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Abstract
The COVID-19 pandemic has taken us unprecedented, and management of comorbidities has become challenging as a consequence. Presence of comorbidities has shown to be an increased risk factor for critical illness. Since it’s a relatively new disease, there is a lack of robust clinical data concerning COVID-19 infection and presence of comorbidities. Among the COVID-19 patients who died in Italy, it was observed that those with comorbidities including hypertension (69%), diabetes (31%), ischemic heart disease (27%), atrial fibrillation (21%), and heart failure (16%) were the most important factors for the increased mortality rates observed (Gruppo Della database, 2020). The highest percentage of association was with hypertension. In a meta-analysis done, it was shown that the extent of hyperglycemia was lower in survivors and non-severe subset of patients. Similarly, presence of hypertension was associated with higher mortality rates and necessity of ICU care. So far there is no evidence to show that hypertension reduces immunity or increases the predisposition toward getting infected with COVID-19.

Introduction
The COVID-19 pandemic has taken us unprecedented, and management of comorbidities has become challenging as a consequence. Presence of comorbidities has shown to be an increased risk factor for critical illness. Since it’s a relatively new disease, there is a lack of robust clinical data concerning COVID-19 infection and presence of comorbidities. Among the COVID-19 patients who died in Italy, it was observed that those with comorbidities including hypertension (69%), diabetes (31%), ischemic heart disease (27%), atrial fibrillation (21%), and heart failure (16%) were the most important factors for the increased mortality rates observed (Gruppo Della database, 2020). The highest percentage of association was with hypertension. In a meta-analysis done, it was shown that the extent of hyperglycemia was lower in survivors and non-severe subset of patients. Similarly, presence of hypertension was associated with higher mortality rates and necessity of ICU care. So far there is no evidence to show that hypertension reduces immunity or increases the predisposition toward getting infected with COVID-19.

Management of Hypertension in the COVID-19 Era and the Possible Role of RAAS Inhibitors
With the current scenario, it becomes very crucial to manage cardiovascular risk factors to reduce significant morbidity and mortality. A significant proportion of these patients are on renin-angiotensin-aldosterone system (RAAS) inhibitors as therapy for their hypertension. The European Society of Cardiology (ESC) has come up with a recent guidance document under the expert panel of health-care professionals managing COVID-19 concomitantly with cardiovascular disease. Multivariable adjusted models have shown cardiac injury, especially elevated cardiac troponin-T levels to be a significant mortality indicator. Studies have reported that in a significant proportion of COVID-19 patients, direct myocardial injury resulting in elevated cardiac troponins is the main effect seen (approximately 8–12% patients). Presence of pre-existing cardiac disease tends to worsen this. Additionally, COVID-19 associated pneumonia...
has shown to induce long-term hypercoagulable state, which again contributes to worsening cardiovascular outcomes. The viral myocarditis has also been responsible for precipitating arrhythmias. Taken into consideration all these factors, ESC has suggested that it’s vital to communicate to seek immediate medical guidance if a patient has been diagnosed with COVID-19 and has significant cardiovascular comorbidities. The emphasis is not to discontinue any of the drugs, either aspirin or RAAS inhibitors unless as advised by the treating specialist.

In a large retrospective study in 2,877 patients admitted with COVID-19 at Huo Shen Shan hospital, Wuhan, 29.5% presented with a history of hypertension. Interestingly, it was observed that in patients who had a history of hypertension but were not under current therapy for the same, the mortality rate was twice as those who were being managed with pharmacotherapy for the same [HR:2.17, (1.03-4.57, p=0.04)]. In fact, the mortality rates were similar for those on RAAS inhibitors versus those on other classes of antihypertensive drugs [HR: 0.85, (0.28-2.58,p = 0.774)], although the results were not statistically significant. In the largest study of its kind, 884 COVID-19 positive patients were enrolled out of which 149 had hypertension, and interestingly majority of the patients were treated with calcium channel blockers. Compared to those without a history of hypertension, this subgroup of patients presented with more severe respiratory symptoms requiring more intensive therapy including use of intravenous immunoglobulin therapy and ultimately longer ICU stay. This again emphasizes the importance of aggressive BP management for better outcomes. In another study from Wuhan province, Yang et al. attempted to understand the role of hypertension further. To remove the possibility of bias due to various confounding variables that may skew the analysis, a propensity score matching (PSM) was done. In the cohort of 226 COVID-19 patients studied, analysis revealed that presence of hypertension could increase death rate significantly (HR: 3.317, CI: 1.709-6.44, p<0.001). Interestingly, elevated D-dimer levels and higher neutrophil-lymphocyte ratio was found to increase mortality risk overall. However, this difference was not significant across the age groups, whether less than 65 years of age or above.

