

The SARS-COV2 (COVID-19) Pandemic: What Clinicians should Know

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In late 2019, a novel coronavirus, now designated SARS-CoV-2, emerged and was identified as the cause of an outbreak of acute respiratory illness in Wuhan, a city in China, named as COVID-19. Since then the waves of the virus exponentially hit many countries around the globe with high rates of spread associated with variable degrees of morbidity and mortality. The WHO announced the pandemic state of the infection in March 2020 and by June 1st 2020 more than 6

million individuals and more than 370 thousands case fatalities were documented worldwide. In this article, we discussed many aspects regarding this emerged infection based on the available evidence aiming to help clinician to improve not only their knowledge but also their practices toward this infection.

INTRODUCTION

In late 2019, a novel coronavirus, now designated as SARS-CoV-2, was identified as the cause of an outbreak of acute respiratory illness in Wuhan, a city in China [1]. The World Health Organization (WHO) named the disease COVID-19 in February 2020. Since the first reports of COVID-19, infection has spread in waves prompting the WHO to declare a public health emergency in late January 2020 and characterize it as a pandemic in March 2020. By June 1st 2020 more than 6,000,000 confirmed cases worldwide were reported with more than 370,000 deaths [2,3].

VIROLOGY

Four genera of coronaviruses (CoV) were identified as α , β , γ and δ CoV. α and β CoV tend to infect mammals while γ and δ CoV can infect birds. COVID-19 is one of the Beta corona viruses. They include; Middle-East Respiratory Syndrome (MERS-CoV), Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV2) the causative agent of COVID-19 pandemic [4,5]. HKU1 and OC43 are also members of Beta corona viruses [5-7]. Alpha corona viruses include NL63 and 229E strains of HCoV. COVID-19 has positive-sense single-stranded RNA (+ss RNA). The virion of COVID-19 is about 50–200 nm in diameter.

There are 2 types of proteins characterizing HCoV-229E; structural [Nucleocapsid (N), Spike (S), Matrix (M) and Envelope (E)], and non-structural proteins [nsp12 and RNA dependent RNA polymerase] [7-8]. Cell entry of SARS-CoV-2 is facilitated by the spike protein which is primed by serine 2 (transmembrane protease; TMPRSS2) [7,8].

After a SARS-CoV-2 virion attaches to a target cell, the cell's protease (TMPRSS2) cuts open the spike protein of the virus, exposing a fusion peptide. The virion then releases RNA into the cell, forcing the cell to produce copies (Figure 1) of the virus that are disseminated to infect more cells [9].

Phylogenetic analysis of 103 strains of SARS-CoV-2 from China, revealed two different types of SARS-CoV-2, designated type L (accounting for 70 percent of the strains) and type S (accounting for 30 percent). The L type predominated during the early days of the epidemic in China, but accounted for a lower proportion of strains outside of Wuhan than in Wuhan. The clinical implications of these findings are uncertain [10].

PATHOGENESIS

The pathogenesis of COVID-19, cannot be caught on, many mechanisms were adopted by the similarity of the clinical presentation to that of SARS and MERS-COV.

Receptor interaction and cell entry:

The main site of viral replication is the mucosa of the upper respiratory tract followed by affection of the lower respiratory tract and gastrointestinal tract. This may be explained by the presence of ACE2 receptors at these sites [9-11].

Viral spike (S) protein plays a major role in penetration of target cells [12]. The outer S protein binds to its specific receptors e.g. ACE2 and CD209L for SARS [13,14], DPP4 for MERS [15], ACE2 for SARS-CoV-2 [16]. Membrane fusion is enhanced by abnormal two-step furin activation in MERS-CoV [17]. SARS-CoV entry mediated by both membrane fusion and endocytosis [18, 19]. After entry into the cells, the viral single stranded RNA passed to the cytoplasm and viral replication is only possible after its translation into structural proteins and polyproteins [20]. The envelope glycoproteins

are inserted into the endoplasmic reticulum membrane, and formation of the nucleocapsid is done (Figure 1) by the union of viral genome and polyprotein. Finally, release of the virus occurs by fusion of the vesicles containing the virus with the plasma membrane [12].

Antigen presentation:

After cell entry by the virus, presentation of its antigens (Ags) to the antigen presenting cells occurs. Major histocompatibility complex is responsible for presentation of viral antigenic peptide followed by viral recognition by specific T lymphocytes. MHC I molecules and to lesser extent MHC II are responsible for antigen presentation of SARS-CoV [21]. Whereas, MHC II molecules, are responsible for antigen presentation in MERS-COV [22].

Humoral and cellular immunity

Both humoral and cellular immune responses are stimulated by antigen presentation. In SARS-CoV-2-infected patients, although the number of cytotoxic and helper T cells in the circulation are significantly reduced, it is excessively activated, as evidenced by high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions [23].

Cytokine storm in COVID-19:

ARDS is the believed fatal sequel of coronavirus. Occurrence of cytokine storm is a major mechanism for ARDS. Cytokine storm is aggressive systemic inflammatory response characterized by the release of excessive amounts of pro-inflammatory cytokines (IL-6, IL-12, IL-18, IFN- α , IFN- γ , TNF- α , , etc.) and chemokines by immune effector cells [24]. The final consequence is ARDS and multiorgan failure, and death in severe cases. A recent multicenter study of confirmed COVID-19 cases in Wuhan, China showed elevated ferritin (mean 1297.6 ng/ml in non survivors vs 614.0 ng/ml in survivors; $p < 0.001$) and IL-6 ($p < 0.0001$), suggesting that mortality might be due to virally driven hyper inflammation [23].

Coronavirus immune evasion:

Corona viruses develop multiple mechanisms to avoid recognition by the host immune response. The most important one is formation of thick wall vesicles that lack protein recognized receptors (PRRs), thereby escaping the immune detection [25]. Other mechanisms including

inhibition of IFN-I pathway [26], and antigen presentation.

ACEI and ARBs drugs: harmful or helpful?

There is a controversy about whether angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may increase susceptibility to the COVID-19 virus infection or not. The concern of increase the susceptibility of COVID-19 infection is due to observation of increased morbidity and mortality of COVID-19 in patients with hypertension treated with ARBs or ACEI [27].

The use of ACEIs and ARBs may increase expression of ACE2 and increase the susceptibility to viral host cell entry and replication. ACE2 has a broad expression in the body with strong expression in the heart, gastrointestinal system, kidney, and type II alveolar cells in the lungs. This is supported by the evidence that ACE2 has been shown to be a co-receptor for viral entry for SARS-CoV-2 [28].

In animal model, ACE2 down regulation by SARS-CoV, lung injury was improved by treatment with ARBs. These preclinical data suggest that increasing ACE2 expression can decrease SARS-CoV-2-induced lung injury, however, there is no direct clinical evidence that has proven ARBs to be an effective treatment for viral-induced lung injury [29, 30].

Coagulopathy and Antiphospholipid Antibodies in Patients with COVID-19:

Recent literature describe clinically significant coagulopathy, thrombocytopenia, an elevated prothrombin time and partial thromboplastin time, and elevated levels of fibrinogen and D-dimer in critically ill patients with COVID-19 [31]. Serologic testing showed the presence of anticardiolipin IgA antibodies as well as anti- β 2-glycoprotein I IgA and IgG antibodies in some cases [31]. Endothelial damage leading to subsequent clotting and diffuse thrombosis has been proposed as the mechanism of multiple organ affection. These data were emphasized by results of autopsies from both China and Europe and consequently anti-coagulants were added to the treatment regimen of ill COVID-19 patients with promising results. Furthermore, the unexplained sudden hypoxia noticed among stable COVID-19 patients would be explained by this diffuse thrombotic state besides the dissociation of hemoglobin noticed among those patients. Recent studies reported significant

deposits of terminal complement components C5b-9 (membrane attack complex), C4d, and mannose binding lectin (MBL)-associated serine protease (MASP)2, in the microvasculature, consistent with sustained, systemic activation of the alternative and lectin-based complement pathways in many tissues including the lung and the skin [32-34].

MODES OF TRANSMISSION

Bat, was suggested to be a natural reservoir host of the virus where it is transmitted to humans by an unknown intermediate host. Like SARS-Co, it is well established that COVID-19 uses angiotensin-converting enzyme 2 (ACE2) receptor to infect humans [29-33]. Following emerging of COVID-19 in Wuhan, China a seafood market was suspected to be the origin of infection but without a strong evidence [35,36]. Phylogenetic analysis showed that many species have a possibility of being an alternative intermediate host, such as pangolin, snakes and turtles [37].

