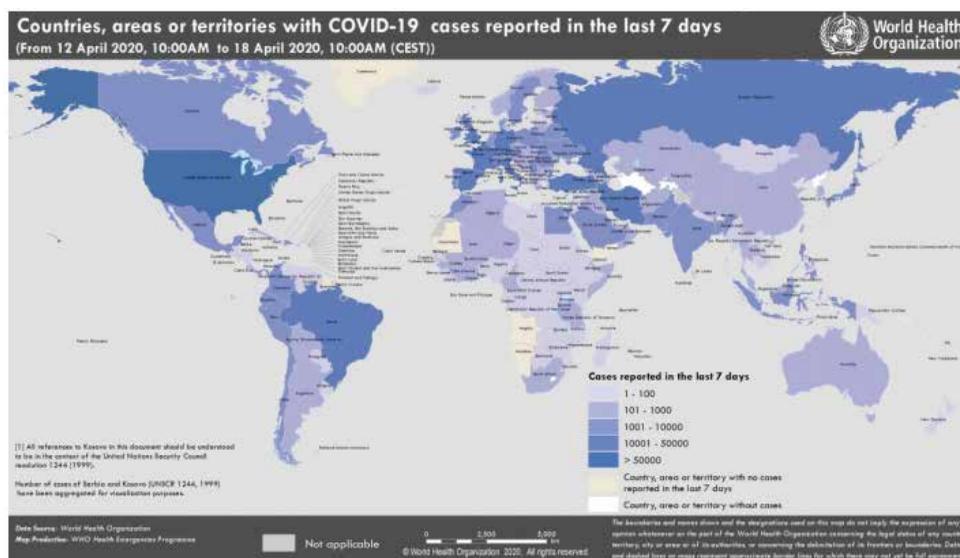
Around 800 cases and 10 deaths have also been reported in passengers travelling on cruise ships [32]. Subsequently the world health organization (WHO) to declare COVID-19 as a pandemic on 12th March 2020. Table 1 gives an estimate of the number of COVID-19 cases; which may be lesser than the actual number as number of asymptomatic individuals is unknown and the testing facilities may vary from region to region [33]. Residents of nursing homes, hospices and elderly homes are more susceptible to the viral infection and are in vulnerable group for severe infection considering age and presence of comorbidities [34].

Health care workers are another susceptible group as they are taking care of severe cases of the infection (likely with high viral loads), close proximity to the case during procedures such as examination, transport, blood sampling, intubation and bronchoscopy. Ancillary reports from China claim 3300 health care professional have been infected and similarly 20% of health care workers from Italy have contracted the infection [35]. With the paucity of personal protective equipment across the globe and long hours of work to deal with extra load on the infrastructure; this risk further increases.

The case fatality rate (CFR) has shown been shown to have a broad range from 0.25-7% may also vary as the denominator comprising of asymptomatic cases is not fully known [10,36]. The case fatality rate is 2-7% depending on age and presence of co-morbid conditions [10,37], especially in the elderly. Preliminary data from United states of America suggest also that younger adult (20-44 years) are 20% hospitalized and 12 % are admitted in ICU [37]. In Italy, the country with a higher mortality rate, 60% of coronavirus cases and 70% of deaths in the country so far have been in men. Similarly 64% mortality in China has also been in men [38].

Further the WHO has shown that the mortality occurring due to COVID-19 was between 2-8 weeks [33]. Thus, the number of deaths may be underestimated. The presentation of the disease is heterogenous with mild disease in 80-95% cases; severe disease is associated with high viral loads (up to 60 times higher in severe versus mild cases) and prolonged viral shedding [20]. The CFR also depends on the age of the patient; early data from United States of America suggest that elderly age group >85 years have 10-27% mortality, 3-11% amongst 65-84 years, 1-3% in 55-64 years and <1% in less than 55 years [40]. Mortality related to disease may be as high as 60% in critically ill patients requiring hospital admission [41].

Table 1: COVID-19 Global case scenario (Source files WHO)

INTERNATIONAL PULMONOLOGIST'S CONSENSUS ON COVID-19		Covid-19 cases	Deaths
1st Edition	March 14st 2020	1,42,543	5392
2nd Edition	April 19th 2020	2,373,850	1,52,551

Globally, as of **2:00am CEST, 19th April 2020**, there have been **2,241,359 confirmed cases** of COVID-19 including **152,551 deaths**, reported to WHO

Confirmed Cases Over Time

2,241,359
confirmed cases
Source: World Health Organization
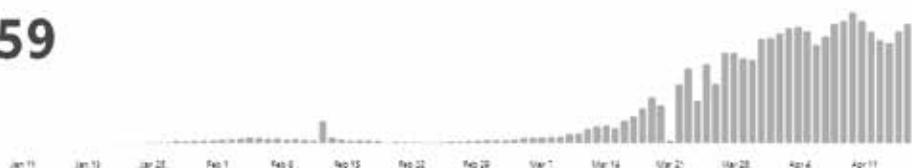
Deaths Over Time

152,551
deaths
Source: World Health Organization

Coronavirus disease (COVID-19) outbreak situation

2 241 359
Confirmed cases

Last update: 19 April 2020, 05:30 GMT+5:30

152 551
Confirmed deaths

Last update: 19 April 2020, 05:30 GMT+5:30

213
Countries, areas or territories with cases

Last update: 19 April 2020, 05:30 GMT+5:30

Case Comparison

WHO Regions

Europe

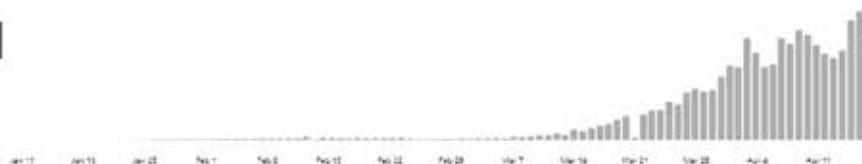|	
Americas	821, 860
	confirmed cases
Western Pacific	130, 696
	confirmed cases
Eastern Mediterranean-	124, 691
	confirmed cases
South-East Asia	27, 319
	confirmed cases
Africa	13, 892
	confirmed cases

④ Pathophysiology of COVID-19

The Coronaviruses are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species. They have a crown-like appearance under an electron microscope (coronam is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. These viruses can also infect humans and cause illness ranging from the common cold to more severe diseases such as MERS, SARS and now Covid-19. To date, seven human CoVs (HCoVs) capable of infecting humans have been identified.

SARS-CoV-2 belongs to the betaCoVs. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm **(Figure 2)**. According to recent research, a spike mutation, which probably occurred in late November 2019, triggered jumping to humans. In particular, Angeletti et al. compared the SARS-Cov-2 gene sequence with that of SARS-CoV. They analyzed the transmembrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3 and found that position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine. [155]

Figure 2: Ultrastructure of SARS CoV-2
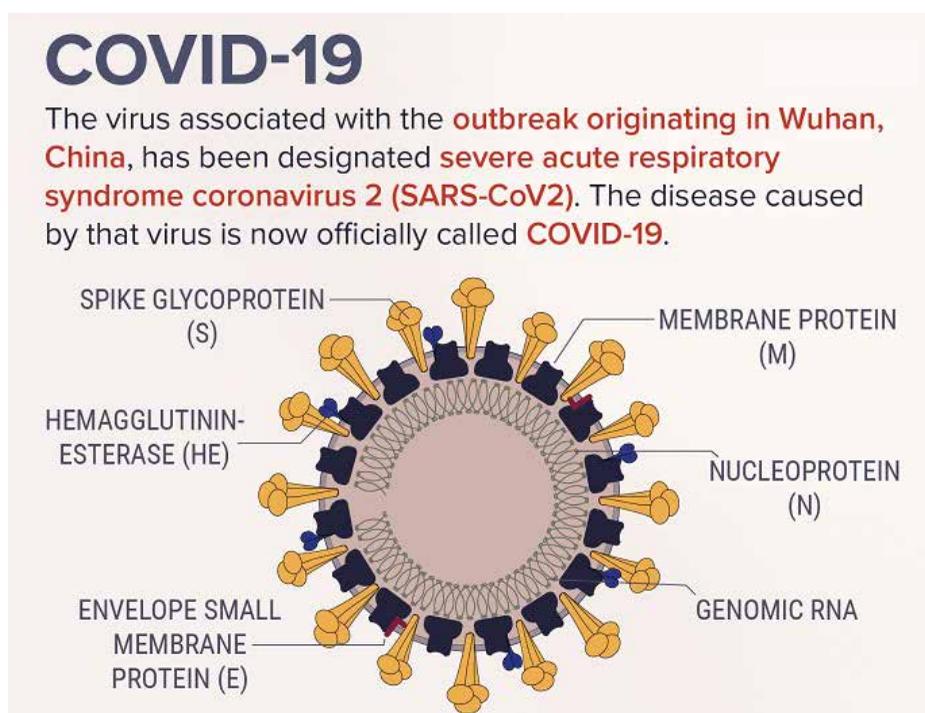
On getting deposited in the nasal and pharyngeal mucus membrane, the virus starts proliferating rapidly and causes Covid-19. The lymphocytes are highly vulnerable to this virus and hence lymphocytopenia is a common feature.

The disease progression can be divided into three distinct phases:

- Early infection phase
- Pulmonary phase
- Severe hyperinflammatory phase

During the **early infection** phase, the initial inflammatory response may cause local symptoms like throat irritation & dry cough and constitutional symptoms like fever, myalgia and headaches. Many patients may be asymptomatic. During this phase, the patient is infective and can transmit the disease. Large number of patients may not progress beyond this phase and recover slowly over a period of 2-6 weeks.

During the **pulmonary phase**, the virus infiltrates the lung parenchyma and begins to proliferate. This stage is characterized by injury to lung parenchyma leading to vaso-dilation, increased endothelial permeability and leukocyte recruitment leading to further pulmonary damage, hypoxemia and cardiovascular stress.

In a subset of patients, the host **inflammatory response** continues to amplify and results in systemic inflammation. This, often labelled as cytokine storm, can injure distant organs. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. This hyperinflammatory response can be confirmed by increased ferritin levels, interleukins and C-reactive protein in the serum.

Interestingly two distinct types of respiratory failure are being recognized. One is ARDS or a **type H patient** that is characterized by high elastance, high right-to-left shunt, high lung weight, and high recruitability. Few case reports of biopsy of involved lungs showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membrane formation, typical of ARDS. [156] These patients may need intubation and benefit from mechanical ventilation with high PEEP.

Another subgroup of patients have been labelled as **type L phenotypes** with lungs having low elastance, low ventilation-perfusion ratio, low lung weight, and low recruitability. These patients are often severely hypoxic without significant dyspnoea. Some have compared this to high altitude mountain sickness kind of presentation. These patients may respond to oxygen therapy alone and may not benefit from high pressure ventilation. [157]

Although the prominent site of infection and hence inflammation is lungs, the amplified inflammatory response can have deleterious effects on other organs, including the heart.
Consistent with this notion, biomarkers of cardiac injury (raised Trop-I and BNP) and electrocardiographic abnormalities correlate with elevated inflammatory markers. SARS-CoV infection appears to down regulate ACE2 receptors, which may contribute to left ventricular dysfunction. There is some evidence of direct myocardial injury as well. Autopsies have conformed mononuclear infiltrates with necrosis thus satisfying criteria for viral myocarditis. [158] Heart may also get stressed secondary to respiratory failure, especially in patients with pre-existing underlying heart disease.

The kidneys often get affected in serious illness, especially ARDS and Covid-19 is no exception. A retrospective study of 201 patients with confirmed COVID-19 pneumonia in China showed that 4.5% developed acute kidney injury (AKI). [159] The cytokine storm alone cannot explain AKI and only a small percentage of ARDS patients developed AKI. Fluid dysregulation, cardiac failure, rhabdomyolysis and sepsis can all contribute to AKI.

5 Clinical Features

5A Incubation period

The incubation period for COVID-19 is thought to be approximately4 to 14 days following exposure [43,44] The average onset from first symptoms to hospitalization is 7 days. [46, 50]

5B Spectrum of severity

In a report from the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed infections with an estimation of disease severity [45]

- Mild (no or mild pneumonia) 81%.
- Severe disease 14%.
- Critical disease 5 %.

In another multi-centre study of 1099 patients, 15.7% of patients met ATS criteria for severe pneumonia [44].The overall case fatality rate was 2.3 percent; no deaths were reported among non-critical cases. This rate rose to 8% in those aged 70-79, 14.8% in those >80 and 49% in those requiring critical care [45].

Co morbidities such as cardiovascular disease, diabetes mellitus, chronic lung disease, hypertension and malignancies are believed to increase the risk of mortality [45].

5C Age

COVID-19 can affect all age groups and asymptomatic infection has been well described. In the large Chinese report, 2 % of infections were in individuals younger than 20 years old. Similarly, in South Korea, 6.3 % of nearly 8000 infections were in those younger than 20 years old [47].

5D Clinical manifestations

Initial presentation

Pneumonia is the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea [49]. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections.

Common clinical features at the onset of illness were [44,50]

- Fever in 88-99 %

- Fatigue in 38-70 %

- Dry cough in 59-68%

- Anorexia in 40 %

- Myalgias in 15-35 %

- Dyspnea in 19-31 %

- Sputum production in 27-34 %

Other, less common symptoms have included

- Headache.

- Sore throat.

- Rhinorrhea.

- Gastrointestinal symptoms (eg, nausea and diarrhea) [46].

Acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease17-29% [46]

5E Complications in ICU patients [46, 50,51]

- Arrhythmias 44%

- Acute cardiac injury 22-31%

- Shock.23-20%

- Acute Kidney Injury8-23%

- Secondary infection 31%

- Cardiomyopathy 33%.

❻ COVID-19 in pediatric population

In this outbreak, **compared with adult cases, there are relatively fewer cases of children, milder symptoms and better prognosis.** Also, children are less frequently exposed to the main sources of transmission. Most infected children recover one to two weeks after the onset of symptoms, and **no deaths had been reported by April 2020.** According to the recent report of the China-WHO Joint Mission Expert Group, the current domestic case data show that children under 18 years of age account for 2.4% of all reported cases, and no deaths have been reported. [52]

6A Probable reasons why children are less affected by COVID-19

1. The time period of the outbreak, is the winter vacation time of the university, middle school and kindergarten. It is a good time for everyone to stay in their own families, which is equivalent to active home isolation. It is a good time to avoid the collective cluster disease by chance.