In a larger scale epidemiological study from Spain, involving 1,139 COVID-19 patients on concurrent therapy with RAAS inhibitors, further attempt was made to understand the effect of this class of drugs (cases) as compared to those on other classes of antihypertensives acting as control subjects. The cases were control matched by a factor of 10 to give a total of 11,390 controls. Interestingly, there was no increase in the severity of COVID-19 symptoms requiring hospital admission or increase in the complication rate leading to more fatality for the cases relative to the controls (OR: 0.94, CI: 0.77-1.15). In another large cohort study of 5,700 COVID-19 patients from the Northwell area, New York, it was seen there was no significant difference in mortality rates between those managed with RAAS inhibitors versus those on other classes of antihypertensives. It’s an established fact that these drugs increase the mRNA expression of cardiac ACE2, but yet their role in determining outcomes in COVID-19 patients remains ambiguous. Although the data studied were observational studies and not randomized control trials (RCTs), there is a certain degree of reassurance that RAAS inhibitors can be safely continued in spite of the infection. One of the studies reportedly employed a Bayesian method of analysis in COVID-19 subjects to determine whether any of the five classes of antihypertensive drugs (ACE-inhibitors, ARBs, beta-blockers, calcium channel blockers and thiazide diuretics) played a role in the severity of infection. One of the advantages of using a Bayesian analysis is that unobserved variables can be accommodated in the process whenever there’s a diagnostic or clinical error thus rendering the analytic process more robust. None of these classes of drugs were associated with worsening outcomes in COVID-19 disease. There has also been reports of usage of RAAS inhibitors resulting in attenuation of inflammatory markers like IL-6; the authors have also reported that calcium channel blockers as a class has also shown mortality benefits; they have also emphasized the use of telemedicine platforms in this pandemic era to provide better access to health-care resources and for better outcomes. Mobile health services have been emphasized especially for the populations with limited access to health-care resources. With just an application on the mobile phone, patients can continuously communicate with the health-care providers as long as self BP monitoring (SBPM) training is provided. In another retrospective review based in Shenzen Third People’s Hospital, 42 COVID-19 positive patients were categorized as those on RAAS inhibitors versus other classes of antihypertensives.
The percentage of patients ending up with severe disease was lower for those RAAS inhibitors (23.5%) with no mortality numbers whereas those on non-RAAS inhibitors the percentage was higher (48%) and one patient died. Also levels of inflammatory markers, IL-6, CRP were lower in the former; in addition the CD3+, CD4+, CD8+ cell count was higher for those on RAAS inhibitors with lower viral load. Although no direct causality can be established with use of RAAS inhibitors and severity of disease, the authors assume that the differences observed could be attributed to the higher levels of Angiotensin-II for those on non-RAAS inhibitors. In a similar retrospective study, 282 hypertensive patients admitted for COVID-19 were identified, out of which 41 subjects were managed with RAAS inhibitors versus 241 who were on alternate class of drugs. Primarily, the authors noted that hypertensive patients as a group were more likely end up critically ill. All cause mortality was higher in this group as per cox regression analysis. Additionally, use of RAAS inhibitors was associated with lower CRP levels and higher CD4+ cell count, with better outcomes. Hence, they emphasize on a holistic approach on managing patients and continuing the antihypertensive therapy no matter what the class of drugs being used.

**RAAS Inhibitors Mechanism of Action and the Pathway of COVID-19 Infection**

There are multiple mechanisms through which RAAS inhibitors work on the cardio-metabolic axis and could potentially interfere with the clinical course of COVID-19 infection.

As far as the discussion above is concerned, there is couple of factors that needs to taken into account. Firstly, how much does hypertension play a definite role in the severity of COVID-19. Sisnieguez et al. has commented in a review study about the possibility of confounding factors that could possibly lead to false conclusions about the association between hypertension and COVID-19 outcomes. They go to explain that the increased mortality observed in the elderly with COVID-19 could be confounded due to increased prevalence of cardiovascular disease in the elderly which has been well established in the multivariate model (where the association between cardiovascular disease and COVID-19 is well established), but this has not been established with hypertension per se. Therefore, before any conclusions could be made concerning hypertension and severity of COVID-19 infection, these confounding factors should be adjusted appropriately. Secondly, the role of RAAS inhibitors in the outcomes of COVID-19 infection seems ambiguous and more research is needed to ascertain further as to whether their use results in better or adverse clinical outcomes in the COVID-19 scenario (Fig. 1 and Flowchart 1).