The most impressive character of COVID-19 is the human to human transmission. This usually occurs between family members, relatives and friends who had intimate contact with patients or incubation carriers [38]. Large droplet during sneezing or coughing is the main method of transmission of COVID-19 [39]. Transmission between healthcare workers was reported in 3.8% of COVID-19 patients as reported by National Health Commission of China on 14th February 2020. Another mode of transmission is direct contact with the intermediate animal host or consumption of wild animals that was suggested to be the main mode of transmission of COVID-19. However, a great debate is still present about the source and routine mode of transmission of infection [40]. Patients remain infectious so long the symptoms are presents and even through the clinical recovery. Some persons are even super spreaders such as those attending conferences. Infection is acquired through inhalation of the infected droplet or by touching a contaminated surface and then touching the nose, mouth or eyes. The virus was also discovered in stool with the potential contamination of water resources and feco-oral transmission [41]. Viral load in the nasal cavity is more than that in the throat but there is no

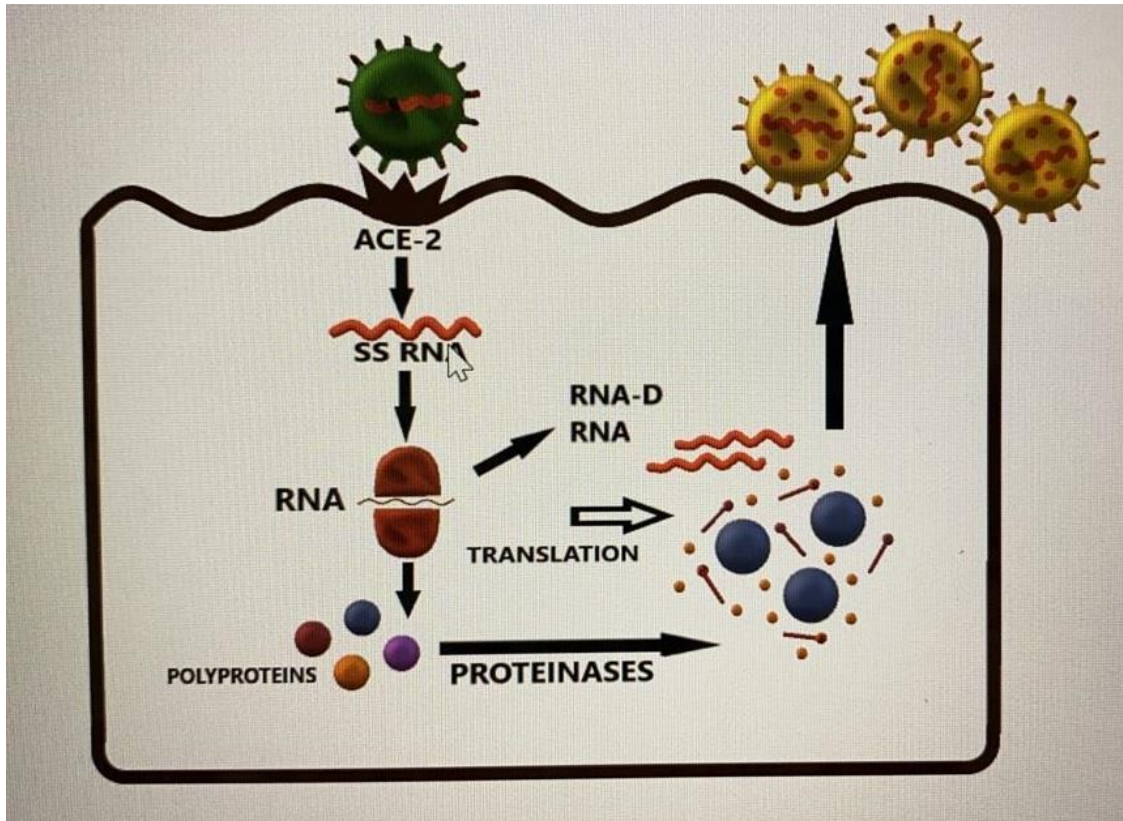


Figure 1: Pathogenesis of the infection. Note that the virus enters the cells through Angiotensin converting enzyme (ACE) 2 receptors.

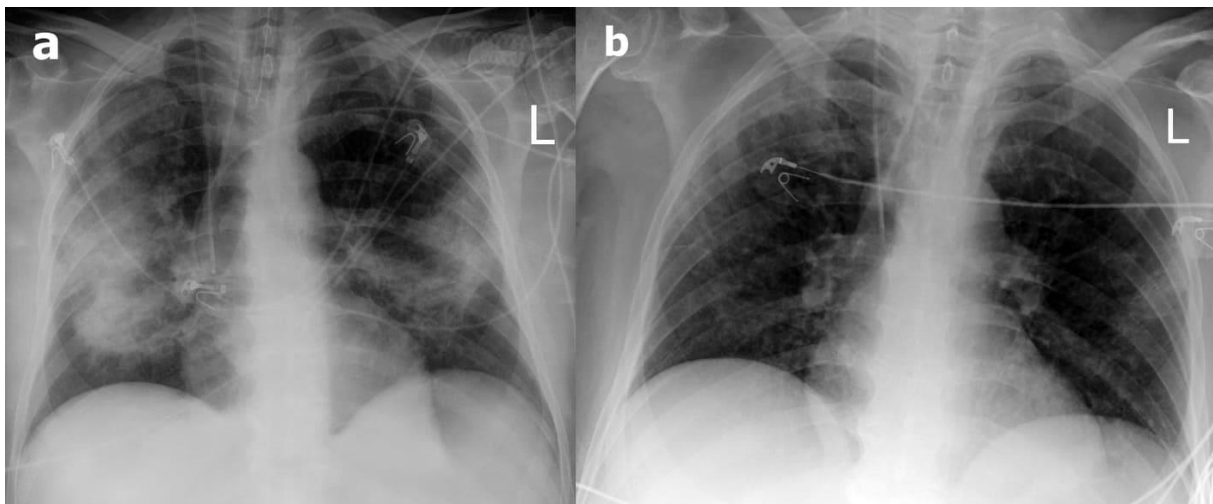


Figure 2: Chest X-ray of COVID-19 patient

- Chest radiography (AP view) at day of admission, showing bilateral and peripheral alveolar consolidations in lower and middle lung zones, more prominent in the right lung, no pleural effusion or hilar lymphadenopathy.
- Chest radiography (AP view) three weeks later showing improvement of the alveolar consolidations together with improvement of the clinical condition of the patient.

difference between symptomatic and asymptomatic cases [42]. The infected droplet can spread within 1-2 meters to settle on surfaces where the virus can stay viable in convenient atmospheric conditions but can be destroyed within a minute by the usual disinfectants [43]. Vertical transmission is not suspected but postnatal neonatal infection of neonates was described [44]. Hospital acquired transmission is suggested to be 41% of patients [45]. The incubation period of the disease ranges from 2-14 days with average of 5 days. The basic case reproduction rate is 2- 6.47 [46] while that for SARS was 2 and for pandemic flu H1N1 2009 is 1.5 [47].

CLINICAL FEATURES

Spectrum of illness severity:

The spectrum of symptomatic infection ranges from mild to critically severe infections. The majority of infections are mild [48,49]. The Chinese Center for Disease Control and Prevention reported an estimation of disease severity as follow [50]:

- Mild (no or mild pneumonia) was reported in 81% of cases.
- Severe disease (e.g., with dyspnea, hypoxia, or > 50% lung involvement on imaging within 24 to 48 hours) was reported in 14% of cases.
- Critical disease (e.g., with respiratory failure, shock, or multiorgan dysfunction) was reported in 5% of cases.

Risk factors for severe illness:

Severe illness mainly occurs in adults with advanced age or underlying medical comorbidities. Comorbidities that associated with severe illness and mortality include [50,51,52,53]:

- Cardiovascular disease
- Diabetes mellitus
- Hypertension
- Chronic lung disease
- Cancer
- Chronic kidney disease

In addition the Centers for Disease Control and Prevention (CDC) includes immune-compromising conditions, severe obesity (body mass index ≥ 40), and liver disease as potential risk factors for severe illness [54].

Asymptomatic infections

Asymptomatic infections have also been described [48]. In a COVID-19 outbreak on a cruise ship, approximately 17 % of the population on board were positive for SARS-Cov-2 and about half of the 619 confirmed COVID-19 cases were asymptomatic at the time of diagnosis [55].

Patients with asymptomatic infection may have objective clinical abnormalities [56,57]. In a study comprised 24 patients with asymptomatic infection who all underwent chest computed tomography (CT), 50 % had patchy shadowing or typical ground-glass opacities. Few days after diagnosis five patients developed low-grade fever, with or without other typical symptoms [56].

Clinical manifestations:

Initial presentation

There are no specific clinical features that can distinguish COVID-19 from other viral respiratory infections. The most common clinical features in a study were [58]:

- Fever in 99 percent
- Fatigue in 70 percent
- Dry cough in 59 percent
- Anorexia in 40 percent
- Myalgias in 35 percent
- Dyspnea in 31 percent
- Sputum production in 27 percent

Fever might not be a universal finding. In one study, it was reported in all patients, but about 20 % of them had a low grade fever $<38^{\circ}\text{C}$ [59]. In another study of 1099 patients from Wuhan and other areas in China, fever was present in only 44 % of patients on admission [60].

Patients with COVID-19 may has smell and taste disorders (e.g., anosmia and dysgeusia) as common symptoms. In a study carried on 59 patients with COVID-19 in Italy, 34 % had either a smell or taste aberration and 19% had both [61]. In addition gastrointestinal symptoms (e.g., nausea and diarrhea) have been reported; and in some patients, they may be the presenting complaint [62].

Kidney injury (direct effect of the virus or late due to cytokine storm) as well as conjunctivitis are also noticed in COVID 19.

DIAGNOSIS

Clinical suspicion and criteria for testing:

Suspected COVID 19 case: The case definition should be considered when, there are acute symptoms suggesting respiratory tract infection (such as at least one of the following: fever, cough, dyspnea) **plus** no other cause explaining the clinical presentation **plus** a history of residence or travel to an endemic area during the last 2 weeks before being symptomatic; **or** close contact with a confirmed or probable COVID-19 case during the last 2 weeks before being symptomatic. Severe acute respiratory illness requiring hospitalization without any other cause explaining the clinical presentation can be considered as a suspected case also [63].