2. Secondly, humoral and cellular immune development in children is not fully developed. This may be one of the mechanisms that lead to the absence of severe immune responses after viral infection.

3. As COVID-19 virus exploits the ACE2 receptors to gain entry inside the cells, under expression, immaturity of ACE2 receptors in children is another hypothe sis in this regard.

4. Moreover, recurrent exposure to viruses like respiratory syncytial virus in winters can induce more immunoglobulins levels against the new virus infec tion compare to adults. There is no direct evidence of vertical mother-to-child transmission, but newborns can be infected through close contact.

6B Clinical features

In recent studies in china, there was no significant gender difference in children and it was suggested that alleges ranged from 1 day to 18 years were prone to infected by the COVID-19 [53]. The symptoms of COVID-19 are similar in children and adults. However, children with confirmed COVID-19 have generally presented with mild symptoms and usually recover within 1 to 2 weeks. Reported symptoms in children may include cold-like symptoms, such as fever, dry cough, sore throat, runny nose, and sneezing. Gastrointestinal manifestations including vomiting and diarrhea have also been reported.

In the 13 pediatric patients (13/20, 65%) that had an identified history of close contact with COVID-19 diagnosed family members. Fever (12/20, 60%) and cough (13/20, 65%) were the most common symptoms. [52] Children with underlying medi-cal conditions and special healthcare needs may be at higher risk for severe illness. There is much more to be learned about how the disease impacts children.

6C Laboratory findings

In the early stage of the disease, the total number of peripheral white blood cells is normal or decreased, the lymphocyte count is reduced, and some children have increased liver enzymes, lactate dehydrogenase (LDH), muscle enzymes, and myoglobin; some critically ill patients have increased troponin, D-dimer and ferritin and the number of peripheral blood lymphocytes have progressively reduced. Like adults, the children with severe and critical illness may be accompanied by elevated levels of inflammatory factors such as interleukin (IL)-6, IL-4, IL-10, and tumor necrosis factor (TNF)-α. [52]

6D Radiology

There are no abnormal findings in the early stages of the disease in the children's plain X-rays with COVID-19 thus plain X-rays it is not recommended especially in the early stages and in whom without symptoms or any positive risk factors. Suspected cases should undergo chest CT examination as soon as possible. The most important finding in early stages is a single or multiple limited ground-glass opacity which mostly located under the pleura or near the bronchial blood vessel bundle especially in the lower lobes. Severe period is very rare, manifested by diffuse unilateral or bilateral consolidation of lungs and a mixed presence of ground glass opacities [54]. Also compared to adults, consolidation with surrounding halo signs is more common in pediatric patients and was suggested as a typical sign in pediatric patients. [52]

6E Treatment

Mainly supportive; no specific antiviral medications are available for children. For more details please refer to treatment section [page no:]

7 Diagnosis

7A Case Definition [55]

Suspected case

Based on the epidemiologic characteristics observed so far in China, everyone is assumed to be susceptible, although there may be risk factors increasing susceptibility to infection.

1) A patient with acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, shortness of breath) AND with no other aetiology that fully explains the clinical presentation AND with a history of travel or residence in a country/area reporting local or community transmission during the 14 days prior to symptom onset;

OR

2) A patient with any acute respiratory illness AND having been in close contact with a confirmed or probable COVID-19 case in the last 14 days prior to onset of symptoms;

OR

3) A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, fever, shortness breath)) AND requiring hospitalisation (SARI) AND with no other aetiology that fully explains the clinical presentation.

Probable case

A suspected case for whom testing for virus causing COVID-19 is inconclusive (according to the test results reported by the laboratory) or for whom testing was positive on a pan-corona virus assay.

Confirmed case

A person with laboratory confirmation of virus causing COVID-19 infection, irrespective of clinical signs and symptoms

Close contacts

Close contact of a probable or confirmed case is defined as

- A person living in the same household as a COVID-19 case;

- A person having had direct physical contact with a COVID-19 case (e.g. shaking hands);

- A person having unprotected direct contact with infectious secretions of a COVID-19 case (e.g. being coughed on, touching used paper tissues with a bare hand);

- A person having had face-to-face contact with a COVID-19 case within 2 metres and > 15 minutes;

- A person who was in a closed environment (e.g. classroom, meeting room, hospital waiting room, etc.) with a COVID-19 case for 15 minutes or more and at a distance of less than 2 metres;

- A healthcare worker (HCW) or other person providing direct care for a COVID-19 case, or laboratory workers handling specimens from a COVID-19 case without recommended personal protective equipment (PPE) or with a possible breach of PPE;

- A contact in an aircraft sitting within two seats (in any direction) of the COVID-19 case, travel companions or persons providing care, and crew members serving in the section of the aircraft where the index case was seated (if severity of symptoms or movement of the case indicate more extensive exposure, passengers seated in the entire section or all passengers on the aircraft may be considered close contacts). [56]

7B Laboratory Findings

White blood cell count (WBC)

- White blood cell count can vary. It does not provide accurate information about COVID-19. [57]

- Leukopenia, leukocytosis, and lymphopenia have been reported.

- Lymphopenia is more common, seen in more than 80% of patients [57]

- Mild thrombocytopenia is commonly seen. However thrombocytopenia is considered as a poor prognostic sign. [57, 58]

Inflammatory markers

Serum Procalcitonin

- Serum procalcitonin is often normal at the time of admission; however it increases in patients who require ICU care. In one study high D-Dimer and lymphopenia are associated with poor prognosis. [57, 58]

C - reactive protein (CRP)

- COVID-19 increases CRP. This seems to track with disease severity and prognosis. In patients suffering from severe respiratory failure with a normal CRP level an alternative diagnosis should always be sought. [57, 58]

7C Types of diagnostic tests for COVID-19

- Tests to detect the virus
- Tests to detect antibodies to the virus

Patients, who meet the criteria for suspect cases, as discussed above, should undergo testing for SARS-CoV-2 and also other respiratory pathogens.

Table 2: Source file: JAMA. [59]

COVID-19 TESTING POSITIVITY RATES		
Sl No.	**Type of Specimen**	**Positive**
1	Bronchoalveolar lavage fluid	93%
2	Bronchoscopic brush biopsy	46%
3	Sputum	72%
4	Nasopharyngeal swab	63%
5	Oropharyngeal swab	32%
6	Feces	29%
7	Blood	1%
8	Urine	0%

Note

- *Nasal swab will detect only 2/3rd of cases and pharyngeal swabs will detect only 1/3rd of cases and Nasal swab testing is better of two for unadmitted patients.* ***(Table 2)***

- *Preferably avoid performing bronchoscopy for diagnosing COVID-19 (Aerosol generating procedure)*

Respiratory specimen collection from the upper and in particular lower respiratory tract should be performed under strict airborne infection control precautions [60]. Preferably **these samples should be obtained as early as symptom onset, since it yields higher virus concentrations.**

Recommendations for collection of samples for diagnosis of COVID-19

- Collection of specimens to test for SARS-CoV-2 from the upper respiratory tract (nasopharyngeal and oropharyngeal swab) is the preferred method for diagnosis

- Induction of sputum collection is not recommended

- Bronchoscopy being an aerosol generating procedure has got the potential to transmit infection to others. In view of this preferably avoid performing it and limit its usage clearing secretions/mucous plugs in intubated patients [61]

- All respiratory specimen collection procedures should be done in negative pressure rooms

- Additional specimens (eg: Blood, stool, urine) can also be collected to rule out alternative/supportive diagnosis.

- **Specimen collection is very important and any mistake in that will result in false negatives.**

- **Tests to detect the virus**

To date, the diagnostic test of choice during the SARS–CoV-2 outbreak has been polymerase chain reaction (PCR) / Reverse transcriptase polymerase chain reaction (RT-PCR) testing (sequencing of the viral genome). For the past 20 years, PCR has been the gold standard for diagnosing viral infectious agents. Using this technique virus was identified as a novel and unique entity by the Chinese in Wuhan.

Rapid amplification PCR based cartridge platforms, used widely for tuberculosis is now available for various viral diseases including SARS-CoV2. This unique diagnostic tool has the potential of being used as a point of care test.

RT-PCR tests takes about 4 hours to perform and with a single real time PCR machine about 100-120 tests can be done in a day. The cartridge based test can be done in 1-2 hours, but the turnaround is much smaller as many samples cannot be done simultaneously.

Advantages of PCR tests

- Primers needed can be produced on needed basis as soon as the viral sequence is known
- Highly specific(100% specificity)
- Tests becomes positive in the early phase of the disease

Disadvantages of PCR tests

- RT–PCR is complicated, expensive, and is thus mainly suited to centralized refer ence laboratories. The actual test only takes 4-6 hours to complete (given enough supplies and reagents); however, the turnaround time is typically 12-24 hours due to logistic hurdles related to the collection, shipping, and batching of the samples

- Sensitivity may be as low as 50-70%. **Reasons:** Number of viral particles may not be large in some infected patients. The best results are obtained using BAL, how ever being an aerosol generating procedure with a potential for transmitting infection to others this procedure is not been preferred much as a diagnostic modality. Currently more emphasis is given for nasopharyngeal swabs and sputum sample.

- PCR can become negative in the later phases of disease as the patients immunity builds up.

- **Tests to detect antibodies to the virus**

Antibody based tests for SARS-CoV2 has been developed. These are mainly of two types. The standard test is ELISA (Enzyme linked immunosorbent azzay). Rapid tests can be done at the point of care without highly trained personal. Two types of antibodies are tested A) IgM antibody which rises first after infection and it is an indicator for an active infection. B) IgG type of antibody rises later and is an indicative of past infection. [59,60] **(Table 3)**

Advantages of antibody based tests

- It can be used for the rapid screening of SARS-CoV-2 carriers, symptomatic or asymptomatic, in hospitals, clinics, and test laboratories.

- COVID-19 Rapid Test qualitatively detects IgG and IgM antibodies to in human whole blood, serum and plasma samples

- The IgM-IgG combined assay has better utility and sensitivity compared with a single IgM or IgG test

- Antibody based tests are cheaper and the results are faster

- Specificity is also food for a screening test

Disadvantages of antibody based tests

- Negative in the early phase of the disease. IgM titers starts to rise only 3-7 days after the onset of symptoms

- The specificity of the test can also be a concern when it is used primarily as a standard diagnostic test.

Figure 3: COVID-19 Rapid Test kit

Table 3: Rapid point of care testing for SARS CoV-2

Rapid point of care testing for SARS CoV-2				
Biomerica	California, USA	Rapid POC IgM/IgG antibody test	lateral flow immunoassay	Commenced shipping samples; seeking FDA EUA approval
Caspr Biotech	California, USA	Ultrasensitive, rapid, and portable coronavirus SARS-CoV-2 sequence detection	Based on CRISPR-Cas12	Proof of principle evaluation
Cepheid	California, USA	Xpert Xpress SARS-CoV-2	Rapid PCR test that runs on GenXpert benchtop system – delivers result in two hours from sample collection to delivery of result	Received FDA emergency use authorization
Guangzhou Wondfo Biotech	Guangzhou, China	Wondfo SARS-CoV-2 antibody test	Lateral flow 15-minute immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	National Medical Products Administration EUA in China; CE mark in Europe
Innovita Biological Technology	Hubei, China	SARS-CoV-2 antibody assay	Lateral flow 15-minute immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	National Medical Products Administration EUA in China
Jiangsu Medomics Medical Technologies	Nanjing, China	SARS-CoV-2 rapid combined IgM/IgG antibody test kit	Lateral flow 15-minute immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	Shipping
Mammoth Biosciences	Massachusetts, USA	SARS-CoV-2 DETECTR	30-minute lateral flow assay	In validation studies
Pharmact	Berlin, Germany	SARS-COV-2 Rapid Test	POC 20-minute test for detecting SARS-CoV-2 exposure through identification of IgG and IgM antibodies	CE-marked and shipping
Sherlock Biosciences, Cepheid	California, USA	Rapid CRISPR-based tests for SARS-CoV-2 and other pathogens	Combines SHERLOCK Cas12 and Cas13 enzymes for nucleic acid detection witCepheid's's GeneXpert test-processing instruments	Intended as proof of concept for a broad product development alliance in infectious disease

Snibe Diagnostic	Shenzhen, China	MAGLUMI 2019-nCoV IgM/IgG kit	Automated central laboratory rapid test that runs on MAGLUMI chemiluminescence immunoassay system	CE mark received 19 February 2020
Sona Nanotech	Halifax, Nova Scotia	Rapid SARS-CoV-2 antigen detection test	Lateral flow screening test for S1 domain of SARS-CoV-2 S1 protein	Assay development and testing with GE Healthcare Life Sciences underway
Sugentech	Daejeon, South Korea	SGTi-flex COVID-19 IgM/IgG	Ten-minute lateral flow immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	CE Mark
Xiamen AmonMed Biotechnology	Fujian, China),	COVID-19 IgM/IgG test kit (Colloidal gold)	Ten-minute lateral flow immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	CE Mark
Zhejiang Orient Gene Biotech	Zhejiang, China)	COVID-19 IgG/IgM Rapid Test	Solid-phase immunochromatographic assay	Aytu Bioscience has sublicensed US distribution rights from L.B. Resources (Hong Kong) and plans to obtain EUA; already has CE mark
Voxtur Bio Ltd	India	COVID-19 IgG/IgM Rapid Test	Ten-minute lateral flow immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	Indian Council of Medical Research (ICMR) approved
HLL life care limited	India	Makesure COVID-19 rapid test kit	POC 20-minute test for detecting SARS-CoV-2 exposure through identification of IgG and IgM antibodies	ICMR approved
Vanguard diagnostics	India	COVID-19 IgM/IgG Antibody Detection Card Test	Ten-minute lateral flow immunoassay that detects IgM and IgG antibodies directed against SARS-CoV-2	ICMR approved
Accucare Lab-care diagnostics	India	IgM/IgG Lateral Flow Assay kit	Lateral flow screening test for S1 domain of SARS-CoV-2 S1 protein	ICMR approved

Current Recommended Diagnostic Modality For Covid 19

- Use RT-PCR as the primary diagnostic modality for detecting SARS-CoV-2 RNA
- A single positive test should be confirmed by a second RT-PCR assay targeting a different SARS-CoV-2 gene
- If initial testing is negative but the suspicion for COVID-19 remains, the WHO recommends re-sampling and testing from multiple respiratory tract sites
- Point of care cartridge PCR may be used in centers where it is available.
- Antibody based tests need not be used as a primary diagnostic test. The main use of antibody tests would be to study the incidence and prevalence of the disease and local outbreaks
- For safety reasons, specimens from a patient with suspected or documented COVID-19 should not be submitted for viral culture.
- Respiratory & serum samples should also be tested for other viral/bacterial pathogens.