**Where do we Stand with the Available Data?**

It’s not surprising that majority of COVID-19 patients are hypertensive and does not necessarily imply any causality between the two conditions. It just is a finding that hypertension as comorbidity is very common in the elderly and COVID-19 is an infection that the elderly are particularly vulnerable to and prone to develop severe clinical presentation of the disease. Hence, most of the data that’s available so far is more of a clinical guidance and not conclusive evidence. In the current pandemic situation, owing to the limited allocation of time and resources so far to deal with the unprecedented situation, most of the data that’s available is observational study data and not RCTs and may not be the best in terms of hierarchy of evidence. We have had prior scenarios where there was discordance between observational and RCT studies, which was attributed to various factors including selection bias, presence of confounding factors, differences in...
statistical power of the study, and issues with study adherence throughout. A classic example was the finding that bisphosphonates decrease risk of postmenopausal breast cancer as ascertained by observational study which was later refuted based on the results from a couple of RCTs.\(^\text{15}\) Hence, one needs to be careful in forming conclusions about the association of hypertension and COVID-19 infection and also about the use of RAAS inhibitors. Yet, it would be reasonable to assume that managing hypertension and other comorbidities would be of high priority. Since there’s no conclusive data showing the deleterious effect of any class of hypertensive drugs, it would be wise to continue the drug to maintain BP control. As discussed earlier, for newly detected hypertension, classes of drugs other than RAAS inhibitors could be considered for initiation of therapy due to the paucity of conclusive evidence concerning either the benefits or possible deleterious effects of RAAS inhibitors on the severity of COVID-19 infection.

**Conclusion**

For newly detected hypertension, classes of drugs other than RAAS inhibitors could be considered for initiation of therapy due to the paucity of conclusive evidence concerning either the benefits or possible deleterious effects of RAAS inhibitors on the severity of COVID-19 infection.

**References**

Emerging and reemerging infectious diseases have plagued mankind and have been potential killers since historic times. The current pandemic of COVID-19 is the latest crisis that has challenged leadership and health infrastructures globally. COVID-19, caused by SARS-CoV-2, began as an outbreak of pneumonia of unknown cause at a local seafood market in Wuhan, China, and soon spread globally claiming more than a million of lives. The virus has a wide spectrum of symptoms due to the ability of its S protein to bind to h-ACE2 receptors on various tissues like lung, heart, kidneys, GI tract, and olfactory epithelium. It transmits predominantly as a respiratory droplet infection from person to person and by direct contact with contaminated surfaces. COVID-19 encompasses a spectrum of asymptomatic/presymptomatic, mild, moderate, and severe to life threatening critical illness. Most common symptoms are cough (53%), fever (43%), myalgia (36%), headache (34%), dyspnea (29%), and sore throat (20%); less common are diarrhea, nausea, vomiting, anosmia, dysguesia, and dermatological manifestations. Risk factors for severe disease are old age, uncontrolled hypertension, diabetes, COPD, cardiovascular disease, obesity (BMI > 30), and malignancy and immunocompromised status. Patients of COVID-19 develop complications like pneumonia with or without respiratory failure, cardiomyopathy, acute myocardial ischemia, arrhythmias, thromboembolic complications, cytokine release syndrome, encephalopathy, ileus, mesenteric ischemia, secondary bacterial infection, sepsis, and septic shock in second week of illness due to inflammatory cytokines. Lab findings reveal lymphopenia, elevated transaminases, CRP, LDH, D-dimer, serum Ferritin, and Troponin-T with most common imaging finding being bilateral peripheral lower lung zone ground glass opacities on HRCT chest. RT-PCR of nasopharyngeal or oropharyngeal swab confirms the diagnosis. There is no magic bullet yet to treat COVID-19 with available options of antivirals (Remdesivir) and immunomodulators (Dexamethasone and Tocilizumab). Even with effective vaccine stringent measures like social distancing, mask wearing, and hand hygiene are our only defense against this infection. Effective governance and efficient health sector alone can help combat the pandemic by dispersing the facts and curbing the myths.
cells and after genomic sequencing was identified as seventh member of the family betacoronavirus, subfamily Orthocoronavirus, quite similar to bat coronaviruses.2 This virus has several dynamic facets from causing asymptomatic to critical life threatening respiratory manifestations. Our understanding of COVID-19 has ever been evolving since its emergence. This formidable foe with its contagiousness and virulence abetted by global trade and tourism was declared a global pandemic on March 11th, 2020, by WHO and continues to be a global threat with both cure and prevention not yet distinctly visible (at the time of writing this chapter). Combating this malevolent virus requires sifting of facts from myths by means of worldwide available accurate scientific information that takes high moral ground and conveys research driven narratives.