Close contact, is defined as a person living in the same house with a confirmed case or having had direct physical contact with confirmed case or face-to-face contact or being in a closed environment within 2 meters for more than 15 minutes with a confirmed case or having unprotected direct contact with infectious secretions of a confirmed COVID-19 case. Also a healthcare personnel and laboratory worker dealing with confirmed case without using personnel protective equipment (PPE) is considered a close contact [64].

Although, suspected cases should undergo testing for COVID 19, they don't need emergency care and should be encouraged to call prior to presenting to a health care facility for evaluation although they should perform strict home isolation precautions. Many patients can be evaluated regarding the need for testing over the phone. The diagnosis cannot be definitively made without microbiologic testing, but limited capacity may preclude testing all patients with suspected COVID-19.

Laboratory findings are usually nonspecific. There is normal leucocytic count or mild leucopenia. Lymphopenia is common; a decrease in the lymphocytes below one thousand commonly occur in severe disease. There is normal platelet count or mild thrombocytopenia. The ESR and CRP usually increase, on the other hand procalcitonin level is within the normal range. Procalcitonin increase indicates a bacterial co-infection and need for ICU. Other lab markers like liver enzyme, coagulation profile, kidney function, LDH, CPK and D-dimer, serum ferritin may increase and high levels of previous

laboratory marker commonly occur in severe disease [65].

Wang et al., [45-57] and US CDC states that collecting the upper respiratory nasopharyngeal swab have more yielding results than oropharyngeal (OP) one. Induction of sputum collection is not recommended [66]. Swab specimens should be collected in a suitable viral transport medium. Bronchoscopy and bronchoalveolar lavage can produce an infectious aerosol which increased risk of transmit infection healthcare workers [67]. All respiratory specimen collection procedures should be done in negative pressure rooms. Additional specimens (e.g., blood, stool, urine) can also be collected to rule out alternative/supportive diagnosis.

During early infection, nasopharyngeal specimens may give false negative results; so bronchoscopy may be used to collect a deeper specimen. On the other hand, COVID-19 testing can be repeated because over time, the probability of the COVID-19 being present in the nasopharynx raises. Saliva specimens testing were positive in some cases, suggesting it is a promising non-invasive method for monitoring, diagnosis and infection control in COVID-19 infections [68]. The percentage of positive testing in a specimen differs according to the site of the specimen.

Regarding SARS-CoV-2, Real-time reverse transcription polymerase chain reaction (RT-PCR) of viral nucleic acid is considered the diagnostic reference standard [66]. A positive test for SARS-CoV-2 generally confirms the diagnosis of COVID-19, although false-positive tests are possible. Results are generally available within a few hours to 2 days. The US CDC developed a PCR Diagnostic Panel for diagnosis and detection of COVID-19 [69]. Three separate PCR reactions target the N gene. One primer/probe set detects all beta corona viruses, while 2 sets are specific for COVID-19. All three measurements must be positive to confirm COVID-19 diagnosis [70]. For safety reasons, viral culture should not be routinely done for suspected SARS-CoV-2 patients [71].

Regarding serologic tests, using lateral flow immuno-chromatography technique, qualitative rapid test detects IgG and IgM antibodies to COVID-19 in blood, serum and plasma samples has been approved by the Food and Drug Administration . The IgM-IgG combo assay is

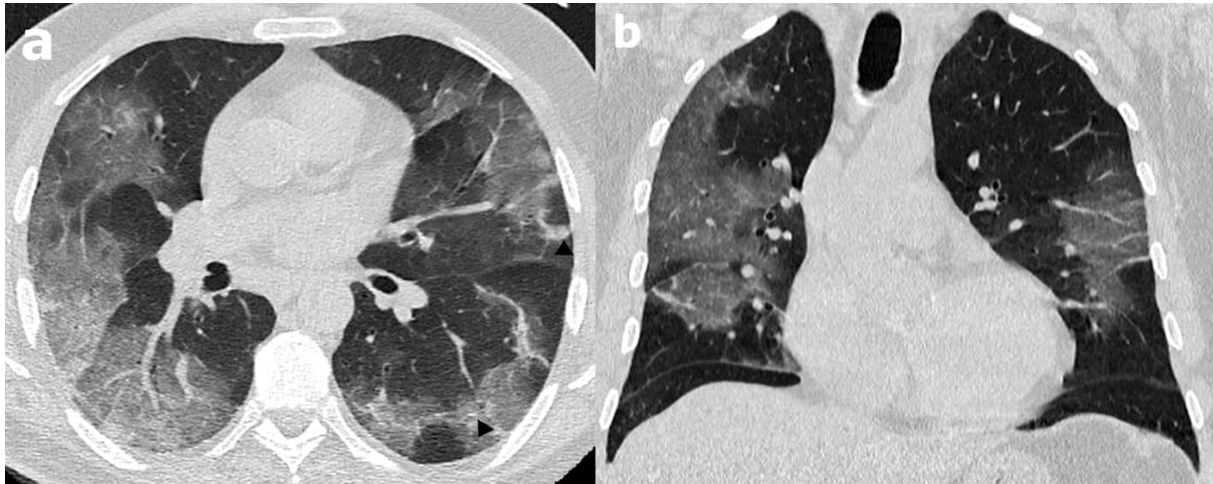


Figure 3: Images in an 83-year-old man who presented with fever, cough, and dyspnea. The polymerase chain reaction assay for the novel coronavirus (SARS-CoV2) was positive one week later.

(a) Axial CT chest at day of admission, showing bilateral multifocal peripheral sub-pleural ground glass opacities with peri-lobular opacities mainly in lower lung lobes which is classical for COVID-19.

(b) Coronal CT scan showing the peripheral sub-pleural distribution of the ground glass opacities in both lungs with more affection of the right lung.

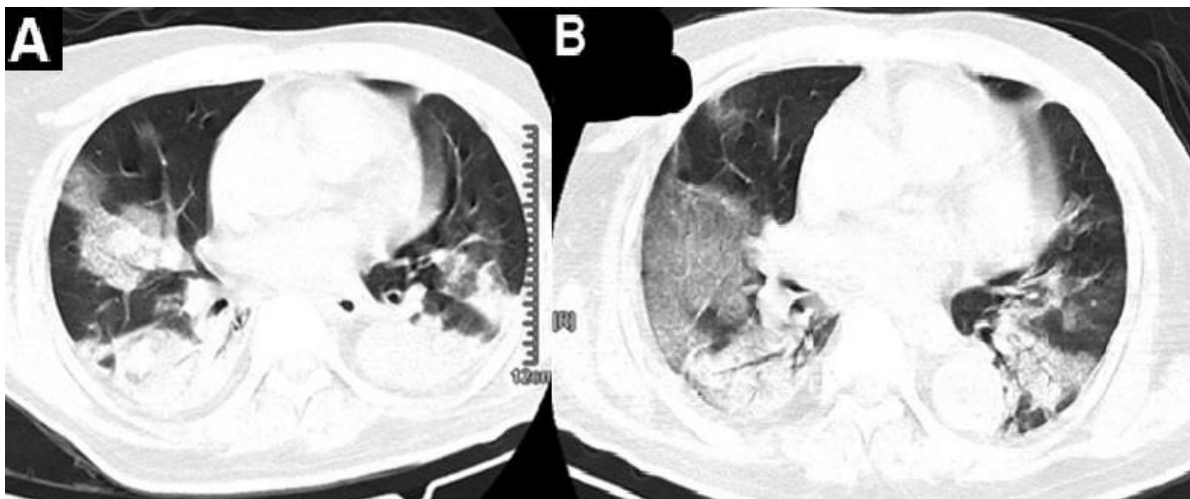


Figure 4: A 62-yr-old male with confirmed COVID-19 required endotracheal intubation and invasive mechanical ventilation. The chest computed tomography scan suggested that, compared with that before intubation (A), the pulmonary disease had progressed 3 days after intubation (B). This progression is thought to be from the disease itself rather than from the invasive ventilation technique.

more sensitive than single IgM or IgG test. It could be considered for rapid screening of COVID-19. The obtained sample from a suspected COVID-19 case should be also investigated for other pathogens causing the same clinical picture. For antibodies to appear in the blood a period of 3-5 days after exposure to the virus needs to be lapsed. Furthermore, false negative cases are not uncommon besides the need to confirm positive cases by PCR. Most patients have detectable IgG antibodies by day 14 following symptom onset, and the likelihood of detection increases over time. In studies, antibody tests that detected both IgG and IgM were positive in 90% of symptomatic individuals by days 11-24 [2-73].

Table (1): Diagnostic Test sensitivity in Days after Symptom Onset.

	Days after Symptoms onset		
	1-7	8-14	15-39
SARS COV-2 Test			
RNA by RT-PCR	67%	54%	45%
Total antibody	38%	90%	100%
Ig M	29%	73%	94%
Ig G	19%	54%	80%

Chest CT is suggested as an important tool for SARSCoV-2 infection diagnosis especially in patients with false negative RT-PCR results, with sensitivity up to 98% [74]. Typical X-ray (**Figure 2**) and CT (**Figure 3**) imaging findings, including, bilateral ground glass opacities, which are multiple, patchy, sub-segmental or segmental lung consolidation (classified as “paving stone-like” changes by fine-grid or small honeycomb-like thickening of interlobular septa) particularly in the middle and lower lobes [75].