7D Bronchoscopy

Deciding the need for bronchoscopy during COVID-19 pandemic is tricky. Bronchoscopist's should be wise enough in choosing any procedure (Risk versus Benefit ratio should be considered). Bronchoscopy being an aerosol generating procedure has the potential to transmit infection to others. Need for all procedures should be reviewed case by case basis and if not an urgent one it should be rescheduled based on clinical priorities **(Table 4-7)**

Broad screening protocol should be followed prior to scheduling any Bronchoscopic procedure. Patients should be asked about symptoms, contacts and history of travel to COVID-19 zones. If any of these criteria is met, then the procedure needs to be rescheduled or a nasopharyngeal swab test should be done.

Table 4: Indications for Emergency Bronchoscopic procedure

Indications for Emergency Bronchoscopic procedure *(To be performed on same day)*	
1	Symptomatic central airway obstruction: • Mass • Foreign body • Mucous plug
2	Massive Haemoptysis
3	Symptomatic Tracheal stenosis
4	Migrated stent (Silicon/metallic)

Table 5: Indications for semi-urgent Bronchoscopic procedure

	Indications for Semi urgent Bronchoscopic procedure *(can wait for 2 to 4 days, preferably send a swab to rule out COVID-19 infection)*
1	Evaluation of lung mass or nodule (Diagnosis/staging)
2	Evaluation of Mediastinal lymphadenopathy
3	Whole lung lavage
4	Suspected pulmonary infection in immunocompromised patients
5	Post lung transplant recipients – Evaluation of Bronchiolitis obliterans syndrome
6	Suspected pulmonary infection in bone marrow/solid organ transplant
7	Evaluation of lobar atlectasis

Table 6: Indications for elective Bronchoscopic procedure

	Indication for Elective Bronchoscopy (Re-schedule till your locality is free of COVID-19)
1	Bronchial Thermoplasty
2	Tracheobronchomalacia evaluation
3	Cryobiopsy for histopathological confirmation of etiology of DPLD
4	Bronchoscopic lung volume reduction procedures

RIGID BRONCHOSCOPIC PROCEDURES DURING COVID-19

- Performing any rigid Bronchoscopic procedure carries a high risk of transmission of infection (Open circuit, excessive air leak through the side of rigid tube due to absence of cuff) compared to endotracheal tube. Also most of the rigid Broncho scopic procedures are prolonged ones.

- Until COVID-19 pandemic ends all rigid Bronchoscopic procedures should be performed by the highly skilled team member as it saves time and there by reduces the chance of transmission of infection.

- Powered Air purifying Respirators (PAPR) kit is the ideal PPE while performing any rigid Bronchoscopic procedure (prolonged) as it avoids breathing resistance/suffo cation and moisture build up associated with using N95 mask along with goggles/ face shield.

Table 7: IIndications for Bronchoscopy in COVID-19 suspected/confirmed cases

	Indications for Bronchoscopy in COVID-19 suspected/confirmed cases
1	**Relatively contraindicated**
2	For swab and sputum negative patients who are strong clinical suspects
3	For patients who are on mechanical ventilator: Mucous plug clearance
4	Evaluation for alternative infection
5	To rule out differentials of non –resolving pneumonia
6	Massive haemoptysis – airway interventions

Essential steps to be followed if bronchoscopy is needed in COVID-19 suspect/confirmed case

- Avoid performing bronchoscopic procedures under conscious sedation(high chance for dissemination of aerosols when patient coughs)
- Preferably do all bronchoscopic procedures under general anesthesia (patient should be sedated & paralysed) since it avoids dissemination of aerosols to a certain extend.
- Consider using a disposable bronchoscope if available, especially in an ICU care setting.
- All Bronchoscopic procedures (COVID-19) should be performed in negative pressure isolation rooms
- Minimize the staff for all bronchoscopic procedures and avoid training your fellows, since it increases the procedure duration.
- All personnel should use standard PPE kits during bronchoscopy and Powered Air purifying Respirators (PAPR) are preferred for prolonged rigid Bronchoscopic procedures.
- Use of safety/ aerosol box have been used at many centers in the world to add extra protection from COVID-19, while performing aerosol generating procedures
- Donning & doffing protocols of PPE should be strictly followed
- Standard disinfection protocols should be followed for cleaning your flexible/rigid bronchoscopes, electrosurgical equipments and video monitors

Recommendations for performing bronchoscopic procedures during COVID-19
[61, 160,161]

- Bronchoscopy is not considered as a diagnostic modality for COVID1-9. Being an aerosol generating procedure performing bronchoscopy has got a high potential for transmission of infection

- Primary/Preferred method for diagnosing COVID-19 is evaluation of nasopharynge al/oropharyngeal swab and sputum analysis

- Always evaluate the need for bronchoscopy & grade them according to risk/benefit ratio (Emergency/semi-urgent & elective)

- Avoid performing bronchoscopic procedures under conscious sedation(high chance for dissemination of aerosols when patient coughs)

- Preferably do all bronchoscopic procedures under general anesthesia (patient should be sedated & paralysed) since it avoids dissemination of aerosols to a certain extend.

- Consider using a disposable bronchoscope if available, especially in an ICU care setting.

- All Bronchoscopic procedures (COVID-19) should be performed in negative pressure isolation rooms

- Minimize the staff for all bronchoscopic procedures and avoid training your fellows, since it increases the procedure duration.

- All essential personal protective equipments (PPE) should be used by health care professionals performing any bronchoscopic procedure.

- Donning & doffing protocols of PPE should be strictly followed

- Standard disinfection protocols should be followed for cleaning your flexible/rigid bronchoscopes, electrosurgical equipments and video monitors.

- Rigid Bronchoscopic procedures carries maximum risk of transmission of infection and hence it should be performed only by a highly skilled individual (shortens the procedure duration)

- Powered Air purifying Respirators (PAPR) kit is the ideal PPE while performing any rigid Bronchoscopic procedure (prolonged) as it avoids breathing resistance/suffo cation and moisture build up associated with using N95 mask along with goggles/ face shield.

- Be wise in choosing any bronchoscopic procedure

7E Radiology In Covid-19 Infection

The findings on chest imaging are not specific of the infection, and could overlap with other entities. There are also recommendations about the performance of the chest radiography, including the fact that it is better to avoid the movement of the patient within the hospital.

Chest Radiography (CXR).

The findings on CXR are not specific, and in the initial phases of the disease the studies could be normal. The most common features include lobar/ multi-lobar / bilateral lung consolidation. [62]

Computed Tomography (CT Chest).

Recent studies have reported the features on CT imaging. Pan et al [63] described the tomographic changes of 21 patients with mild to moderate disease who recovered from the disease, and they describedfour stages

- **Early stage** (0-4 days after the onset of the symptoms), in which ground glass opacities (GGO) are frequent, with sub-pleural distribution and involving predominantly the lower lobes. Some patients in this stage could have a normal CT.

- **Progressive stage** (5-8 days after the onset of the symptoms), the findings usually evolved to rapidly involvement of the two lungs or multi-lobe distribution with GGO, crazy-paving and consolidation of airspaces.

- **Peak stage** (9-13 days after the onset of the symptoms), the consolidation becomes denser and it was present in almost all of the cases. Other finding was residual parenchymal bands.

- **Absorption stage** (>14 days after the onset of the symptoms), no crazy paving pattern was observed, the GGO could remain.

Shi et al [64] also described the CT findings in 81 patients in Wuhan, China. All of the patients had an abnormal CT, and the features include: GGO, smooth and irregular interlobular septal thickening, crazy paving pattern, air bronchogram and irregular pleural thickening. Usually affecting the subpleural regions and the lower lobes.

The Radiological Society of North America (RSNA) Expert Consensus Statement on reporting chest CT Findings related to COVID-19 was released on March 25th 2020, in order to standardize the reports. [65] They proposed four COVID-19 imaging classifications. **(Table 8)**

- Typical appearance
- Indeterminate appearance
- Atypical appearance
- Negative for pneumonia.

Table 8: The Radiological Society of North America (RSNA) Expert Consensus
Statement on reporting chest CT Findings related to COVID-19

COVID-19 penumonia imaging classification	CT Findings	Suggested Reporting Language
Typical Appearance	Peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy paving") Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy paving") Reverse halo sign or other findings of organizing pneumonia	"Commonly reported imaging features of (COVID-19) pneumonia are present. Other processes such as influenza pneumonia and organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern."
Indeterminate Appearance	Absence of typical features AND Presence of: Multifocal, diffuse, perihiliar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral. Few very small GGO with a non-rounded and non-peripheral distribution	"Imaging features can be seen with (COVID-19) pneumonia, though are nonspecific and can occur with a variety of infectious processes".
Atypical Appearance	Absence of typical or indeterminate features AND Presence of: Isolated lobar or segmental consolidation without GGO Discrete small nodules (centrilobular, "tree in bud") Lung cavitation Smooth interlobular septal thickening with pleural effusion	"Imaging features are atypical or uncommonly reported for (COVID-19) pneumonia. Alternative diagnoses should be considered."
Negative for Pneumonia	No CT features to suggest pneumonia	"No CT findings present to indicate pneumonia." (Note: CT may be negative in the early stages of COVID-19).

Recommendations

- CT chest is not a substitute for RT-PCR, consider testing according to local recommendations and procedures for and availability of RT-PCR

- Routine screening CT for diagnosis or exclusion of COVID-19 is currently not recommended by most professional organizations.

Lung ultrasound. (USG)

The USG findings are also not specific for COVID-19 infection. Little information is available to date on this matter. The findings include: Irregular pleural lines, sub-pleural areas of consolidation, areas of White lung and thick B lines [66]. It is a tool that could be used at bed side avoiding the need for shifting infected patients to a Radiology suite [67].

7F Pulmonary Function Tests (PFT)

Sources of cross infection in pulmonary function lab can occur due to close contact, direct contact and through aerosolized particles. Among these Droplets/aerosolized particles is the most common mode of transmission of infection. Numerous factors play a role in the virulence of an organism: source & strain of pathogen, route of infectivity, particle size, room temperature and infective dose of pathogen. [68,69]

Recommendations

- **All kinds of pulmonary function tests should be avoided among patients with a strong suspicion of upper or lower Respiratory tract infection.**

- **In COVID 19 endemic zones it would be wise to avoid PFTs for a major propor tion of patient to avoid spread of infection and usage of PFT should be limited for time being for only pre-operative fitness assessment.**

- All patients who are enrolled to perform a PFT should be segregated, since this helps in preventing the spread of infection. Performing a chest x-ray prior to PFT would help to rule out Respiratory infections to certain extent. [68]

- Contact in waiting room with potentially infectious patients should be minimized. Surgical facemasks, tissues, and waste container, alcohol-based sanitizers -should be made easily available for infectious patients.

- All connections between the patient and the PFT machine (tubing's & valves) should be cleaned and disinfected before re-use.

- Disposable items in PFT lab like mouth pieces can be a reservoir of microorganisms and hence should be disposed carefully.

- Usage of personal protective equipments helps in reducing the risk of cross contamination.

Table 9 : Investigations to be done for all hospitalized COVID-19 patients (Confirmed/Suspected)

Investigations to be done for all hospitalized COVID-19 patients (Confirmed/Suspected)	
Lab parameters to be assessed	CBC, RFT, LFT, metabolic panel, CPK
Viral serologies	HIV,HBV, HCV panel
For risk stratification (may be repeated every 2-3 days if abnormal or in case of clinical deterioration)	• D-dimer • Ferritin • Procalcitonin • CRP/ESR • LDH • ECG and Cardiac enzymes
Blood cultures -2 sets (Aerobic& Anaerobic bacterial)	To be done if clinically indicated
SARS CoV-2 test (Nasopharyngeal swab/sputum)	A single positive test should be confirmed by a second RT-PCR assay targeting a different SARS-CoV-2 gene
Sputum bacterial culture (aerobic) Induced sputum (to be avoided)	To be send at the time of admission Anaerobic culture: Only if indicated
Respiratory viral panel	Send if available
AFB smear/Gene Xpert/Fungal culture	In case of clinical suspicion
Atypical pneumonia panel	In case of clinical suspicion
Radiology	• Portable chest x-ray to be done at the time of admission and can be repeated every 3 day/ in case of clinical deterioration • CT Chest: Has got limited role. No specific pattern is seen in COVID-19. Indicated in case of non-resolving pneumonia to rule out alternative pathologies
Bronchoscopy	Avoid using for diagnosing COVID-19 (aerosol generating procedure) **Indications:** • Mucous plug clearance in ventilated patients • Lung malignancies (diagnose & stage) • Haemoptysis • Foreign body aspiration
IL-6	In case of clinical deterioration/features suggestive of ARDS. IL-6 levels needs to be assessed to rule out cytokine release syndrome
Immunocompromised patients	Rule out Pneumocystis infection Sputum: Quantitative PCR Avoid induced sputum. If patient cannot expectorate sputum, send blood for β-D-glucan

8 **Initial Management**

8A COVID-19 Infected Patients

At the moment, the therapeutic strategies to deal with the infection are only supportive, and prevention aimed at reducing transmission in the community is our best weapon. Aggressive isolation measures in China have led to a progressive reduction of cases in the last few days. In Italy, in geographic regions of the north, political and health authorities are making incredible efforts to contain a shock wave that is severely testing the health system.

8B Who All Needs Isolation?

1. Any person diagnosed with SARS CoV 2 infection by means of laboratory testing at a government recommended testing laboratory.

2. Anyone who has symptoms of fever and respiratory illness, and has a history of close contact of a person who has either been diagnosed as COVID-19, or has a history of travel to a COVID affected region within the last 14 days.

3. Any health care worker with symptoms of fever and respiratory illness who has been involved directly in treating COVID- 19 patients, or has close contact with persons involved in treating COVID- 19 patients during the last 14 days.

8C If Needed Where To Isolate?