Regarding atypical X-ray and CT imaging findings, sub-pleural grid-like or honeycomb-like thickening of interlobular septum which is single or multiple, bronchial wall thickening, and thick strand-like and tortuous opacity. Multiple patchy consolidations, less commonly mild pleural effusion or enlargement of mediastinal lymph nodes, could be seen. Single or multiple solid nodules or consolidated nodules in the center of lobule, surrounded by ground-glass opacities are another less common picture [75].

The differential diagnosis of COVID-19 involves various respiratory tract viral infections [non

COVID-19 coronavirus, respiratory syncytial virus, para influenza, influenza and adenovirus], atypical bacterial infection such as mycoplasma, chlamydia and legionella. The differentiation of COVID-19 from such infections is sometimes not possible. So travel history becomes essential. However, as the epidemic spreads, the travel history will become irrelevant [76].

TREATMENT

No FDA-approved specific antiviral therapies are recommended for COVID-19 and there is no specific vaccine available until the date of writing this review [77]. Until now, the therapeutic strategies to deal with COVID-19 are only supportive. There are some anti-viral therapies created based on observational studies and case reports and no strong recommendation to hold up to date. These anti-viral therapies will be discussed in this review.

Indication for early antiviral treatment: Some studies have shown that the earliest possible start of antiviral therapy reduces serious complications of the disease (especially acute respiratory failure). The anti-viral treatments are highly indicated in patients with virologically ascertained diagnosis of infection by COVID-19 who had:

- Mild symptoms but with the presence of comorbidities or increased mortality risk;
- Clinical manifestations of moderate or severe disease.

REMEDESIVIR (compassionate use only) [78]

- ❖ Investigational antiviral drug, which initially developed for treatment of Ebola. It has been shown to inhibit SARS-CoV-2 in vitro.
- ❖ Phase 3 trials are not published.
- ❖ Mechanism of action: nucleotide analogue, inhibiting RNA-dependent RNA polymerase.
- ❖ Dose: Pediatric: < 40 kg: 5 mg/kg on day 1, followed by maintenance dose of 2.5 mg/kg q24h. Adult: loading dose: 200mg on day 1 then maintenance dose of 100mg OD for another 4 to 9 days according to clinical response, the dose should be intravenously infused over 30 to 120 minutes.
- ❖ Side effects- Elevated transaminases, reversible kidney injury, hypotension during infusion.
- ❖ Drug metabolism: it is a prodrug requiring CYP3A4 for activation thus there is potential

for reduced conversion in the presence of CYP3A4 inhibitors like lopinavir/ritonavir.

CHLOROQUINE/HYDROXYCHLOROQUINE

- ❖ Clinical studies have shown activity of chloroquine phosphate in vitro and in animal models as antiviral against the SARS virus [79].
- ❖ Mechanism of action: it increases the pH of the phagolysosome, which interrupts virus/cell fusion, as well as interferes with the glycosylation of cellular receptors of SARS-CoV [79].
- ❖ Dose: [80]
 - Hydroxychloroquine: Adult, 400mg PO Q12h x 1 day, 200mg PO Q12h x 4 days. 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)(Half-life is 22.4 days).
 - Chloroquine: 500mg bid for 7 days for adult aged 18-65years with body weight over 50Kg; 500mg bid for Days 1 & 2 and 500mg qd for Days 3-7 for adults with body weight below 50Kg.
- ❖ Chloroquine/Hydroxychloroquine is generally safe drug for short term use, with few drug-drug interactions and inexpensive.
- ❖ Hydroxychloroquine may be used for chemoprophylaxis (800 mg divided into 2 doses for the first day then 400 mg weekly or 200mg daily for frontline healthcare workers and 200 mg every 5 days for others).
- ❖ Side effects: Nausea and diarrhea, QTc prolongation, Most toxicities are associated with long-term use, Retinopathy with prolonged use (>5 years), not in the acute setting.
- ❖ G6PD testing only recommended for patients of Asian, African and Mediterranean descent.
- ❖ Safe in pregnancy.
- ❖ No dosing adjustment for hepatic or renal impairment or obesity.

Monitoring for Hydroxychloroquine (HCO) [81]:

- The estimated half-life is 40 days
- Monitor for hemolytic anemia with CBC every 2 days. Post-marketing studies suggest the risk of hemolysis is very low. Hydroxychloroquine can be started in most patients while waiting G6PD testing.
- Avoids taking hydroxychloroquine with antacids. At least 4 hours apart between administrations of these drugs.

- CrCl <10 and hemodialysis: reduce dose to 400mg po x 1 day then 200mg po, OD.
- Risk of QT prolongation: should be used with caution if other QT prolonging agent such as azithromycin or fluoroquinolones or if electrolytic imbalances (Keep potassium > 4.0 mg/dL and Magnesium > 0.82 mmol/L).
- Cardiac monitoring guidance [82]:

Given the growing evidence of myocarditis and arrhythmias with COVID, HCQ should be used with caution in this group of patients.

- Obtain baseline ECG.
- If on telemetry, check QTc and see if that corresponds to ECG QTc, if yes, use telemetry for further QTc monitoring. Otherwise use ECG for monitoring as noted below.
- Discontinue all other QT prolonging agents.
- Do not start Hydroxychloroquine if baseline QTc > 500 msec (or QTc > 550 msec in wide QRS patients) or discuss with cardiology if benefit vs risk is deemed high.
- Be cautious if Baseline QTc > 470 msec (or QTc>520 msec in wide QRS patients).
- Check Telemetry QTc/ Acquire ECG, preferably >2 hours after the 2nd dose of 400 mg Hydroxychloroquine.
- If QTc increases by less <50 msec; and if absolute QTc < 500 msec (<550 in wide QRS), use lower dose.
- If QTc increases by >50 msec; or if absolute QTc > 500 msec (>550 in wide QRS), use lower dose and recheck ECG daily for 2 days.
- Any evidence of Torsades on Telemetry, discontinue Hydroxychloroquine regardless of QT interval.
- Note that wide QRS defined as QRS > 120 msec.

The efficacy of hydroxychloroquine or chloroquine, when used alone or with a macrolide, was recently questioned(needs more studies). Furthermore, the in-hospital outcomes for COVID-19 was even worse. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19 [83] (needs evidence).

Lopinavir/Ritonavir [84]:

- ❖ Reduces viral replication by 50% in MERS – COV in vitro.
- ❖ Definite efficacy not proven in treatment of COVID-19.

- ❖ Mechanism of action: it is a known antiretroviral second generation which inhibits the viral protease of HIV.
- ❖ It is tried in combination with Interferon alpha and/or Ribavirin in treatment of MERS-COV.
- ❖ Potent CYP3A4 inhibitor – monitor for drug interactions.
- ❖ Side effects: Elevated transaminases, hyperbilirubinemia, Nausea, Vomiting, Significant drug interactions (e.g., azoles, anticoagulants, anti-epileptics).
- ❖ Liquid and oral formulations are available.
- ❖ Safe in pregnancy.
- ❖ Dose:
 - Adult: one tablet contains (Lopinavir 200mg/ritonavir 50mg), give 2 tablets PO Q12h for 6-10 days.
 - 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

Favipiravir [85]:

- ❖ It is a novel antiviral drug
- ❖ Mechanism of action: Favipiravir specifically targets the RNA Dependent RNA Polymerase (RdRP) but does not interfere with host RNA and DNA polymerases, meaning it is a selective inhibitor of viral RNA synthesis.
- ❖ Favipiravir is active against a broad range of RNA viruses.
- ❖ Used by Japan and China to treat uncomplicated influenza.
- ❖ At this moment, its efficacy and safety have not been established.
- ❖ Dose: limited data available on the optimal duration & dose, 1800mg BD for one day, then 800mg BD for 7 to 14 days, no need dose adjustment in renal impairment.

Ribavirin [86]:

- ❖ It was used in clinical practice during the SARS epidemic and the MERS-CoV epidemic. No study results yet in SARS CoV2.
- ❖ Mechanism of action: Inhibitor of RNA polymerization.
- ❖ Dose: loading dose: 2,000 mg po, followed by 10mg/kg q8h, po for 10 days.
- ❖ High risk of toxicity: hemolytic anemia or cytopenia. Therefore, if ribavirin is to be used, the patient should be closely monitored

for hemolytic anemia and other major adverse effects

- ❖ Renal dose adjustment is necessary.

TOCILIZUMAB

- ❖ Tocilizumab is FDA-approved for the treatment of several disorders, including cytokine release syndrome [87].
- ❖ The interest in using tocilizumab to treat persons with COVID-19 is based on the observations that some persons with COVID-19 develop a massive inflammatory response that can result in acute respiratory distress syndrome (ARDS), multi-organ failure, and potentially death [33]. This massive systemic inflammatory response has been characterized as a cytokine storm and very high levels of IL-6, thereby suggesting IL-6 may play a central role in the acute clinical decompensation [88].
- ❖ Tocilizumab is a humanized monoclonal antibody that binds to interleukin (IL)-6 receptors, thereby could potentially diminish this massive systemic inflammatory response [89].
- ❖ To this end, we recommend Tocilizumab be restricted to a much selected group of patients.

❖ **Inclusion Criteria**[90]:

Criteria for initiation of Tocilizumab in patients who are at high-risk for developing cytokine storm, includes (2 or more of the following):

1-Positive COVID-19.