- Asymptomatic cases with exposure to Covid-19 positive patients can be quaran tined at their homes, but to be under strict surveillance by the government authorities

- Suspected patient to be isolated in well ventilated, preferably separate rooms.

- Symptomatic COVID- 19 positive patients should be hospitalized in isolation room and also should be monitored adequately by medical team

- Sputum/BAL samples (if needed) should be collected from isolation rooms or a separate space with HEPA filters/negative pressure ventilation

8D Preparation Of Isolation Room

- Ensure that appropriate hand washing facilities and hand-hygiene supplies are available.

- Stock the sink area with suitable supplies for hand washing, and with alco hol-based hand rub, near the point of care and the room door.

- Ensure adequate room ventilation

- Post signs on the door indicating that the space is an isolation area.
- All Avisitors should consult the health-care worker in charge before being allowed into the isolation areas. Keep a roster of all staff working in the isolation areas, for possible outbreak investigation and contact tracing. Some centers have banned all visitors.
- Remove all non-essential furniture and ensure that the remaining furniture is easy to clean.
- Stock the PPE supply and linen outside the isolation room or area (e.g. in the change room). Setup a trolley outside the door to hold PPE. A checklist may be useful to ensure that all equipment is available.
- Place appropriate waste bags in a bin. If possible, use a touch-free bin. Ensure that used (i.e. dirty) bins remain inside the isolation rooms.
- Place containers for disposal of sharps inside the isolation room or area.
- Keep the patient's personal belongings to a minimum.
- Dedicate non-critical patient-care equipment (e.g. stethoscope, thermometer, blood pressure cuff and sphygmomanometer) to the patient, if possible. Thoroughly clean and disinfect patient-care equipment every time before using in next patient.
- Adequate equipment required for cleaning or disinfection inside the isolation room should be kept and room should be cleaned on a daily basis
- Set up a telephone or other method of communication in the isolation room or area to enable patients, family members or visitors to communicate with health-care workers. This may reduce the number of times the workers need to don PPE to enter the room or area.

8E Wearing And Removing Personal Protective Equipment (PPE)
Before entering the isolation room or area:

- Collect all necessary items.
- Ensure to perform hand hygiene with an alcohol-based hand rub or soap and water;
- Use PPE in the order that ensures adequate placement of PPE items and prevents self-contamination and self-inoculation while using and taking off PPE.
- **Figure 4 & 5** illustrates an example of the order in which to don PPE and what all are required.

Figure 4: Steps of putting personal protective equipments

A. Putting on PPE (when all PPE items are needed)

1
- Identify hazards and manage risk.
- Gather the necessary PPE.
- Plan where to put on and take off PPE.
- Do you have a buddy? Mirror?
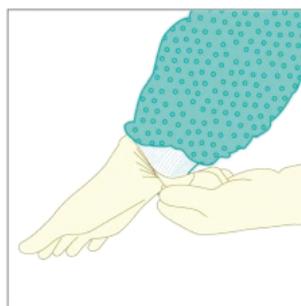- Do you know how you will deal with waste?

2　　Put on a gown.

3　Put on particulate respirator or medical mask; perform user seal check if using a respirator.

4　Put on eye protection, e.g. face shield/goggles (consider anti-fog drops or fog-resistant goggles). Caps are optional: if worn, put on after eye protection.

5　Put on gloves (over cuff).

Figure 5: Steps of removing personal protective equipments

B. Taking off PPE

1
- Avoid contamination of self, others and the environment.
- Remove the most heavily contaminated items first.

Remove gloves and gown:
- peel off gown and gloves and roll inside, out;
- dispose of gloves and gown safely.

2   Perform hand hygiene.

3
- Remove cap (if worn).
- Remove goggles from behind.
- Put goggles in a separate container for reprocessing.

4   Remove respirator from behind.

5   Perform hand hygiene.

8F Leaving The Isolation Room Area

- Either remove PPE in the anteroom or, if there is no anteroom, make sure that the PPE will not contaminate either the environment outside the isolation room or area, or other people.

- Remove PPE in a manner that prevents self-contamination or self-inoculation with contaminated PPE or hands. General principles are:

- Remove the most contaminated PPE items first;

  - Perform hand hygiene immediately after removing gloves

  - Remove the mask or particulate respirator last (by grasping the ties and discarding in a rubbish bin);

  - Discard disposable items in a closed rubbish bin;

  - Put reusable items in a dry (e.g. without any disinfectant solution) closed container; an example of the order in which to take off PPE when all PPE items are needed is gloves (if the gown is disposable, gloves can be peeled off together with gown upon removal), hand hygiene, gown, eye protection, mask or respirator, and hand hygiene

  - Perform hand hygiene with an alcohol-based hand rub (preferably) or soap and water whenever ungloved hands touch contaminated PPE items.

8G Patient In Isolation Room

- Preferably wear face mask as much as time possible in a day

- Restrict movement of patient for chest xays/CT scans/labs as this lead to dissemination of infection to other places

- Attached urinals/wash room facility in all isolation rooms

- Separate portable stethoscopes/xray/CT units/USG machines should be dedicated for patients suffering from COVID-19

- Patient needs to be kept in isolation till his both respiratory samples turns out to be negative.

9 Treatment Options For COVID 19

There are no specific antiviral treatments recommended for COVID-19, and no vaccine is currently available at the time of writing this article. [70, 71]

9A COVID-19 Management In A Nut Shell

There are no proven or approved treatments for COVID-19. The following treatment plan is suggested on the on the basis of information available till date on various investigational treatment approaches.

Table 10 : COVID-19 Management In A Nut Shell

CATEGORY	SEVERITY OF ILLNESS	PLAN
A	**Mild illness** without any risk factors/ Co-morbidities	• Patient should be isolated at COVID centers • Droplet & contact precautions • Symptomatic treatment
	Mild illness with Co-morbidities	• Symptomatic treatment + consider starting Hydroxychloroquine (HCQ) 400mg BID x one day followed by 400mg OD x 4days.
B	**Moderate Illness** • Dyspnoea • Respiratory rate > 22/min • SPo2 <94% on room air	• Admit in hospital isolation room • Oxygen support • Start empirical antibiotics as per local community acquired pneumonia treatment guidelines • Consider starting HCQ 400mg BID x one day followed by 400mg OD x 4days. • **Azithromycin** 500mg OD x 5 days (Given in many centers). Be cautious when you add it with HCQ (QTc prolongation) • **Oseltamivir** 75 mg BID x 5days (If H1N1/Swine flu is predominant in your locality.
	Severe Illness • Respiratory rate > 24/min • SPo2 <92% on room air • >50% lung involvement on imaging **High risk factors for severe illness** Age >60years, Male sex Underlying chronic Respiratory disorders, Hypertension, Diabetes, Mellitus, chronic kidney/liver disease, Malignancy, Post bone marrow/ solid organ transplant	• **Initiate/continue** the treatment plan for moderate illness (if not given before) • **High flow O2 support** (HFNC/NIV) taking adequate precautions to reduce aerosolization • **Awake proning** can be tried as a rescue measure • **Anti-virals** can be initiated on a compassionate basis. No proven benefit (Better to start before clinical deterioration) • **Options available:** Lopinavir/Ritonavir, Darunavir/Cobicistat Darunavir/Ritonavir, Atazanavir, Remdesivir • **Anticoagulation:** Prophylactic dose of Low molecular weight heparin (LMWH)
C	**Critical Illness** • Respiratory failure • Shock • Multi organ dysfunction	• *Careful using these drugs in patients with multi-organ damage* • **Tocilizumab** can be considered for COVID-19 patients with persistent fever, elevated inflammatory markers, Signs of cytokine release syndrome or macrophage activation syndrome. (check IL-6 level prior to starting Tocilizumab). • **Convalescent plasma** (Preliminary trials:shown to improve symptoms, PaO2/FiO2, SOFA score and reduce viral load) • Continue IV antibiotics and supportive care • Rule out ventilator associated pneumonia/ catheter related infections and other secondary bacterial/viral/ fungal infections • Always keep in mind the to rule out differentials of non – resolving pneumonia • **In ventilated patients:** follow ARDS NET protocol strategy • Consider Prone ventilation/ECMO if need arises • **IV steroids:** Not indicated. Use only in case of refractory shock (not responding to inotropes) & macrophage activation syndrome **Anticoagulation:** Therapeutic dose of LMWH (if not at high risk of bleeding) • Refractory or progressive cases in ICU: **Interferon beta B1** can be considered. However it should be combined with an anti-viral (Lopinavir/Ritonavir) and hydroxychloquine

9B WHO ALL NEEDS ADMISSION IN COVID-19? [71]

Severe Disease (14%)

- Respiratory rate > 30/min
- SPo2- <93%
- PaO2/FiO2 <300
- Lung infiltrates >50% within 24- 48 hours

Critically ill (5%)

- Respiratory failure (need of mechanical ventilation)
- Septic shock
- MODS

9C ANTI-VIRAL THERAPY

No anti-viral therapy has been proven to work for COVID-19 in humans. Multiple RCTs are ongoing; hopefully they will bring us further information soon. [70,71]

Whenever possible, patients should be enrolled in RCTs.

- Information is provided below about some of the more popular agents which are being used by some practitioners.
- Inclusion in this chapter is not a recommendation to use one or more of these medications. This information is simply provided as a background to help us understand these therapies.
- A focus is placed on lopinavir/ritonavir and chloroquine since these agents are currently available.
- Practitioners are encouraged to review available evidence and reach their own conclusions regarding whether to use these medications.

INDICATIONS FOR ANTI-VIRAL THERAPY

Retrospective data from SARS suggests that earlier treatment (e.g. within 1-2 days of admission) may be more effective than reserving therapy until severe organ failures occur (Chan 2003). This is consistent with data from influenza that suggests a finite treatment window occurring relatively early in the disease course.

- The vast majority of patients will do fine without any therapy, so in most cases there's no need for antiviral therapy.

- However, waiting until patients are severely ill before initiating therapy could cause us to miss an early treatment window, during which the disease course is more modifiable.
- Predictors of adverse outcome might be useful in predicting who will do poorly and thus who might benefit most from early anti-viral therapy, but data is limited.

ANTI-VIRAL MOLECULES UNDER TRIAL (Experimental options)

LOPINAVIR/RITONAVIR

- In vitro reduces replication by 50% in MERS corona virus (72)
- Definite efficacy not proven
- WHO has mentioned as an agent that can be tried
- May be also tried in combination with Interferon alpha orRibavirin
- Potent CYP3A4 inhibitor – monitor for drug interactions
- Oral and liquid formulation is available
- **Dose: Adult:** 400/100mg PO Q12h
- **Pediatric:** Pediatric (based on lopinavir): Oral solution
- < 15kg: 12mg/kg/DOSE q12h
- 15-40kg: 10mg/kg/DOSE q12h
- >40kg: 400mg q12h
- **Oral tablet**
- ≥15-25kg: 200mg q12h
- ≥25-35kg: 300mg q12h

  >35kg: 400mg q12h

REMDESIVIR (For compassionate use only)

- Several randomized trials are underway to evaluate the efficacy of Remdesivir (73,74,75)
- No published phase 3 trials till date
- Investigational antiviral drug with reported in vitro activity against SARS-CoV-2
- Mechanism of action: Extrapolated from MERS CoV
- Premature termination of viral RNA transcription

- Has been found to reduce pulmonary pathology in in vitro studies
- Remdesivir cannot be used in combination with other experimental antiviral agents
- Tried in Ebola virus too
- Side effects- Hepatotoxicity
- **Dose: Adult:** 200mg IV on day 1(loading dose) followed by 100mg IV OD x 9 days
- **Pediatric:** < 40 kg: 5 mg/kg IV on day 1, then 2.5 mg/kg IV q24h

RIBAVIRIN

- Inhibitor of RNA polymerization [76]
- Studies done in MERS
- Concentration required to inhibit MERS-CoV in vitro exceeds peak levels in the blood after therapeutic doses in humans.
- High risk of toxicity
- Renal dose adjustment is necessary
- Boxed warning for hemolytic anemia
- No study results yet in SARS CoV2
- **Dose (Oral):** 2 grams x 1 dose, then 600mg q8h

DARUNAVIR/COBICISTAT

- Viral protease inhibitor
- In-vitro studies shows SARS-COV-2 inhibition
- **Dose:** 800mg/150mg PO OD x 5 days [163]

FAVIPIRAVIR

- Investigational molecule for treatment of COVID-19 and at this time its safety and efficacy have not been established.
- Predominantly used by China & Japan to treat influenza
- **Dose** [164] : Optimal dose and duration unknown, limited data available (Phase 3 trials ongoing); 1,600 mg twice daily on day 1, followed by 600 mg twice daily for a total duration of 7 to 14 days

OSELTAMIVIR

- Neuraminidase enzyme inhibitor in influenza
- Not seen in SARS CoV2

- No trials on COVID-19

- Many patients with similar presentation of COVID 19 might be influenza. Hence better to give the drug to avoid patient worsening due to influenza

- **Dose:** 75mg PO BID x 5 days

9D Other Available Treatment Options

CHLOROQUINE/HYDROXYCHLOROQUINE (CQ/HCQ)

- No conclusive evidence till date regarding the effectives of CQ/HCQ for the treat ment of COVID-19 [77]

- However CQ/HCQ is extensively used for treatment of COVID-19 patients across the world as it has shown to reduce viral shedding (Hampers the low pH depend ant steps of viral replication) and may be associated with improved clinical outcome. [78,79]

- Compared to CQ, HCQ has shown better tolerability and lower incidence of toxicity.

- No renal or hepatic dose adjustments necessary

- HCQ has also been proposed for prophylaxis- however lacks evidence (For more details please refer to prophylaxis section)

- **Dose** (Adult): Day 1: 400mg PO every 12 hours. Day 2 onwards: 400mg OD or in case of gastrointestinal intolerance 200mg PO Q12h x 4 days

- **Dose** (Pediatric): 6.5mg/kg/DOSE PO q12h x 1 day, then 3.25mg/kg/DOSE PO q12h x 4 days (up to adult maximum dose)

- Adverse effects: QTc prolongation. Clinicians should obtain follow-up ECG daily for the first 48 to 72 hours.

- If QTc increases to >500 ms, HCQ or CQ treatment should be discontinued

- Avoid in cases of documented myocarditis or cardiomyopathy

- Use with caution in presence of multi organ dysfunction

- Renal or liver impairment: No dosage adjustment necessary.

- Retinopathy if often seen only with long term usage of CQ/HCQ

AZITHROMYCIN

- HCQ plus azithromycin appeared to lead to faster reduction in viral carriage [81,82]

- Results are not adequate to support clinical use of this combination

- Combining Azithromycin along with HCQ has shown to increase the risk of QTc prolongation [80]
- **Dose:** 500mg OD for 5 days. (Monitor QTc interval especially when combined with HCQ)

TOCILIZUMAB

- IL-6 pathway inhibitor
- Proposed to reduce the cytokine storm in COVID-19 [83]
- Adverse effects: elevation of liver enzymes, increased risk of re-activation of other Respiratory infections.
- **Dose:** 4-8 mg/kg (max 400mg) IV and can be repeated up to three times 8 hours apart
- **Other IL-6 inhibitors:** Sarilumab and Siltuximab (evaluated in clinical trials) [84]

CONVALESCENT PLASMA

- The use of convalescent plasma was recommended as an empirical treatment during outbreaks of Ebola virus in2014. [89]
- It was also used for treatment of Middle East respiratory syndrome (MERS) corona virus
- Usage of convalescent plasma was also effective in SARS-CoV, H5N1 avian influenza and H1N1 influenza [85-92]
- Very few studies published till date on the role of convalescent plasma contain ing neutralizing antibodies in SARS-Cov2
- Two recently published studies have shown promising results especially in critically ill patients [86,92]
- Convalescent plasma with neutralizing antibodies have shown to improve clini cal status, SOFA score, PAo2/FiO2 ratio and reduced viral load significantly
- Clinical trials including a large group of people are needed in order to assess the potential effectiveness of this mode of treatment

ACE INHIBITORS (ACEi) /ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

- Off late there is lot of interest in the potential role of ACE-inhibitors (ACEi) / angi otensin receptor blockers (ARBs) in the pathophysiology of this disease since the SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry
- Theoretically it can be blocked by ARBs

- But ACE2 is a negative regulator of RAS(It inactivates angiotensin 2), hence the suggestion might be counterintuitive
- ACE (CD143) appears on the macrophage plasma membrane during activation
- **Proposed reduction of cytokine storm**
- Currently there are no data to support either starting or stopping ACEi/ARBs on any patients with COVID-19.

INTERFERONS

- IFN-α2a, IFN-α2b orIFN-β1a
- SARS CoV2 attenuates the interferon (IFN) response of the innate immune system
- **Impair the antiviral adaptive type 1 T-helper cell**
- But in vitro effects hasn't been fully shown to be working

CORTICOSTEROIDS

- **Not indicated in treating SARS CoV2 as per available evidence**
- Might prolong viral shedding
- Use only in cases of refractory shock(not responding to inotropes) and Macrophage activation syndrome (MAS)
- **Dose:** 1-1.5mg/kg bodyweight

ASCORBIC ACID

- Ascorbic acid did appear to improve mortality in the multi-center CITRIS-ALI trial. [93]
- Extremely limited evidence suggests that ascorbic acid could be beneficial in animal models of corona virus (Atherton 1978).
- Administration of a moderate dose of IV vitamin C could be considered (e.g. 1.5 grams IV q6 ascorbic acid plus 200 mg thiamine IV q12). This dose seems to be safe. However, there is no high-quality evidence to support ascorbic acid in viral pneumonia.

ANTI BACTERIAL THERAPY

Initial empirical antibiotics [94]

- COVID-19 itself is not an indication to start antibiotics.
- However antibiotics can be initiated to treat secondary bacterial pneumonia.
- Broad spectrum antibiotics to be initiated according to the institution based guidelines

Delayed bacterial super infection [94]

- Bacterial pneumonia can emerge during the hospital course (especially ventila tor-associated pneumonia in patients who are intubated).

- This may be investigated and treated similarly to other ventilator-associated pneumonias, or hospital-acquired pneumonias.

OTHER AGENTS

- Baricitinib
- Umifenovir
- Baloxavir
- Galidesivir
- Leronlimab
- Brilacidin

- Nitazoxanide
- Sarilumab
- Siltuximab
- Statins
- Ivermectin (Human trials not done)
- Traditional medicines in different countries

Usage of inhalers (controller medications for Asthma& COPD) during COVID-19 [165,166]

- People with asthma & COPD should continue to use their inhaled controller medications

- At this point of time there is no scientific evidence to support that inhaled corti costeroids should be avoided for asthma & COPD patients.

- Stopping inhaled corticosteroids might potentially lead to increased rate of exacerbations.

Nebulized Medications

- Usage of nebulized medications should be preferably avoided for COVID-19 suspect/ diagnosed patients due to increased risk of aerosolization leading to potential transmission of SARS-CoV-2 167

- Nebulised bronchodilator therapy should be reserved for acute bronchospasm and metered dose inhalers with a spacer should be used for management of chronic conditions

- Sputum induction using nebulised hypertonic saline should be avoided

- If nebulized therapy is initiated, patients should be kept in negative pressure isolation room and all airborne infection control precautions should be adopted by the health care professional monitoring the patient.

Table 11: Summary of currently available drugs which can be potentially used
for treatment of COVID-19
Disclaimer: The options listed below are not licensed for the treatment of COVID-19

Agent	Classification	Mechanism of action	Dosage	Side effects
Hydroxychloroquine	Off label use	Hampers low PH dependant steps of viral replication	400 mg BIDx 2 doses, then 200 mg BID for 5 days	QT prolongation
Oseltamivir	No trials on COVID-19	Neuraminidase enzyme inhibitor in influenza	75mg BID for 5 days	GI intolerance Headache Insomnia
Remdesivir	Investigational (can be used only on compassionate basis)	RNA dependent RNA polymerase inhibitor	200 mg IV loading dose, then 100mg IV daily, up to 10 days	GI intolerance Hepatotoxicity
Lopinavir/Ritonavir	Off label use	3CLpro (viral protease) inhibitor	400/100 mg BID for up to 10 days	QT prolongation Hepatotoxicity
Interferon Beta B1	Off label use	Immunomodulatory; enhancement of innate and adaptive viral immunity		Flu like syndrome depression
Tocilizumab	Off label use	Monoclonal antibody to IL6 receptor / treats cytokine release syndrome	4-8 mg/kg (max 400mg) IV and can be repeated up to three times 8 hours apart	Elevation of liver enzymes Increased risk of re-activation of other Respiratory infections
Antibiotics (Broad spectrum)	Initiate as per institution based CAP/VAP policy	Secondary bacterial infection (CAP)/VAP	-	-
Corticosteroids	✦ Not indicated in treating SARS CoV2 as per available evidence. Might prolong viral shedding. ✦ Use as per indicated in refractory shock/macrophage activation syndrome/if patient has other indications for steroid use			
Convalescent Plasma with neutralizing antibody	Off label use	Antibodies from convalescent plasma ight suppres viraemia. Theoretically: Better to start at early stage of disease	Consider IVIG at standard dose of 1 gm/kg daily x 2 doses	Might interact with anti-virals

🔟 Critical care management of suspected or confirmed COVID-19 disease patients

Respiratory system related complication is the most common presentation of COVID-19 requiring inpatient hospital admission. Even though this is in only a small percentage of cases it carries a significant risk of rapid progression and poor prognosis especially when this leads to ICU admission. Most cases develop mild symptoms with an uncomplicated progression while 14% will need admission for more severe disease needing oxygen therapy. A smaller percentage of up to 5% will need ICU admission and go on to develop septic shock and multiorgan failure including renal and cardiac injuries.

Higher SOFA score and D- dimer >1 ug/l on admission and older patients with co morbidities portended poor prognosis [95]. Critical care management of these cases are not any more complex than the previous known viral infections and their related critical care issues but for the fact that hospital course is not clearly predictable and the sudden case load of such severely sick patients can overwhelm any health care system. The fear of contracting this illness easily by the health care providers plays a crucial role in management of these patients as well. The art is to provide optimal care yet limit exposure. IPC – Infection prevention and control using standard personal protective equipment (PPE) as well as standard precautions such as hand hygiene when taking care of COVID -19 patients is a must and has been covered in detail elsewhere in this document. This review is specially for the front line pulmonary and critical care physicians who are taking care of the COVID 19 infected patients in the ICU.

The data is very limited about management of COVID-19 in all population and particularly deficient in the pediatrics and pregnancy. From all the published reports from China there does not seem to be any unusual presentation in these population and the guidance of treatments enumerated herein including supportive and management therapies will need to be tailored to suit the special situations. There was a total of 14.8% health care providers that were confirmed to have been infected in Wuhan, China with a case fatality rate of 0.3 % [101]. The numbers from Italy look a little different. On the whole we are still in the midst of pandemic, which is evolving, and ongoing data will eventually influence changes in practice.

The initial step is to identify suspected cases early, assess their severity and triage to best preferred destination – i.e. ICU or non ICU isolation bed. Choice of bed is important to avoid too many internal patient transfers but this can often be very difficult in these cases because worsening of these patients tends to typically occur in the second week after the initial prodrome. This deterioration is thought to be related to immunopathologic injury rather than a direct injury from the virus as the viral load decrease during the second week of the illness as seen with the 2003 corona virus SARS [96].

10A Critical Care Admission Criteria And Management

* Severe pneumonia with acute respiratory failure, respiratory rate > 30 /min, Severe respiratory distress; SpO2 < 93% on room air

* All cases of ARDS: Berlin criteria with Kigali modification 97,98

Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms.

Chest imaging (Radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.

Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present

Oxygenation impairment in adults

* **Mild ARDS:** 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O, or non-ventilated)

* **Moderate ARDS:** 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O, or non-ventilated)

* **Severe ARDS:** PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O, or non-ventilated) When PaO2 is not available, SpO2/FiO2 ≤ 315 suggests ARDS (including in non-ventilated patients).

But a word of caution from the Italian group is that the usual P/F ratio is less helpful than the clinical performance and close monitoring of the saturations [99] which they believe helps predict those that are going to rapidly progress. Older patients with underlying co morbidities developed symptoms early unlike the younger patients. They also noted that young patients tend to deteriorate rapidly once oxygen saturation hit 93% despite O2 therapy. Even after adequate treatment the overall outcome and response to treatment is not fully understood. Compared to similar aetiologies from the past, COVD-19 seems to follow a more rapid fluctuation in its course.

The recent experiences have advised against rapid de-escalation of invasive/non-invasive respiratory care in these patients due to risk of recurrence of deterioration within the next several days needing respiratory support in the ICU.

3. Sepsis and Septic Shock: Defined as 'dysregulated host response to infection' occurs in a small percentage (5%) of cases of Covid-19 based on the data from Wuhan, China. Case fatality rate 50% in those that were admitted to the ICU and predominantly occurred in those with multiple comorbidities especially the older patients (>80 years)[100]. COVID-19 suspected patients like other viral infections often can present related to the viral infection or related to worsening of an already chronic disease in the setting of the viral infection or may altogether another acute infection. In the setting of an already weakened immunity and several co morbidities there is a multiplied effect with an overall poor prognosis. Sepsis definition is no different in these patients and surviving sepsis guidelines should be followed.

Septic shock is designated when infection is suspected or confirmed and vasopressors are used to maintain mean arterial pressure (MAP) ≥ 65 mmHg with a serum lactate of ≥ 2 mmol/L, in absence of hypovolemia. These are preferably managed in the ICU even in the absence of shock as there is a high risk for rapid deterioration. But the decision for ICU admission will once again have to be decided based on availability and optimization of resources.

10B Systemwise management of COVID-19 cases in the icu

Respiratory

Acute Respiratory Failure and early ARDS in a nonintubated patient

Obtaining Samples for testing – when and how nasal swab, oropharyngeal swab and bronchoscopy is indicated has been covered elsewhere.

Monitor oxygenation and work of breathing - Closely monitor oxygenation and continue supplemental O2 via nasal cannula. If patient continues to improve usual care is advised. If there is sign of deterioration High Flow Nasal Cannula should be the next step followed by non invasive ventilation (NIV aka CPAP and BiPAP).

HFNC oxygen and NIV has one major issue which also restricts use of nebulizers in these cases - Droplet aerosolization. Coughing can spread to about 2.5 meters on HFNC[104]. This complicates when space is in shortage which can be expected during such pandemics. HFNC in the previous MERS and SARS epidemic had a high failure rate of 92% [105] and hence this option should be considered with caution and only when close monitoring is available. Erring on the side of safety for everyone by elective intubation versus an emergent intubation maybe the way to go.

Patients placed on NIV and HFNC should be closely monitored as the potential for deterioration quickly has been seen in both the cohorts – China and Italy.

Acute Respiratory Failure progressing to need intubation

Like in every other case of infectious pneumonia related respiratory failure, criteria and management is not very different when it comes to timing of intubation but a word of caution – Intubation is a high-risk procedure in COVID 19 patients due to exposure. It is preferable to intubate only when absolutely necessary and procedure to be done by experienced personnel. Rapid sequence intubation using video laryngoscope when available and preferably using paralytic would be safer as there will be minimal cough and effort from the patient, minimizing aerosol exposure. Personal protective equipment (gloves, gown, safety goggles) in addition to N95 respirators or mask are an absolute must during intubation preferable in a negative pressure room.

Ventilator strategies

Most of this data and recommendation comes from ARDS related to other diseases and is not specific for COVID- 19. There are some anecdotal case reports that point to presence of increased atelectasis and pulmonary edema in these cases.

The principles of mechanical ventilation in ARDS usually followed include:

- Maintaining a low tidal volumes strategy ~4-6 ml/kg IBW
- Always maintain Plateau pressure < 30 cm of H2O
- Higher PEEP rather than is preferred

NMBA should be used as for ARDS from any other etiology but limiting this is preferable as these patients may need to be placed on steroids for managing cytokine storm which increases the risk for critical illness neuropathy and results prolonged hospital stay Allowing permissive hypercapnia Prone ventilation for 12-16 hours per day as recommended with other etiologies of ARDS Nitric oxide to buy time as an adjunct in severe hypoxemia

Given the risk of running into shortage with ventilators careful triage prior to placing a patient on ventilator is a must. Innovations would need to be considered which may include converting outpatient CPAP/BiPAP into ventilators, introducing a t-piece into the inspiratory and expiratory limbs of the ventilators to connect more than one patient to one ventilator, etc. This is not the recommendation but in the scenario such as this pandemic, innovations may become the need of the hour as the idiom goes - **'Necessity is the mother of innovation'**

Extracorporeal Membrane Oxygenation

Extracorporeal Life Support Organization (ELSO) has guidelines but this is limited based on only about 50 patients with COVID 19 in Japan and South Korea. ECMO even on the best times is a very resource intensive treatment strategy. Overwhelming of health care systems needs to be taken into consideration before offering this treatment. Looking at it from the specific disease standpoint – data is being gathered to see the ultimate pathology and cause of death. If this turns out to be multiorgan dysfunction and septic shock, ECMO may not be the appropriate choice of treatment.