2-All of the following respiratory findings:

- Abnormal chest imaging consistent with COVID-19.
- Rapidly deteriorating gas exchange/respiratory status over 24-48 hours and requiring more than 4-6 L/min O₂
- Absence of systemic fungal or bacterial co-infection.
- Mechanical ventilation for ≤48 hours.
- Does not have a poor prognosis where they are unlikely to survive >48 hours.
- High clinical suspicion for cytokine release syndrome supported by:
 - Serum IL-6 ≥3x upper normal limit.
 - Ferritin >300 ug/L (or surrogate) with doubling within 24 hours.
 - CRP > 100 mg/L with doubling within 24 hours

- Elevated D-dimer (>1 mg/L).
- Ferritin > 600 ug/L at presentation and LDH >250.

❖ **Exclusion Criteria[90]:**

- Active Tuberculosis.
- Active Hepatitis B and Hepatitis C.
- Sepsis by other pathogens.
- Transaminases 10 times above reference values.
- Neutropenia (<1000 cell/mm³).
- Thrombocytopenia (<50,000 /mm³).
- Patients on concomitant immunosuppressants, such as methotrexate or corticosteroids.
- ❖ Adverse effects: increased risk of reactivation of other Respiratory infections, elevation of liver enzymes, anemia and neutropenia.
- ❖ Dose: 4-8 mg/kg (usual dose: 600 mg/dose; max: 800 mg/dose) by IV infusion, maximum 2 doses 12 hours apart.
- ❖ Other IL-6 inhibitors: Sarilumab and Siltuximab (evaluated in clinical trials).

CONVALESCENT PLASMA (CP) [91,92]

- ❖ The use of convalescent plasma was recommended as an empirical treatment during outbreaks of Ebola virus in 2014.
- ❖ It was also used for treatment of MERS-COV.
- ❖ Mechanism of action: CP is a classic adaptive immunotherapy. When given to a susceptible person, this antibody will circulate in the blood, reach tissues, and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months. The principle of passive immunity builds on the premise that antibodies from CP may contribute to the clearance of the virus and also the improvement of symptoms. In addition to viral neutralizing antibodies, acceleration of infected cell clearance by antibodies.
- ❖ Dose: One unit of ABO compatible COVID-19 convalescent plasma will be administered. The duration of infusion will usually take 1 to 2 hours (rate of 100 to 250 mL/hr).
- ❖ It is strongly recommended that convalescent plasma immediately transfused to the recipients on the same day it was obtained. It is also recommended that convalescent

plasma administered at the early stage of disease.

- ❖ Very few studies published on the role of convalescent plasma containing neutralizing antibodies in SARS-Cov2, Two recently published studies have shown promising results especially in critically ill patients.
- ❖ Convalescent plasma with neutralizing antibodies have shown to improve clinical status, SOFA score, PAo₂/FiO₂ ratio and reduced viral load significantly.

Anticoagulation [93]:All patients should receive standard prophylactic anticoagulation with Low molecular weight heparin (LMWH) (enoxaparin 40 mg SC per day if D- dimer less than 1000 and 1 mg /kg/BID if D-dimer more than 1000) in the absence of any contraindications (Contraindications include platelet count less than 25,000 or active bleeding); monitoring is advised in severe renal impairment; abnormal PT or APTT is not a contraindication.

- ❖ If LMWH contraindicated due to renal failure (Creatinine Clearance < 30mL/min), Unfractionated Heparin 5000 units SC q12 (UFH) can be used as an alternative.
- ❖ Fondaparinux is preferred in those with heparin-induced thrombocytopenia.
- ❖ Direct acting anticoagulants(not used in CrCl<30,Child-Pugh B,C) as rivaroxaban(10 mg per day for prophylaxis if D- dimer less than 1000 and 15 mg twice per day if D-dimer more than 1000)and apixaban may be used with caution as antivirals and azithromycin may increase their plasma level.
- ❖ The duration of prophylactic anticoagulants is 31-39 days for post-discharge moderate and severe cases while the therapeutic anticoagulants are continued for 3 weeks .

AZITHROMYCIN [83,94]:

- ❖ No activity for SARS-CoV-2. Single study of combination therapy with hydroxychloroquine does not convincingly suggest added benefit to azithromycin combination therapy, given the study was recently retracted and concern for antibiotic overuse.

Corticosteroids [95,96]:There is significant interest and controversy surrounding the role of corticosteroids for the management of severe covid-19 pneumonia.

- ❖ The potential benefit of these agents to blunt the inflammatory cascade seen in severe disease needs to be carefully weighed against

the concerns for secondary infections, adverse events, and other complications of corticosteroid therapy.

- ❖ The data for corticosteroids are inconsistent, confusing, and inconclusive. Clinicians need to carefully weigh the risks and benefits of corticosteroids on the individual patient level. This need for a risk benefit assessment in individual patients and careful consideration of dose is exemplified in the COVID-19. Diagnosis and Treatment Guide from the National Health Commission of the People's Republic of China where the authors state "Based on respiratory distress and chest imaging, may consider glucocorticoid that is equivalent to methylprednisolone 1-2 mg/kg/day for 3-5 days or less.
- ❖ Large-dose glucocorticoid suppresses immune system and could delay clearance of SARS-CoV-2." A recent consensus statement from the Chinese Thoracic Society recommends a lower dose, $\leq 0.5-1$ mg/kg/day methylprednisolone for ≤ 7 days in select patients, after careful consideration of risks and benefits. Dexamethasone 6 mg /day/10 days oral or I.V. are recommended for patients on mechanical ventilation or not but require supplemental oxygen[166].
- ❖ WHO and CDC do not recommend the routine use of steroids in patients with COVID-19 pneumonia at this time. Use of steroids in patients with severe disease (requiring oxygen support or mechanical ventilation) could be considered as part of the supportive care regimen for patients with ARDS on a case-by-case basis.

ASCORBIC ACID [97]:

- ❖ Ascorbic acid has numerous proven biological properties (anti-inflammatory, anti-oxidant, immune enhancing, antiviral) that are likely to be of benefit in patients with COVID-19 disease.
- ❖ Furthermore, it is important to stress that ascorbic acid has proven synergistic effects when combined with corticosteroids. Therefore, steroids are recommended in patients with COVID-19 and respiratory failure. The benefit of ascorbic acid (without corticosteroids) in patients with severe respiratory failure appears to be limited.
- ❖ While the optimal dose of ascorbic acid is unknown, we suggest 3 g IV q 6 hourly. It should be noted that in the presence of free iron (released from ferritin) ascorbic acid may

potentially have pro-oxidant effects. Therefore, the trends in CRP and ferritin need to be closely monitored; in those patients who ferritin and CRP are increasing, reducing the dose to 1.5g q 6 hourly should be considered.

- ❖ However, no high-quality evidence supports the use of ascorbic acid in viral pneumonia.

Vitamin D [98]:

- ❖ Vitamin D has important immune-enhancing effects. Much of the population, especially the elderly have sub-optimal vitamin D levels, particularly during the winter months. Low vitamin D levels have been shown to increase the risk of developing viral upper respiratory tract infections. Therefore, prophylactic vitamin D should be considered especially in the elderly.

ZINC [99]:

- ❖ Zinc (Zn++) inhibits viral RNA dependent RNA polymerase (replicase). Chloroquine and hydroxychloroquine are potent Zn ionophores that increase intracellular Zn concentrations.
- ❖ This provides an interesting basis for further studies into the use of zinc- ionophores as antiviral compounds, although systemic effects have to be considered
- ❖ It has only been observed in-vitro. Oral supplementation of Zn has not been investigated. Zn needs special ionophore to be transported into a cell, to inhibit RNA replication.

Melatonin [100]:

- ❖ Very recent data suggests that in addition to being a potent anti-oxidant, melatonin may have direct antiviral effects against COVID-19. In healthy people, melatonin levels plummet after the age of 40 years. This may partly explain the increased risk of death in patients with COVID-19 who are over the age of 40. Melatonin may therefore have a role in both the prevention and treatment of COVID-19.

ANTI BACTERIAL THERAPY [101]:

- ❖ Bacterial pneumonia can emerge during the hospital stay (especially ventilator-associated pneumonia in patients who are intubated).
- ❖ They can be treated similarly to other hospital-acquired pneumonias or ventilator-associated pneumonias. Data has shown secondary bacterial infections are late manifestation of the COVID-19 disease process.

- ❖ Broad spectrum antibiotics can be started to treat secondary bacterial pneumonia according to the local institutional guidelines.
- ❖ Routine use of empiric antibiotics is strongly not recommended in COVID-19.
- ❖ Antibiotics can be started if high suspicion for secondary bacterial infection (ie PCT \geq 0.5).
- ❖ Doxycycline (may be used for prophylaxis), linezolid and azithromycin have antiviral effect.

Angiotensin-receptor blockers and Angiotensin converting enzyme inhibitors [102]:

Whether patients with COVID-19 and hypertension who are taking an ACE inhibitor or angiotensin-receptor blocker should switch to another antihypertensive drug remains controversial and there is no evidence support discontinuation of ACEi/ARB therapy to decrease risk for more severe COVID-19 at this time. There is some growing evidence showing that ARBS and ACE inhibitors improve clinical outcomes in COVID-19 patients [102].

Recombinant ACE-2 enzyme, as an inhaler may be useful to reach the receptors in the lung locally, and antiviral drugs could be interesting combination. However, the exact efficacy of this combination in COVID-19 treatment is not proved.