Use of ECMO revolves around personnel (skilled and availability to cover all shifts), equipment needs, facilities (in the setting of strict infection and contamination prevention) and systems (communication, quality assurance, contingency plans) [115].

Once ECMO is instituted the following principles are to be followed:

Ultra-protective mechanical ventilation – plateau pressure < 24 cm H2O with PEEP of 10 cm of H2O, respiratory rate of 10-30 /min. The benefits if ECMO are mainly to rest the lung and provide a bridge while the lung recovers. The choice of Veno-Venous versus Veno- Arterial ECMO will depend on underlying cardiac involvement and function. In COVID 19 cases one can expect cardiac failure related to myocarditis, myocardial infarction or sepsis related cardiomyopathy[108]. Disposal of cannulas and catheters will also need additional attention as compared to the routine ECMO patients. Weaning and decannulation protocols are no different to other diagnosis[23].

Corticosteroids in ARDS related to SARS-Covid 1914:

In a case report of a patient with COVID-19 published in the lancet Feb 17th 2020, Zhe Xu et al found that the pathological features of lung biopsy taken at autopsy resembled SARS and MERS coronavirus infections i.e. diffuse alveolar damage with cellular fibromyxoid exudates, pulmonary edema. Significant hyaline membrane formation was also noted. This suggests **probably using corticosteroids early on in the treatment maybe reasonable.**

Angiotensin Converting Enzyme 2 receptor is the site for virus binding to gain access into the cell. These receptors are found in the heart, lung, kidney, intestines and hence results in multi organ dysfunction which portends poor prognosis, but these are also potential sites for treatment16 to decrease progression of ARDS, cytokine storm and cardiac injury.

Infectious Diseases

While in an epidemic situation it a common occurrence to forget other typical ICU pathologies. It is important to **remember the usual community infections and pathologies in addition to hospital acquired infections** in the setting of COVID19 infection. If there is a suspicion of another etiology, usual management including antibiotics and other treatments are advised. Hence workup and management should include all that would have been done usually for such patients prior to this epidemic. Sampling and testing for the COVID-19 infection has been covered elsewhere and hence will not be covered in here.

Empirical antimicrobials must be given within one hour based on the clinical diagnosis, local epidemiology and susceptibility data to cover all likely pathogens causing community acquired pneumonia even if suspected to have COVID.

As with every other cause of sepsis and septic shock, crystalloids are the preferred resuscitation fluid at 30 ml/KBW initial bolus. This is followed by conservative fluid management strategy as the risk for ARDS and cardiac failure is high in these patients. Vasopressors preferred is nor epinephrine.

Medications for specific treatment of COVID 19 is constantly changing. There are multiple trials being done at this time. Antivirals protease inhibitors i.e. lopinavir/ritonavir, Antimalarial chloroquine, hydroxychloroquine, azithromycin and remdesivir are being evaluated and opinions are fluctuating on a daily basis. Critical care patient with COVID 19 should receive treatment based on institutional policy. Careful dose adjustments will need to be considered given risk of multiorgan dysfunction noted in these ICU patients.

Cytokine Storm Syndrome

This seems to occur due to an overreaction of the immune system in response to the viral infection which is related to cytokine release. This immune response then becomes harmful to the host causing multiorgan dysfunction. This has been seen in the **2ⁿᵈ** week of hospital stay for these patients based on the Wuhan and Italian experience. This is driven by multiple immune factors including **IL-2, IL-6, IL-7, GCSF, TNF alpha** to name a few[116]. This diagnosis carries a poor prognosis and needs to be addressed with appropriate medications early on.

Cardiovascular Disease

COVID -19 patients seem to have a preponderance of cardiac disease – Wuhan study (non-survivors HTN 49%, CVD 13%)(15). **Myocardial injury** maybe related to cytokine storm manifested by elevated levels of IL-6, ferritin, LDH, and D-dimer and direct myocardial injury(16). 7.2% of cases as per the Wuhan study had increased biomarkers high sensitive troponin, new ECG changes or echocardiographic abnormalities[113]. Cause of death was shock in 40% of cases presumed to be related to fulminant myocarditis [114].

Hematology

Hematological effects of this virus are similar to other viral infection presenting with **leucopenia and some bone marrow suppression** in relatively stable patients. Secondary Hemophagocytic Lymphohistiocytosis (sHLH) characterized by leucopenia (WBC <5000 per mm3or hemoglobin < 9.2 gm/dl or platelets <110K or all of these criteria to gather [109], has been noted in severe viral illnesses and is associated with higher mortality based on HScore [110] – 14 times increased higher. There is growing evidence for treating these sHLH in other cases of sepsis and is being suggested to be offered to COVID-19 cases as well. At present there are case reports of immuno-suppressive treatment using tocilizumab (IL-6 blocker) and JaK(Janus Kinase) inhibition, the latter being another venue for treating cytokine storm by controlling viral entry into the cell and thereby decreasing inflammation [111]. In most developing countries steroids are an option that is easily available to suppress inflammation but WHO has recommended against use of the same as there maybe concerns of increased viral shedding. The Chinese group is recommending methylprednisone at a dose of 0.5-1 mg daily [112] to suppress this inflammatory reaction.

Close monitoring of **coagulation profile** shows significant abnormalities including but not limited to deranged d- dimer, LDH and INR. Part of this maybe related to the multi-organ dysfunction which is noted in these cases especially with liver injury from the ACE 2 pathway.

Deep vein thrombosis prophylaxis should be considered given high risk of DVT related to sepsis and immobilization and probable chance of prolonged ICU stay.

Metabolic

Acute renal failure occurs as a part of MODS or all by itself representing septic shock in COVID -19 cases. Management is similar to any other sepsis or septic shock. Infection control issue during haemodialysis in patients COVID 19 raises a conundrum and risks other patients if the procedure is done in close proximity with other non COVID cases. Diabetics are at risk of getting sick with this disease. While in critical care close monitoring of sugars are advised.

Liver involvement is usually part of the MODS and needs appropriate evaluation and care.

Early enteral feeding is advised but this gets tricky in unstable non intubated patients on non-invasive ventilation. Usual precaution is advisable. Intubating a hypoxemic unstable patient with a full stomach is a very well known nightmare. Add to it the highly contagious COVID-19 viral infection.Adequate nutritional support with balanced proportions of proteins, carbohydrates, vitamins and minerals boosts immunity to fight the infection.

Other standard of care precautionary measures include Head of Bed Elevation, gastrointestinal prophylaxis with H2 antagonist or proton pump inhibitors as would be done in any critically ill patients.

Early mobilization, physical therapy and adequate sugar control as done in the regular protocol for ICU patients is to be followed in COVID 19 cases as well.

10C Prevention of infection among critical care professionals

Protecting health care workers and preparedness of ICUs to confront an epidemic cluster should be the main priority to avoid health care professionals to acquire infection and Covid- 19, based on experiences learnt from MERS-coronavirus and 2003 SARS coronavirus [100].

Recently, antiseptic hand rubbing using ethanol-based disinfectants was found to be less effective than hand washing in inactivating influenza virus under experimental conditions [101]. For patients with coronavirus suspicion in the ICU, airborne plus contact precautions and eye protection should be implemented. **During aerosol-generation procedures,** wearing a fit-tested N95 mask in addition to gloves, gown and face/eye protection is recommended.

Open suctioning of the respiratory tract, manual ventilation before intubation, nebuliser treatment, and chest compressions were identified as risk procedures during the SARS outbreak [102]. Close-circuit suctioning may reduce exposure to aerosols in intubated patients. Thus, support with early diagnosis, implementation of effective infection control measures, and limitation of procedures associated with risk of environmental and personal contamination, such as aerosolization, bronchoscopies or transfers for CT scans should be implemented. Ventilator strategies favouring aerosolization, such as non-invasive mechanical ventilation (NIV), which may quite delay but not avoid intubation, should be limited, and hypoxemia rescue therapies such as nitric oxide should be implemented.

Use of non-invasive ventilation is controversial, showing limited efficacy in MERS and is associated with very high levels of aerosol spread, exposing staff at much greater risk of infection [103,104]. However, NIV can avoid the need for ventilation, at least in SARS. There is therefore an argument that it may be appropriate only if adequate levels of staff protective equipment are available [105]. In influenza, a small cohort of patients showed that high-flow nasal cannula was associated with avoidance of intubation in 45% of patients, although those with shock or high severity of illness required intubation [106]. Thus, efforts should be done not to delay intubation in patients with viral pneumonia and acute respiratory failure. Rapid sequence intubation, lung protective strategies are the priority to ventilate such patients.

In summary, it is necessary to go beyond China, as some results and practices may not be feasible elsewhere. **A priority should be to protect healthcare workers from exposure.** ICU doctors should participate in early identification and lead the management of these patients.

All COVID-19 cases must be reported by the local health authorities to the national body within 24 hours in their own jurisdiction and transferred to isolation cabin in the ICU. Many ICUs are not equipped with negative pressure regulations. If negative pressure ICU isolation rooms are not available, an alternative approach is to use HEPACarbonPhotocatalysis air purification systems for source control.[99]

The SSC COVID-19 subcommittee panel (36 experts from 12 countries) issued following suggestions which are best practices based on high-quality evidence

- Healthcare workers performing aerosol-generating procedures (e.g. intubation, bronchoscopy, open suctioning, etc.) on patients with COVID-19 should wear fitted respirator masks, such as N-95, FFP2 or equivalent – instead of surgical masks – in addition to other personal protective equipment, such as gloves, gown and eye protection.

- Aerosol-generating procedures should be performed on ICU patients with COVID-19 in a negative pressure room, if available. Negative pressure rooms are engi neered to prevent the spread of contagious pathogens from room to room.

- Endotracheal intubation of patients with COVID-19 should be performed by healthcare workers with experience in airway management to minimize the number of attempts and risk of transmission.

- Adults with COVID-19 who are being treated with non-invasive positive pressure ventilation or a high flow nasal cannula (HFNC) should be closely monitored for worsening respiratory status and intubated early if necessary.

10D When to discharge a covid-19 positive isolated/treated patient

- Significant resolution of symptoms
- Radiological clearance
- Documented virological clearance in 2 samples(more than 24 hours apart)
- Patients who are discharged from hospital should be advised home quarantine for atleast 2 weeks, in view of recent reports emerging from china regarding persistence of virus in respiratory secretions inspite of adequate treatment. Also these individuals should be warned about the possibility of a re-infection of COVID-19.

⑪ Prognostic Factors

The vast majority of infected patients (>80%) don't get significantly ill and don't require hospitalization. [117]

Among hospitalized patients [117-118]

- 10-20% of patients are admitted to ICU.

- 3-10% requires intubation.

- 2-5% dies.

Mortality appears lower than that in patients with severe acute respiratory syndrome (SARS-CoV) or Middle East respiratory syndrome (MERS) (119-121). Patients with no reported underlying medical conditions had an overall case fatality of 0.9%. Case fatality is higher for patients with comorbidities. **(Table 12)**

Table 12: Risk Factors For Severe Illness

RISK FACTORS FOR SEVERE ILLNESS [2-5]		
Age & Comorbid Conditions	Clinical Parameters	Lab Parameters
- Male sex - Older age (ARDS more seen in >64years old) **Any one of the following medical conditions** - Cardiovascular disease (10.5%) - Diabetes Mellitus (7.3%) - Chronic respiratory disease (6%) - Hypertension (6%) - Cancer (6%) - Chronic kidney disease (6%) - Prior stroke (4%) **Other medical conditions at high risk** - Advanced liver disease - Post solid organ transplantation on immunosuppressive therapy - Treatment for graft versus host disease - HIV infection, with low CD4 cell count - Recent history of bone marrow transplantation	- Respiratory rate >24/min - Persisting fever - Heart rate >125/min - SPO2 <92% at room air	- D-dimer >1000ng/ml - CPK >twice upper limit of normal - CRP >100 - LDH >245 U/L - Elevated troponin levels - Admission absolute lymphocyte count <0.8 - Ferritin >300 ug/L

⑫ Role of Prophylaxis in COVID-19

The Novel corona virus infection which started as an outbreak in China in December 2019 has rapidly spread all over the world, such that on 11 March 2020 WHO declared this disease as pandemic [117,118]. The emergency that the world faces today demands that we develop urgent and effective measures to protect people at high risk of exposure[119]

The various strategies for prevention of transmission and infection tried against this disease are:

1) **Non Pharmacological interventions:** isolation at home, voluntary quarantine at home, the social distancing of population at riskincludingthe closure of schools, universities,non-essential workplacesetc to limit people gathering in clusters to help break the chain of transmission of infection.[120]

2) **Pharmacological interventions include:**

     1. Antiviral agents

     2. Chloroquine-HydroxyChloroquine (HCQS)

     3. Vaccination

Antiviral Agents

Antiviral agents like Oseltamavir which is a neuraminidase inhibitor is known to reduce viral shedding in respiratory secretions and is used for treatment of influenza [121]. Similarly, certain protease inhibitors like Lopinavir have shown to be strong inhibitors of the protease enzyme present in SARS-CoV which is important for the life cycle function of this virus [122[. Ritonavir has been used to boost this action of Lopinavir in HIV patients [123]. However, the largest study reported till date on use of Lopinavir plus Ritonavir for its efficacy in patients infected with COVID-19 conducted in China found no difference in the clinical outcome when compared to standard care alone [124]. There is currently a trial NCT04304053 ongoing to look into the efficacy of Darunavir/Cobicistat plus chloroquine treatment in all patients found to be infected. Currently, there is no recommendation for use of antiviral agents for prophylaxis of COVID-19.

Chloroquine-HydroxyChloroquine Sulphate (HCQS)

Chloroquine is a widely known, easily available and affordable antimalarial agent for both treatment and prophylaxis. Various mechanisms have shown it to have a role in SARS CoV infection too. The SARS-CoV2 is known to bind to human cells via the Angiotensin-Converting Enzyme 2 (ACE 2) receptor. Chloroquine in the in-vitro studies

has shown to affect the glycosylation process of ACE2 receptor thus causing the vero cells pre-treated with chloroquineto be refractory to SARS-CoV infection.This could be the mechanism through which even human cells can become refractory to this infection [125]. It has also been seen that treatment with chloroquine prevents the spread of SARS-CoV infection in the postinfection period [126].

HCQS has the same mechanism of action, but a better safety profile and hence makes it a prefer drug. Both these drugs have also shown to have immunomodulatory effects and can suppress the increase immune factors [126]. Studies have also demonstrated HCQS to have superior in vitro anti-viral effect in comparison to chloroquine [127].

The first-ever human trial of chloroquine against COVID-19 was conductedin China on more than 100 patients found chloroquine to be superior in reducing symptom duration, exacerbation of pneumonia, radiological improvement and lead to virus-negative seroconversion [128]. The French group of investigators studied hydroxychloroquine along with azithromycin. It was an open-label non randomizedcontrol trial. They included 36 patients in the trial, 20 patients were given hydroxychloroquine at a dose of 600mg daily along with azithromycin. The authors showed significant reduction in viral load on day 6 of the treatment and much lower average carrying duration of the virus as compared to the control group [129]. However, recently several questions have been raised on the validity of this study and deficiencies of a non-randomized open labeled design which can be riddled with bias. Currently many trials are underway to study the effect both for prophylaxis and treatment (Table1)

Indian Council of Medical Research (ICMR) has initially recommended the use of HCQS for prophylaxis from Covid 19 infection [130]:

- All health care workers those involved in the care of suspected/confirmed cases of COVID-19 can take400mg twice a day on day 1, followed by 400mg once weekly for next 7 weeks(with meals)

- Asymptomatic household contacts of laboratory-confirmed cases: 400mg twice a day on day 1, followed by 400mg once weekly for next 3 weeks; to be taken with meals.

Currently, due to **lack of Randomized Clinical Trials (RCTs), (Tabel 13)** clinical guidance on the use, dosing, and duration of HCQ for prophylaxis or treatment of SARS-CoV-2 infection is lacking from Centers of Disease Control (CDC).

Similarly, JHMI clinical guidance currently does not recommend pre or post-exposure prophylaxis in individuals with suspected exposure to SARS-CoV-2 [131].

Precautions

Patients taking these drugs should be frequently monitored for hematological parameters, serum electrolytes, blood glucose, hepatic and renal functions. As these drugs are known to cause QTc prolongation, routine ECG is essential prior to starting these drugs. Co-administration of other drugs known to cause QTc prolongation should be avoided.

Table 13: Summary of clinical trials of Prophylaxis Strategies

Summary of clinical trials of Prophylaxis Strategies		
Trial number	**Study Title**	**Drugs to be tested**
NCT04303507	Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting; a Randomised, Placebo-controlled Prophylaxis Study (COPCOV)	Chloroquine vs Placebo
NCT04313023	The Use PUL-042 Inhalation Solution to Prevent COVID-19 in Adults Exposed to SARS-CoV-2	4 doses of PUL-042 Inhalation Solution vs Placebo
NCT04308668	Post-exposure Prophylaxis for SARS-Coronavirus-2	HCQS vs Placebo
NCT04251871	Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection	TCM vs Placebo
NCT04283461	Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) to Prevent SARS-CoV-2 Infection	Phase 1 trial of the vaccine
NCT04304053	Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention (HCQ4COV19)	Darunavir/cobicistat and HCQS vs Placebo

COVID-19 Vaccines

There is considerable investment and research activity to develop a vaccine. The US (NIAID) collaborated with Moderna to develop an RNA vaccine. A Phase I safety clinical trial of the vaccine candidate, called mRNA-1273, is underway with recruitment of 45 volunteers completed on 19 March 2020 [132]. Another, Phase I safety trial of a recombinant adenovirus vaccine candidate (CanSino Biologics Inc. (Tianjin, China)), Ad5-nCoV, recruiting 108 healthy adults in Wuhan, China in March [133]. However, a possible vaccine in development may or may not be safe or effective in future. We hope that the results of the ongoing trials give us more insight on prophylaxis and help in better prevention and thus decreasing the transmission of this widely spreading disease.

**BCG Vaccine:** No proven role in COVID -19 as per WHO [162]

⑬ Prevention

13A Who is a contact?

- A person living in the same household as a COVID-19 case

- A person having had direct physical contact with a COVID-19 case (e.g. shaking hands);

- A person having unprotected direct contact with infectious secretions of a COVID-19 case (e.g. being coughed on, touching used paper tissues with a bare hand);

- A person having had face-to-face contact with a COVID-19 case within 2 metres and > 15 minutes;

- A person who was in a closed environment (e.g. classroom, meeting room, hospital waiting room, etc.) with a COVID-19 case for 15 minutes or more and at a distance of less than 2 metres;

- A healthcare worker (HCW) or other person providing direct care for a COVID-19 case, or laboratory workers handling specimens from a COVID-19 case without recommended personal protective equipment (PPE) or with a possible breach of PPE;

- A contact in an aircraft sitting within two seats (in any direction) of the COVID-19 case, travel companions or persons providing care, and crew members serving in the section of the aircraft where the index case was seated (if severity of symptoms or movement of the case indicate more extensive exposure, passen gers seated in the entire section or all passengers on the aircraft may be consid ered close contacts). [56]

- **COVID-19 in asymptomatic people:** According to a study published in NEJM by Sebastian Hoehl et.al a symptom-based screening process was ineffective in detecting SARS-CoV-2 infection in 2 persons who later were found to have evidence of SARS-CoV-2 in a throat swab and said that shedding of potentially infectious virus may occur in persons who have no fever and no signs or only minor signs of infection [134]

13B **Can the virus stay on inanimate surfaces?**

- **Yes**. Hence terminal disinfection is important even after the patient getting discharged [135]

- SARS-COV-2, depending on the inoculums shed, has been shown to remain viable and infectious in aerosols for hours and on surfaces up to days [135] . **(Figure 6)** It is more stable on plastic and stainless steel up to 72 hours after application to these surfaces and less on copper and cardboard
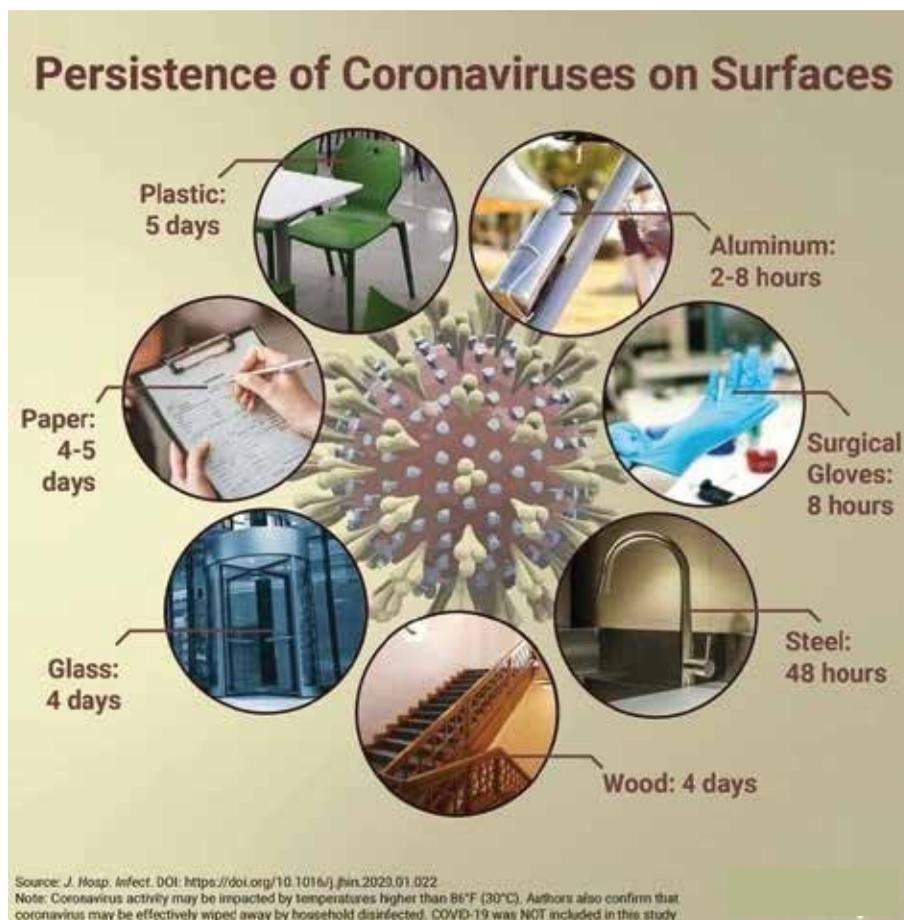
Figure 6: Persistence of coronaviruses on surfaces

Virus can be efficiently inactivated by surface disinfection procedures: [135]

- 62–71% Ethanol

- 0.5% Hydrogen peroxide solution

- 0.1% Sodium hypochlorite solution

- Other biocidal agents such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective.

13C **What should include ideal personal protective equipment (PPE)?**

Figure 7: Essentials in a PPE kit

PPE FOR AT-RISK HEALTH FACILITIES

Airborne precautions should be adopted for all aerosolized generating procedures

1) Gloves

- Gloves nitrile, powder-free, non-sterile. (eg. minimum 230mm total length. Various sizes ranging from small, medium , large

2) Mask

- Medical mask, good breathability, internal and external faces should be clearly identified

3) PARTICULATE RESPIRATOR, GRADE N95 OR HIGHER

- N95 or FFP2 respirator or higher Good breathability with design that does not collapse against the mouth (e.g. duckbill, cup-shaped)

Figure 8: Mask vs. Respirator

Mask **vs** **Respirator**

N95 vs. FFP3 & FFP2

- The most commonly discussed respirator type is N95. This is an American standard managed by NIOSH – part of the Center for Disease Control (CDC). [34] Europe uses a "filtering face piece" score (FFP). This comes from EN standard 149:2001 – drafted and maintained by CEN (European Committee for Stand ardization).

Figure 9: Different types of Respirators commonly used

N95 (95%) = FFP2 (94%)

N100 (99.97%) = FFP3 (99.95%)

Table 14: Filter capacity of different types of Respirators

Respirator standard	Filter capacity(removes x% of all particles that are 0.3 microns in diameter or larger
FFP1	80%
FFP2	94%
N95	95%
FFP3	99.95%
N100	99.97%

Are N95/N100 actually better than FFP2/FFP3?

- Whilst the specifications for the NIOSH (N95/N100) are marginally higher than FFP, that doesn't mean the respirators are any better. [136]

Can Surgical Masks Filter the Corona virus?

Figure 10: COVID-19 & usage of surgical Mask

Whilst FFP2/FFP3 or N95/N100 are the gold standard as far as face protection goes, **what about surgical masks,** do they provide any protection? [136-137]

- Surgical masks are primarily designed to protect vulnerable patients from medi cal professionals. Stopping the wearer from spreading their germs when cough ing/sneezing/speaking. So they're designed to protect patients, not to protect the wearer. There isn't currently research available on the efficacy of surgical masks (or even respirators), for protecting wearers against the corona virus.

Powered Air purifying Respirators (PAPR)

A PAPR is a battery-powered blower that provides positive airflow through a filter, cartridge, or canister to a hood or face piece [154]. **(Figure 11)**The type and amount of airborne contaminant will dictate the type of filter, cartridge or canister required for the PAPR. The National Institute for Occupational Safety and Health (NIOSH) tests the quality of the respirator model used to ensure the safety of the person using it. Quality of the PAPR kit depends upon the filter, cartridge or canister used in it. It would be wise to use a PAPR kit which has HEPA filter (Filter at least 99.97% of particles 0.3 μm in diameter and are oil proof. Also the preferred one for infection control precautions)

Figure 11: Powered Air purifying Respirators (PAPR)

Advantages of using a PAPR kit during COVID-19 pandemic

- Most of the PAPR kits use HEPA filters which give a greater level of respiratory protection than N95 masks [154].

- Extremely useful for doctors who are performing prolonged surgical procedures and health care workers posted in COVID19 isolation areas as it avoids breathing resistance/suffocation and moisture build up associated with using N95 mask along with goggles/face shield.

- Provides head and neck protection

- Approved for people with facial hair and it does not require fit testing because of a full hood

RECOMMENDATIONS FOR USAGE OF SURGICAL TRIPLE LAYER MASK & RESPIRATORS

- Asymptomatic individuals staying at home wearing masks of any type is not recommended. However one to should to wear a triple layer mask at public places, until COVID-19 pandemic ends.

- People with respiratory symptoms or who are taking care of COVID-19 patients at home should receive triple layer surgical masks/ respirator (depending upon availability). [138-140]

- Respirators(N95, FFP2 or equivalent standard) should be reserved for aerosol generating procedures (Bronchoscopy, Tracheal intubation, non-invasive ventilation, tracheostomy, bronchoscopy and cardio pulmonary resuscitation) along with other personal protective equipments (PPE)

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- Health care workers who are involved in direct care of COVID -19 patients should use Respirator (N95, FFP2 or equivalent standard) and other essentials in PPE kit (eye protection, gloves, shoe cover and gown/fluid resistant apron)

- Medical and Nursing staff involved in Intensive care unit should use Respirators(N95/FFP2 or an equivalent)

- During the present pandemic situation respirators (e.g., N95, FFP2 or equivalent standard) can be used for an extended time, especially while caring for multiple patients who have the same diagnosis without removing it. Evidence shows that respirators maintain their protection when it is been used for extended periods. [138-140]

- Always prioritize the use of N95 respirators for those personnel at the highest risk of contracting infections.

- Most often an N95 mask can be used for up to 8hours on a continuous or intermittent basis and ideally it needs to be removed after that.

- Avoid touching the inside of the respirator. If inadvertent contact is made with the inside of the respirator, perform hand hygiene.

- PAPR kit should be considered (depending upon availability) for doctors who are performing prolonged surgical procedures and health care workers posted in COVID19 isolation areas as it avoids breathing resistance/suffocation and moisture build up associated with using N95 mask along with goggles/face shield

- Used mask should be considered as a potentially infected material and it should be disposed separately in an infectious waste disposable bag.