Ibuprofen/NSAIDs [103]:

- ❖ Do not discontinue these therapies for COVID-19 disease. Paracetamol is the preferred fever reducer for use in COVID-19. Although there has been theoretical concern raised for these agents worsening outcomes, no data currently exist to support this.
- ❖ FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms.

OTHER AGENTS under investigation

- ❖ Darunavir/Cobicistat
- ❖ Umifenovir (Arbidol)- 200 mg TDS
- ❖ Ivermectin : Patrì and Fabbrocini hypothesized that “hydroxychloroquine (HCQ) and ivermectin could act in a consequential and synergistic manner. HCQ would behave as a first-level barrier by inhibiting the entry of the virus into the host cell, while ivermectin could reduce viral replication if the virus did get in, strengthening HCQ antiviral

effects”[163]. Ivermectin is metabolized in liver and excreted in stool over 12 days. The half-life is 18 hours[165]. The suggested dose is 300 microgram per kg /day for 3 successive days for treatment and 300 micrograms per kg /day to be repeated after 48 hours (2 doses only) for prophylaxis of contact of positive case. It also may be used for one dose (300 micrograms per kg) every week (most common side effects are gastritis and sleepiness) with weekly HCQ as a prophylaxis for the frontline health care workers (needs human clinical trials).

- ❖ Nitazoxanide (with azithromycin).
- ❖ Traditional medicines in different countries as Traditional Chinese Medicine (TCM) treatment (Yin Qiao San, Yu Ping Feng San, Sang Ju Yin and Yu Ping Feng San, Lian Hua Qing Wen Capsule, Shuang Huang Lian and Ma Xin Gan Shi Tang), Madagascar covid 19 organic syrup made from *Artemisia annua* (sweet wormwood) and herbs (in some African countries) and Honey and Nigella Sativa in Pakistan Trial Against COVID-19.
- ❖ Human Mesenchymal Stem Cells: Under clinical trials for treatment of critically ill covid 19 patients.

The need for ICU management

Most patients with COVID-19 only show mild illness (81%); however, 14% approximately of the patients requires hospitalization and oxygen support. 5% of the patients requires monitoring in the Intensive Care Units [104,105].

Patients with mild illness do not need to be hospitalised, but isolation of them is necessary to contain spread of the virus [106-107]. Provide them with symptomatic treatments including antipyretics for fever associated with the infection, and counsel them to ask for medical help if any complications take place [106-107]. Provide patients with *supplemental* oxygen therapy immediately that are with SARI and respiratory distress, shock or hypoxemia and target SpO₂ > 94% [106,107].

Adults with critical signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma, or convulsions) should receive airway management and oxygen therapy during resuscitation to target SpO₂ \geq 94%.

Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO₂ ≥ 93% during resuscitation; or use face mask with reservoir bag (at 10–15 L/min) if patient in critical condition. Once patient is stable, the target is > 90% SpO₂ in non-pregnant adults[94] and ≥ 92–95% in pregnant patients [106,107].

Patients with hypoxemic respiratory failure should receive non-invasive ventilation (NIV). Patients with hypoxemic respiratory failure should receive high-flow nasal oxygen (HFNO). Patients treated with either HFNO or NIV should be closely monitored for clinical progression [106,107].

An RCT of ECMO for adult patients with ARDS was stopped early and found no statistically significant difference in the primary outcome of 60-day mortality between ECMO and standard medical management (including prone positioning and neuromuscular blockade) [108]. However, ECMO was associated with a reduced risk of the composite outcome of mortality and crossover to ECMO [108] and a post hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions [109]. In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort

Table (2): Treatment protocol for patients with COVID-19(modified)[164].

Severity of illness	Clinical presentation	Plan
Mild Uncomplicated Infection illness Symptomatic patient with leucopenia or lymphopenia with no radiological signs of pneumonia.	-Age less than 60y. -Fever less than 38. -SaO ₂ >92. -Heart Rate <110. -Respiratory rate <25. -Neutrophils/lymphocytes ratio <3.1. -Controlled comorbidities. -Non Pregnant. -No active malignancy. -Not on chemotherapy. -BMI <40. -Not on immunosuppressive drugs.	❖ Patient should be isolated at home. ❖ Droplet & contact precautions ❖ Clinical observation(if any deterioration occurs ,back to hospital). ❖ No specific antimicrobial advised ❖ Supportive treatment:: Vitamin C 500mg BID. Lactoferrin.; twice per day. Zinc 50 mg per day. Vitamin D3 1000-4000 u/day. Acetylcystiene 200 mg tds. Symptomatic drugs e.g antipyretic(paracetamol is preferred). ❖ Hydroxychloroquine, 400mg PO Q12h x 1 day, 200mg PO Q12h x 6 days or Ivermectin 300 microgram per kg /day for 3 successive days or Favipiravir .
Mild Uncomplicated Infection illness Symptomatic patient with leucopenia or lymphopenia with no radiological signs of pneumonia.	-Age >60y. -Fever more than 38. -SaO ₂ <92. -Heart Rate >110. -Respiratory rate >25. -Neutrophils/lymphocytes ratio >3.1. -Uncontrolled comorbidities. -Pregnant. -Active malignancy. -On chemotherapy. -BMI >40(morbid obesity). -On immunosuppressive drugs.	❖ Should be isolated at COVID centers. ❖ Supportive & Symptomatic treatment as above. ❖ Consider starting hydroxychloroquine, 400mg PO Q12h x 1 day, 200mg PO Q12h x 6 days or Ivermectin 300 microgram per kg /day for 3 successive days or Favipiravir . ❖ Observe closely. ❖ Avoid Nebulization and if inhaler medications are needed, use metered-dose inhaler(MDI)and spacer device.
Moderate Illness	-Pneumonia on radiology associated with symptoms. -<50% lung involvement on imaging.	❖ Supportive & Symptomatic treatment and isolation as above. ❖ Enoxaparin 40-60mg day (if not contraindicated; dose adjust with CrCl < 30ml/min)or 1mg/kg/ BID if D-dimer >1000. ❖ Consider starting hydroxychloroquine, 400mg PO Q12h x 1

study [110]. ECMO should be offered only in expert centers with a sufficient case volume to maintain expertise and that can apply the IPC measures required for adult and pediatric COVID-19 patients [111-112].

Acute hypoxemic respiratory insufficiency or failure requiring oxygen and ventilation therapies is a common complication of COVID-19. Sometimes the disease progress in spite of mechanical ventilation (**Figure 4**) [45,104]. In a recent report 14% of patients reported to developed dyspnea, desaturation with peripheral oxygen saturation (SpO₂) ≤ 93%, tachypnea with a respiratory rate ≥ 30 per minute ,poor oxygenation with a ratio of partial pressure of arterial oxygen (PaO₂) to fraction of inspired oxygen (FIO₂) <300 mmHg, or lung infiltrates > 50% within 48 hours [60].

Suggested therapeutic protocols for COVID-19 patients [77,113]:

No proven therapeutic protocols for treatments of COVID-19. The following therapeutic protocols are suggested on the basis of information available till date on different investigational treatment approaches.

		<p>day, 200mg PO Q12h x 9 days plus Ivermectin 300 microgramper kg /day for 3 successive days OR Lopinavir/Ritonavir(2 tab/12h) with ripavirin (400mg/12h for 14 d, not if symptoms started more than 7 day) OR Favipiravir .</p> <ul style="list-style-type: none"> ❖ Corticosteroids if patient is dyspneic or chest CT deterioration. ❖ N/C O2, 2L /min if needed (max 4 L/min; consider early transfer to ICU for escalation of care). ❖ Avoid Nebulization and if inhaler medications are needed, use MDI and spacer device. ❖ Avoid non-invasive ventilation. ❖ Start empirical antibiotics(azithromycin , doxycycline or levofloxacin) as per local institutional protocol for treatment of community acquired pneumonia(add meropenem or cefepime + linezolid if needed).
Severe Illness	<p>-Respiratory rate > 30/min. -SpO2 <92% on room air. ->50% lung involvement on imaging.. -PaO2/FiO2<300 -High risk factors for severe illness.</p>	<ul style="list-style-type: none"> ❖ 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 ❖ Consider starting hydroxychloroquine, 400mg PO Q12h x 1 day, 200mg PO Q12h x 9 days plus Ivermectin 300 microgram per kg /day for 3 successive days OR plus Lopinavir/Ritonavir plus azithromycin or doxycycline. OR Lopinavir/Ritonavir+ribavirin+interferon +azithromycin or Doxycycline OR Favipiravir OR Remdesivir .
Critical Illness	<p>-Respiratory failure, Shock, Multi organ dysfunction. - PaO2/FiO2<200.</p>	<ul style="list-style-type: none"> ❖ Continue Supportive and symptomatic treatment with some modifications: Vitamin C: 3g every 6 hours, IV till extubated or for at least 7 days. Early termination may result in a rebound effect. Magnesium: Prevent hypomagnesemia (which prolongs Qtc and increases the cytokine storm). Melatonin: 6-12 mg at night (the optimal dose is unknown). ❖ Antiviral as severe case. ❖ Continue IV Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin(PCT) levels (≥ 0.5) and respiratory culture (no bronchoscopy). ❖ Rule out catheter related infections, ventilator associated pneumonia and other secondary bacterial, fungal, viral infections. Rule out differentials of non – resolving pneumonia. ❖ Corticosteroids: a) During the early viral replicative stage, corticosteroids should be avoided. b) During the hyperimmune/hypercoagulable phase (day 6-8 onward) in patients with hypoxia: methylprednisolone 1mg/kg/d(2mg/kg/d for ventilated patients) for 6 days is suggested or dexamethasone 6mg /day for 10 days. ❖ Anticoagulation: Therapeutic dose of LMWH (if not at high risk of bleeding) enoxaparine 1mg/kg BID. ❖ Using Carefully these drugs (if available) 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. Convalescent plasma (Preliminary trials: showed to improve symptoms, PaO2/FiO2, SOFA score and reduce viral load) ❖ Steps of escalation of respiratory support; (Try to avoid intubation if at all possible) • Accept “permissive hypoxemia” (O2 Saturation should be > 90%) • nasal cannula O2, 1-6 L/min • High Flow Nasal canula (HFNC) up to 60-80 L/min • Attempt proning (cooperative proning of non-intubated patient). • Intubation: a) By Expert physician; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided. b) Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cmH2O. c) Moderate sedation to prevent self-extubating. d) Prone positioning e) ECMO < 55 yrs , no severe comorbidities/organ failure,MV less than 7d , conscious and PaO2/FiO2<100 despite prone.

Discharge Guidance: The criteria of discharge from isolation are described in Table 3.

Recently; discharge are divided into:

1. Time based discharge: After 10 days of positive test (for asymptomatic cases).
2. Symptom based discharge: After 10 days of start of symptoms with the last 3 days without symptoms (no fever or respiratory symptoms) (mostly for mild symptomatic cases), SaO₂ >92% on room air with stable chest imaging (for moderate cases).
3. Test based discharge: For hospitalized patients with risk factors and morbidity (table 3).

Table (3): Comparison of current guidelines on de-isolation of COVID-19 cases

	Asymptomatic infected persons, isolated at home or institutional	hospitalized Symptomatic cases
CDC USA Interim guidance for discontinuation of transmission-based precautions and disposition of hospitalized patients with COVID-19 [114].	At least negative 2 consecutive rRT-PCR test of nasopharyngeal and throat swabs collected ≥ 24 hours apart from a patient with COVID-19 (a total of four negative samples) Note: decision to be taken on a case-by-case basis in consultation with clinicians and public health officials	Negative rRT-PCR results from at least 2 consecutive samples of nasopharyngeal and throat swabs collected ≥ 24 hours apart from a patient with COVID-19 (a total of four negative samples). AND improvement in illness signs and symptoms, resolution of fever without use of antipyretic medication. Note: decision to be taken on a case-by-case basis in consultation with clinicians and public health officials.
Italy Ministero della salute, Consiglio Superiore di Sanità [115].	Negative SARS-CoV-2 PCR test from respiratory samples at 14 days after the initial positive test (end of the quarantine period).	A COVID-19 patient can be considered cured after the resolution of symptoms and 2 negative tests for SARS-CoV-2 from respiratory samples at least 24-hour intervals. For patients who clinically recover earlier than 7 days after onset, an interval of 7 days between the first and the final test is recommended. Note: Virus clearance is defined as viral RNA disappearance from bodily fluids of symptomatic and asymptomatic persons, accompanied by appearance of specific IgG.
ECDC [116].		COVID-19 patients may be discharged from hospital and moved to home care based on: clinical criteria (e.g. no fever for > 3 days, improved respiratory symptoms, pulmonary imaging showing obvious absorption of inflammation, no hospital care needed for other pathology, clinician assessment). Laboratory evidence of SARS-CoV-2 clearance in respiratory samples; 2 to 4 negative rRT-PCR tests for respiratory tract samples (nasopharynx and throat swabs with sampling interval ≥ 24 hours). Testing at a minimum of 7 days after the first positive RT-PCR test is recommended for patients that clinically improve earlier. Serology: appearance of specific IgG when an appropriate serological test is available.
China CDC Diagnosis and treatment protocol for COVID-19 patients (trial version 7, revised) [117].		Patients meeting the following criteria can be discharged: <ul style="list-style-type: none"> • Improved respiratory symptoms. • Afebrile for >3 days. • pulmonary imaging shows obvious absorption of inflammation, and • Negative PCR test for SARS-CoV-2 twice consecutively from respiratory samples (sampling interval ≥ 24 hours). After discharge, covid-19 patients are recommended to continue 14 days of isolation management and health monitoring, wear a mask, reduce close contact with family members, live in a single room with good ventilation, keep hands clean and avoid outdoor activities, eat separately. It is recommended that discharged patients should have follow-up visits after 2 and 4 weeks.
National Centre for Infectious Diseases (NCID) Singapore De-isolation of COVID-19 suspect cases [118].		Discharge patient with advisory and clinic follow-up if indicated and with daily wellness calls until day 14 after last possible exposure, under the following conditions: <ul style="list-style-type: none"> • Afebrile ≥ 24 hours, • 2 respiratory samples tested negative for SARS-CoV-2 by PCR in ≥ 24 hours,

		<ul style="list-style-type: none"> • Day of illness from onset \geq 6 days OR • Alternative etiology found (e.g. bacteremia, influenza) OR • Does not require in-patient care for other reasons. • Not a close contact of a COVID-19 case.
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PROTECTION

A vaccine against COVID 19 is not expected to become available soon, so the main strategy of managing this pandemic is trying to decrease its spread, through various measures seeking to reduce the rate of new infections [119-120].

General:

The general precautions are the mainstay in facing this rapidly spreading pandemic. The lines of general protection include social distancing with home stay. Maintain a distance of at least 1.8 meter with other people. Hand hygiene practice, accurately with water and soap for at least 20 second if not actually available or applicable, can use hand sanitizer an alcohol-based with 60% concentration at least, and do not touch face with unwashed hands. Avoid crowdedness in different occasions to reduce the risk of transmission. In fact, many countries around the globe practiced different polices based mainly on avoiding personal crowdedness and some countries even applied widespread institutions shut down and curfew [121].

Contact:

Contact with persons suspected or confirmed to be infected with COVID-19 must wear at least minimum amount of PPE, different styles may be necessary to perform health related duties, which are disposable gloves, isolation coveralls and respirator mask as fit size N-95; facemasks are an acceptable alternative, and protection of the eye (disposable goggles or shield that must fully covers the face front and sides [122].

Healthcare workers:

Aerosols generating procedures on COVID-19 infected patients admitted in the ICU, it recommended to use approved fitted size respirator masks by healthcare workers, as compared to surgical masks, with other PPE in a negative-pressure room. Performing endotracheal intubation on infected patient is suggested by using, if available video guided laryngoscopy, over direct laryngoscopy. Usual care for non-ventilated infected patients is by using surgical masks, as compared to respirator masks with other PPE [123]. Ensure trained personnel wearing suitable personal protective equipment (PPE), when dealing or transporting suspected cases. Globally, the incidence of health care

workers catching the infection from handling the patients is increasing with high proportion of mortality, that is why an algorithm for dealing with health care workers is proposed (Figure 5).

Environment disinfection procedures in hospitals

- Surface disinfection is by whipping with chlorine-containing disinfectant at least 1000mg/L concentration then wipe twice with ethanol 75% every four hour.
- Disinfection of equipment in the contaminated area is by wiping with disinfectant 2000mg/L chlorine, while in the other areas are wiped with concentration 500-1000 mg/L chlorine or disposable disinfectant wipes alcohol-containing two times at a day.
- Disinfection of air is by shutting off the whole air conditioners especially the central to guard against spread of air contamination. Ventilation by door opening, more than 30 minutes, every 4 hours and inner shielding door closure when disinfection of air suspected, spraying air with 1000mg/L chlorine disinfectant two times per day. Air disinfection is conducted for half hour before other patient examination.
- Disinfection of the ground is done by wiping it with chlorine disinfectant 1000 mg /L concentration, every four hours.
- Disinfection should be done when visible contamination occur, absorbent disposable materials should be used to remove the pollutants firstly, then soak it with 2000 mg /L chlorine disinfectant for at least half hour before whipping it [124].

CARDOIVASCULAR AFFECTION WITH COVID 19

Cardiac injury:

Recent studies stated that acute cardiac injury is an important manifestation of COVID- 19. Here, acute cardiac injury is defined as either increased cardiac troponin level $>99^{\text{th}}$ percentile alone or a composite of troponin elevation plus ECG or echocardiographic abnormalities [45, 125,126].

Evidence of cardiac injury tend to occur in patients with comorbidities, including baseline hypertension, diabetes, coronary heart disease, and heart failure [125, 127] and associated with worse outcomes, including ICU admission and death [45,25,127].

Arrhythmia

Arrhythmias have been reported in some patients with COVID-19 during their hospitalization with higher rates among ICU patients [45].

Arrhythmias including ventricular tachycardia or ventricular fibrillation were observed [127]. These findings are consistent with arrhythmias documented in influenza, which has been known to cause both AV node dysfunction and ventricular arrhythmias [128].

Heart failure, cardiogenic shock and myocarditis:

Heart failure and myocardial dysfunction have been described in COVID-19 [126], [129-132]. Some reports confirmed fulminant myocarditis by cardiac MRI [131]. In some case series [127], myocardial damage or heart failure contributed to 40% of deaths overall with 7% attributed only to circulatory failure without respiratory failure.