- Health care system at every locality should adopt appropriate steps for disposal of used masks. [141]

4) Face Shield

- Made of clear plastic and provides good visibility to both the wearer and the patient, Adjustable band to attach firmly around the head and fit snuggly against the forehead, Fog resistant (preferable), Completely cover the sides and length of the face, May be re-usable (made of robust material which can be cleaned and disinfected) or disposable.

5) Scrubs, tops

- Tunic/tops, woven, scrubs, reusable or single use, short sleeved (tunic/tops), worn underneath the coveralls or gown.

6) Scrubs, pants

- Trouser/pants, woven, scrubs, reusable or single use, short sleeved (tunic/tops), worn underneath the coveralls or gown

7) Apron, heavy duty

- Straight apron with bib, Fabric: 100% polyester with PVC coating, or 100% PVC, or 100% rubber, or other fluid resistant coated material, Waterproof, Sewn strap for neck and back fastening. Minimum basis weight: 300g/m2covering size: 70-90 cm (width) X 120-150cm (height) Reusable (provided appropriate arrange ments for decontamination are in place)

8) Gown

- Single use, disposable, length mid-calf.

9) Shoe cover, hood

10) Goggles, protective

- Good seal with the skin of the face, Flexible PVC frame to easily fit with all face contours with even pressure, Enclose eyes and the surrounding areas, Accomo date wearers with prescription glasses, Clear plastic lens with fog and scratch resistant treatments, Adjustable band to secure firmly so as not to become loose during clinical activity, Indirect venting to avoid fogging, May be re-usable (pro vided appropriate arrangements for decontamination are in place) or disposable.

| Less Protection | More Protection | Maximum Protection (Ideal one) |

13D Strategies to tide over shortage of PPE

Reuse Of Masks

With the pandemic of COVID 19 spreading fast and wide, more and more people are getting sicker and so we are we falling short of respirator masks. These masks are important for the safety of health care professionals handling a patient so that they do not get infected in the process. **The three different types of masks in vogue are:**

The surgical masks, the N95 masks and the elastometric respirators.

1. The surgical masks

These are single use, loose, inexpensive cloth mask mainly designed to protect the wearer against large droplets, body fluids or any other spray of hazardous fluids. They are often loose at the ends and hence do not provide adequate protection against smaller airborne particles. The primary recommended function of these types of masks is that it be worn by the diseased person so as to prevent from spreading the disease germs to immediate surroundings. Currently there are no guidelines available for reuse of these masks. They are to be disposed after single-use.

2. N-95 Filtering Facepiece Respirator (FFR) masks

These masks are designed such that they filter 95% or more of ≥0.3 micron sized particles. They are sealed, tight-fitting and should be tested for leaks before declared safe. They are ideally designed for single use only. CDC gives guidance for extended use and reuse of these masks to be practiced only as crisis capacity strategy.

Extended use: Refers to the practice of wearing the same N95 respirator for repeated close contact encounters with several patients, without removing the respirator between patient encounters. Extended use may be implemented when multiple patients are infected with the same respiratory pathogen and patients are placed together in dedicated waiting rooms or hospital wards. Extended use has been recommended as an option for conserving respirators during previous respiratory pathogen outbreaks and pandemics [142].

Reuse: Refers to the practice of using the same N95 respirator for multiple encounters with patients but removing it ('doffing') after each encounter. The respirator is stored in between encounters to be put on again ('donned') prior to the next encounter with a patient. Even when N95 masks reuse is practiced, restrictions are in place that limit the number of times the same masks or Filtering face piece Respirator (FFR) is reused. Thus, N95 respirator reuse is often referred to as "limited reuse" [143,144].

Reuse should be practiced after an effective FFR decontamination method to reduce the pathogen burden, maintain the function of the FFR, and have no residual chemical hazard. Researchers have investigated the impact of various decontamination methods on filtration efficiency, facepiece fit of FFRs, and the ability to reduce viable virus or bacteria on the FFRs.

The methods of decontamination are described below:

A. Ultraviolet germicidal irradiation (UVGI):

In this method, the UV-C lamp (80W, 254nm) is used. The contaminated FFRs are exposed to UV radiation dose of ≥1 J/cm2 for 15 minutes on each side of the mask. This results in average log reduction of 4.81 of viable virus. The effect of UVGI has been tested on the filtration performance and structural integrity of the FFR. Lindsey et al in their study had shown at doses of upto 950 J/cm2, UVGI had a small effect on filtration performance and essentially no effect on flow resistance. The structural integrity of the respirators showed a noticeable decrease at lower doses. The strength of the respirator straps was less affected by UVGI than the strength of the body material [145]. This method has shown to pass fit performance even after 3 cycles. Heimbuch et al studied the effect of 1 J/cm2 of UVGI against Influenza A (H1N1), Avian influenza A virus (H5N1), Influenza A (H7N9) A/Anhui/1/2013, Influenza A (H7N9) A/Shanghai/1/2013, MERS-CoV, and SARS-CoV. They reported virus inactivation from 99.9% to greater tha 99.999% [146].

Important points to be kept in mind are that effect of UV light is based on line-of-sight, and any part of the mask in shadow will not be disinfected. There are various designs of masks available - some masks designs may not allow penetration to inner layers, some strap designs may inhibit UVGI disinfection and after multiple times of recycling the seal integrity might be compromised. This is an active area of research and more robust data is likely to emerge in near future.

B. Vaporous Hydrogen peroxide:

Hydrogen peroxide (H2O2) vapour, an industrial decontaminant has been shown to inactivate viruses while not damaging the N95 masks. Battelle Memorial Institute, in their pilot study showed that this method is efficacious and maintains structural integrity even after 50 cycles of decontamination [147]. Kenney et al in their study first co-contaminated 3M 1870 FFRs with three bacteriophages, T1, T7, and Phi 6. They then decontaminated the FFRs using H2O2 vapour generated from the Bioquell's BQ-50 system. This treatment inactivated >99.999% of all phages which was below the limit of detection [148].

C. Moist Heat method:

FFRs subjected to heat and relative humidity (RH) for a particular time period have shown to cause inactivation of the viruses. Heimbuch et al. decontaminated FFRs infected with H1N1 using moist heat, of 65°C and 85% RH, and achieved a minimal of 99.99% reduction in virus [149]. The CDC highlights the use of 60°C and 80% RH as well as 65°C and 85% RH. This temperature and humidity can be applied using incubators, environmental chamber or proofing oven. Other methodologies to achieve these conditions are in research phase yet. One concern of this method is the uncertainty of the disinfection efficacy for various pathogens.

D. Mask rotation:

COVID-19 needs a host to survive. It is known to survive on a metal surface for up to 48 hours, on plastic for 72 hours, and on cardboard for 24 hours [150]. So when a mask is left to dry for 3-4 days, the virus no longer survives. This principle is used in the decontamination technique of mask rotation. The health care professional acquires a set number of N95 masks and rotates their use each day, thus allowing them to dry long enough such that the virus is no longer.

AIIMS, New Delhi, India has set a precedent in the country by accepting the CDC recommendation of reuse of the same N95 FFR every fourth day after letting it dry in a paper bag for three days. And such reuse to be done for upto five times before discarding [151].

E. Ethylene oxide (EtO)

Use of EtO gas concentrations ranging from 725 to 833 g/L for one hour at 55˚C has known not to harm the filtration performance [152]. Concern remains of persistence of toxic EtO gas on the masks as this gas is known to be carcinogenic and teratogenic. Long aeration cycles are needed to ensure no off-gassing into the breathing zone of the wearer.

3. Elastometric respirators

Elastomeric Respirator masks are larger, full or partial face-covering masks with removable filter elements designed to be re-usable. The standard reprocessing procedure recommended by Occupational Safety and Health Administration (OSHA) and the manufacturers of these elastomeric respirator mask elements is: Cleaning followed by disinfection. Filter cartridges should be removed from the masks, and the filter cover, straps and any other surfaces should be subjected to the full repro-cessing procedure. [153]

OSHA cleaning guideline recommends the use of a mild detergent at 110°F maxi-mum followed by rinsing and draining with cold water. For disinfection, immersion in a solution of water and 0.1% household bleach for 2 minutes, then rinsing and drying is recommended. To disinfect cartridges, wiping all external surfaces with an alcohol quaternary microbial cloth and allowing to dry is recommended. When properly implemented, a reprocessing procedure for elastomeric respirator masks can take 7-8 minutes per mask. However, only limited guidance exists regarding the cleaning and disinfection of reusable elastomeric respirators in health care, and there is a distinct lack of guidance available on the recommended frequency of cleaning versus disinfection and other standardized procedures.

Recommendation:

It is always advisable to use a new N95 masks whenever such a mask is required. However, in times of crisis, when reuse is needed certain points need to be consid-ered:

1. We should be aware that that no known method is suitable to achieve the ideal levels of reusability (i.e. >6 Log reduction of viable virus and bacterial spores) while avoiding all forms of degradation.

2. Best practice would be to return the same mask to the same person for each use. This may help reduce cross contamination between masks and may reduce the loss of seal integrity due to refitting masks to differently shaped faces.

3. Health care workers should to be trained for proper methods of donning and doffing of these masks each time.

13E **Essential steps needs to be taken to reduce the risk of transmission of infection in community**

◉ **Social Distancing**

2 mtrs away

Novel coronavirus are spread by people who have the virus coming in to contact with people who are not infected. The more you come in to contact with infected people, the more likely you are to catch the infection. Social distancing is infection control action that can be taken by public health officials to stop or slow down the spread of a highly contagious disease.

In addition to social distancing measures taken by governments, we can ourselves choose to reduce physical exposure to potentially sick people, for example:

◉ Exploring the option to work from home if your job allows for it.

◉ Maintaining six feet (two meters) distance from others when they have to leave home

◉ Avoiding large public gatherings such as sporting events. Or situations where you may come in to contact with crowds of people, for example in busy shopping malls.

◉ Interacting with people over the phone/video calls, instead of in person.

These types of steps may be an impediment to normal life. However the intention is that these will be a short term measure (not forever!). A risk with a pandemic is that the initial spread is so quick that it overwhelms the health services. A key aim for any country should be to avoid that, and social distancing can help.

- **Regular hand washing** *(After touching surfaces in public)*

The CDC recommends regular hand washing with soap and water for at least **20seconds.**

Prioritize washing prior to eating and after being out. Regular hand washing dries the hands, which at an extreme, may make them vulnerable to infection. To mitigate this, regularly use a glycerin based moisturizer with pump or squeeze mechanism.

Alcohol Based Hand Sanitizer

- The CDC recommends that if soap and water are not available, use an alco hol-based hand sanitizer with **at least 60% alcohol**. Leave to air dry.

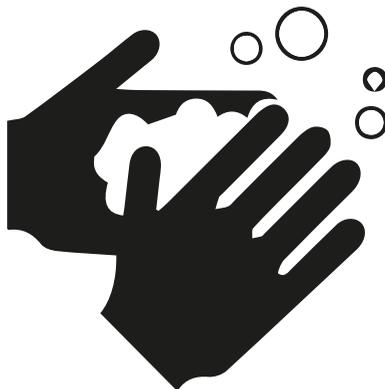- **Maintain Respiratory hygiene**
- Cover your cough and sneeze

Cover
Your **Cough**

Stop the spread of germs!

Use a tissue to cover your mouth and nose when you cough or sneeze
Throw you tissue in the waste basket

or

Cover your cough or sneeze
with your inner elbow,
not your hands

Wash
your **Hands**

After coughing or sneezing,
wash for 20 seconds with soap
and warm water or clean with
hand sanitizer

- **Maintain adequate hygiene of the objects/surfaces that are frequently touched**

- **Sanitize your phone**

Given how often we use our phones, this seems like the next logical priority to be sanitized. Using **antibacterial wipes or alcohol swabs (typically 70% alcohol) to clean your phone** and other items is a good option. If the antibacterial wipes claim to be able to kill the flu virus (H1N1) – that's a good sign they may be able to do similar for the corona virus. Once finished wiping, leave it to air dry.

Sanitize other items you touch regularly, including:

- Computer keyboard and mouse
- House and car keys
- Re-usable water bottles
- Car steering wheel
- Clothing pockets
- Door handles
- **Avoiding touching your eyes, nose, and mouth**
- **Keep your immune system healthy**

Examples of action you can take to maintain a healthy immune system: [37-38]

- Sleep – Get adequate, high quality sleep. For most people 'adequate' means 7-8 hours. It's no coincidence that "burning the candle at both ends" increases risk of illness. A 2004 literature review concluded that "sleep deprivation has a considerable impact on the immune response" and "should be considered a vital part of the immune system"

- **Exercise** – Exercise regularly, but don't overdo it. To quote a 2007 study on exercise and the immune system – "moderate exercise seems to exert a protective effect, whereas repeated bouts of strenuous exercise can result in immune dysfunction

- **Healthy diet** – rich in proteins and vitamins. Also make sure to hydrate well.

ESSENTIAL STEPS NEEDS TO BE TAKEN TO REDUCE THE RISK OF TRANSMISSION OF INFECTION IN COMMUNITY

- Social Distancing (2 meters away)

- People should wear facemask at public places on a mandatory basis (Universal Masking stratergy)

- Regular hand washing (After touching surfaces in public)

- Maintain Respiratory hygiene (Cover your coughs & sneezes)

- Maintain adequate hygiene of the objects/surfaces that are frequently touched

- Avoiding touching your eyes, nose, and mouth

- Keep your immune system healthy (Good sleep, Exercise and a healthy diet)

⑭ Conclusion

Corona virus disease 2019 (COVID-19) was reported as a cluster of disease in China in December 2019 and it has since spread to all continents except Antarctica, which made WHO declare it as a pandemic. Infection mainly gets transmitted via respiratory droplets and fomites leading to both upper and lower respiratory tract infections. Elderly people with various comorbities are more affected. Severe cases have a mortality rate of 2.3 to 5%. Presently there is no standardized treatment or vaccine available for COVID-19. There are some nuances that we are finding as more case series and reports are being published from the hardest hit areas across the world. This disease and treatments are currently a moving target and some management choices may change in the coming weeks. But at the helm of all this management is prevention of spread to other contacts seems to be the best way to slow down this pandemic.

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