Putative Mechanisms of Cardiovascular Manifestations in SARS-CoV2 [127,133]:

- Direct viral myocardial injury.
- Microvascular injury.
- Stress cardiomyopathy.
- Acute coronary syndrome.
- Myocardial injury secondary to oxygen supply and demand mismatch.
- Systemic hyper-inflammatory response with resulting myocardial injury.

LIVER AFFECTION WITH COVID 19

COVID-19 also affects liver because ACE2 is expressed by liver and bile duct cells and COVID-19 uses ACE2 as its entry receptor causing damage to bile duct cells [134].

Pathology of affected liver with COVID-19 is moderate microvascular steatosis and mild portal and lobular activity [135]. Also asymptomatic COVID-19 patients who had less AST abnormality than symptomatic COVID-19 patients who had symptoms as fever and dry cough before their diagnosis. Liver damage is predominant in severe cases than mild cases of COVID-19 [60,136,137]. By lab investigation COVID-19 patients have an elevation of liver enzymes. In primary biliary cholangitis, COVID-19 aggravates cholestasis also it causes an

elevation in alkaline phosphatase and GGT. Patients with Hepatic cirrhosis and malignancy are more vulnerable to be infected with COVID-19 due to their decreased immunity [60].

COVID 19 , GIT MANIFESTATIONS AND ENDOSCOPY

Regarding COVID 19, respiratory symptoms are usually the presenting symptoms [138]. Less commonly, GIT symptoms were noticed, such as nausea, vomiting, abdominal discomfort, GIT upset and diarrhea. These symptoms usually appear prior to respiratory symptoms [139].

GIT tropism of SARS-CoV infection can be detected by intestinal biopsy and in the stools of discharged patients. This may explain the GIT symptoms of SARS-CoV and its potential recurrence [138].

Noted that the first case diagnosed in the United States reported 2 days history of nausea and vomiting on admission then developed loose stool during hospitalization [138]. The SRARS-COV 2 sequence could detected in the self-collected saliva of most infected patients even not in naso-pharyngeal aspirate [139]. During hospitalization, viral load declining should be noticed in serial salivary specimens [139]. Many efforts should be made to be alert on the initial digestive symptoms of COVID-19 for early detection, diagnosis and isolation[138].

COVID-19 and GIT Endoscopy

SARS-CoV-2 coronavirus is a highly infectious disease. Patients with chronic diseases, autoimmune diseases and elderly are at high risk. Spread through contact, respiratory droplets and aerosols.

As endoscopy is a high aerosol generating procedure. Endoscopists must be careful and take precautions. Upper GIT endoscopy can generate aerosols during scope intubation, coughing and vomiting. Lower GIT endoscopy can generate aerosols through passing flatus during procedure [140-143].

Recommendations [142,143]:

Globally there is no consensus regarding performing GIT endoscopy in the era of COVID-19. However, different endoscopic societies and different health care facilities released different regulatory recommendations for performing GIT endoscopy. The recommendations listed down are consistent with the global medical trend to differ non-emergency procedures to a later time

after the pandemic had been controlled. These recommendations are mainly released to both protect health care workers, interfere with spread of the infection and ensure high quality procedures.

- 1- Postpone all elective endoscopic procedures. Emergency procedures should be performed under the strict precautions described below. Also, cases where the endoscopy will change their line of management i.e. time sensitive conditions e.g. patients with suspected malignancies should not be postponed.
- 2- Efficient history taking before endoscopy which includes (travel history, contact, occupational exposure and clustering)
- 3- Efficient clinical examination (Fever more than 38 C°, Chest examination to detect chest diseases, abdominal examination to detect GIT symptoms and signs). Both will effectively triage patients presented for endoscopy.
- 4- Upper GIT endoscopies carry a higher risk of infectivity.
- 5- Lower GIT endoscopies could be infective.
- 6- Confirmed COVID-19 patients should undergo urgent procedures only (GIT bleeding, foreign body extraction, ERCP for cholangitis).
- 7- Personal Protective Equipments (PPE) during endoscopy:
 - Respiratory mask (FFP2/FFP3, CAPR, N95)
 - Waterproof full sleeve single use gown
 - Gloves (some recommend double gloves with checking of its integrity before the procedures) [144].
 - Protective eyewear
 - Single use hairnet
 - Single use shoe covers

Operating theaters:

- a) The essential medical staff is preferred in the endoscopy room to decline the spread of SRAS-Cov-2 virus.
- b) Pitfalls in using PPE are frequently encountered, so formal training on donning and doffing PPE and safe disposal is essential to prevent transmission within hospitals and especially the endoscopy unit.
- c) Prior donning and post doffing PPE hand washing and sterilization.
- d) If procedure needs endotracheal intubation, it is preferred to perform the procedure in a negative pressure room. Consequently, the

- e) endoscopy units needs to increase or develop their negative pressure room if not available.
- e) During intubation, it is preferred that only the Anesthesia consultant and assisting nurse to be existing only in the theatre.
- f) Between procedures, Room must be cleaned by veridical agents and disinfection.
- g) When supplies of PPE are low, extended use is preferred over reuse due to lower risk of direct contamination resulting from frequent touching of the mask [145].
- h) The endoscopy standard reprocessing instructions are efficient to destroy SARS-Cov-2 after revising the manufacturer's instructions.
- i) Endoscopy disinfection should follow the standard disinfection guidelines. However, an extra 30 minutes disinfection after confirmed cases of COVI-19 may be advised.
- j) It is advisable not to reuse disposable accessories.
- k) However, we feel that follow-up of patients after endoscopic procedures is important during the COVID-19 pandemic, to help the endoscopy unit monitor the effectiveness of its policies and adjust them based on the rate of post-procedure infections.

NEUROLOGICAL MANIFESTATIONS OF COVID 19

Neurological manifestations of COVID-19 have not been properly studied .Some patients, especially those with severe illness, have CNS manifestations [161]. The COVID 19 virus disseminates through the cribriform plate and olfactory bulb as well as trans-synaptic transfer . The refractory respiratory failure seen in critically-ill COVID-19 patients may be due to invasion of the medullary cardiorespiratory center by the virus [162]. The most common reported neurological symptoms are headache, hyposmia, weakness, altered consciousness, encephalopathy and delirium. Neurological complications include Cerebrovascular accident, acute encephalitis, Guillian barre syndrome and acute transverse myelitis. Neurological manifestations can precede the typical COVID 19 symptoms [160,162].

CUTANEOUS MANIFESTATIONS OF COVID 19

The dermatologic manifestations associated with COVID-19 are many, nonspecific and varied. Nearly all patients could be classified in these groups, and a few unusual cases are seen [146].

- 1.-Acral areas of erythema-oedema with some vesicles or pustules (pseudo-chilblain) (19% of cases). These lesions may resemble chilblains and have purpuric areas; affecting hands and feet.They were usually asymmetrical [147].
- 2.-Other vesicular eruptions (9%). Some presented on the trunk and consisted of small monomorphic vesicles (unlike polymorphic vesicles in chickenpox) .They may also affect the limbs, have haemorrhagic content, and become larger or diffuse [148].
- 3.- Urticarial lesions (19%): mostly distributed in the trunk or disperse. A few cases were palmar [150].
- 4.- Other maculopapules (47%). Some of them showed perifollicular distribution and varying degrees of scaling. Some had been described as similar to pityriasis rosea. Purpura may also be present, either punctiform or on larger areas [151]. A few cases showed infiltrated papules in the extremities, mostly dorsum of the hands, that look pseudovesicular or resemble erythema elevatum diutinum or erythema multiforme [152].
- 5.- Livedo or necrosis (6%). These patients showed different degrees of lesions suggesting occlusive vascular disease, including areas of truncal or acral ischemia [149].

The mechanisms of COVID-19 cutaneous disturbances are not yet well known, but some common theories are prevalent [153]. It can be postulated that the viral particles present in the cutaneous blood vessels in patients with COVID19 infection could lead to a lymphocytic vasculitis similar to those observed in thrombophilic arteritis induced by blood immune complexes that activate cytokines [154]. Keratinocytes may be a secondary target after Langerhans cells activation, inducing a spectrum of different clinical manifestation [155]. It can be postulated that the virus does not target the keratinocyte, but rather immune response to infection leads to Langerhans cells activation, resulting in a state of vasodilation and spongiosis. Further theories suggest livedo reticularis-resembling manifestations can result due the accumulation of microthromboses originating in other organs, thus reducing blood flow to the cutaneous microvasculature system [156]. Similarly, low grade disseminated intravascular coagulation and hypoxia-related accumulation of deoxygenated blood in venous plexes may further explain such manifestations

[157]. Additionally, pauci-inflammatory thrombogenic vasculopathy with deposition of C5b-9 and C4d as well as co-localization of these with COVID-19 spike glycoproteins [158]. It is still unclear whether cutaneous symptoms are a secondary consequence of respiratory-related infection or a primary infection of the skin itself. It is more likely that a combination of such mechanisms is responsible for the cutaneous manifestations found in COVID-19+ individuals [159].

POST-VIRAL SYNDROME POST COVID-19

Perrin et al proposed that once an acute COVID-19 infection has been overcome, a subgroup of remitted patients are likely to experience long-term adverse effects resembling Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) symptomatology such as persistent fatigue, diffuse myalgia, depressive symptoms, and non-restorative sleep [167].Also George et al stated that data from previous coronavirus infections such as severe acute respiratory syndrome and Middle East respiratory syndrome, as well as emerging data from the COVID-19 pandemic, suggest there could be substantial fibrotic consequences following SARS-CoV-2 infection[168].

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