Virology, Epidemiology, and Transmission

SARS-CoV-2 is a positive sense ssRNA enveloped virus with viral spike(S) peplomers, belonging to the human betacoronavirus family, order Nidovirales, and subgenus Sarbecovirus similar to SARS-CoV-1 and MERS but a different clade.2 The S protein contains the region that binds the human-angiotensin converting enzyme 2 receptor ACE-2 (h-ACE2) receptor on respiratory epithelial cells.3 Phylogenetic analysis of the virus revealed two different strains designated as the L type (70%) and S type (30%). High viral titers are detected in nasopharyngeal secretions in the early phase of illness (in first week post exposure) and decline after that.5 Virus is also detected in other body fluids such as blood, saliva, semen, and stools but role in transmission is unclear.6 The virus after its initial emergence in Wuhan, spread rapidly across whole of China and to Italy, Iran, Japan, South Korea, the US, and across the globe by means of community transmission and super spreading events. It predominantly affects middle aged adults and elderly and males.7 Though no gender or age group has been spared. Usually respiratory coronavirus outbreaks are seen during winter in northern hemisphere but in some parts of the world like Thailand they persist throughout the year, whereas SARS-CoV-2 shows no such seasonality.

Early transmission dynamics revealed the major mode of transmission to be large droplet mediated direct person to person (within ~6 ft distance) as well as through direct contact with contaminated surfaces. Aerosol (droplets of size 20–500 µm) transmission is a major mode of transmission to health care workers in hospital settings.8 Airborne and animal to human transmission is yet debatable. SARS-CoV-2 has a median survival of ~1.1–3 hours in aerosol and up to 72 hours on inanimate objects.9 Asymptomatic or pre-symptomatic viral shedding is the major mode of disease transmission since, serial interval (SI) (mean 5.8 days) is shorter than the incubation period (IP). Infectiousness begins 2.3 days before symptom onset (pre-symptomatic transmission), peaks 0.7 day before symptom onset and declines within 7 days.10 Shorter SI (SI/IP), higher reproductive numbers (R0: 2.2–2.7 in initial phase) and secondary attack rate of up to 15%11 make the virus highly contagious and difficult to contain.

Pathogenesis

SARS-CoV-2 virus enters human respiratory epithelial cells through attachment of its spike (S) protein to the h-ACE2, similar to SARS-CoV-1 aided by cellular protease TMPRSS2. This is followed by the initial replicative phase and phase of innate immunity in the early phase causing influenza like illness with mild symptoms due to direct cytopathic effect of the virus. If no intervention occurs at this stage, it leads to phase of adaptive immunity leading to massive cytokine release syndrome and complications like acute respiratory distress syndrome (ARDS) and multi-organ dysfunction.12

**TABLE 1 Blueprint priority diseases by WHO**

<table>
<thead>
<tr>
<th>Blueprint Priorities by WHO</th>
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<tbody>
<tr>
<td>Crimean–Congo hemorrhagic fever (CCHF)</td>
<td></td>
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<tr>
<td>Ebola virus disease and Marburg virus disease</td>
<td></td>
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<tr>
<td>Lassa fever</td>
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<tr>
<td>Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS) coronavirus</td>
<td></td>
</tr>
<tr>
<td>Nipah and Henipaviral diseases</td>
<td></td>
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<tr>
<td>Rift Valley fever (RVF)</td>
<td></td>
</tr>
<tr>
<td>Zika</td>
<td></td>
</tr>
<tr>
<td>Disease X</td>
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</table>

*From the World Health Organization. Known diseases are listed in alphabetical order.*
TABLE 2 Stages of severity of COVID-19 infection

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe (14%)</th>
<th>Critical illness (5%)</th>
</tr>
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<tbody>
<tr>
<td>Fever and/or uncomplicated upper respiratory tract infection without dyspnea or hypoxemia</td>
<td>Pneumonia with no signs of severe disease</td>
<td>Severe respiratory distress requiring mechanical ventilation (invasive or noninvasive)</td>
<td>Rapidly progressive Type 1 respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Chest X-ray: Bilateral lung infiltrates involving &lt;50% of lung fields</td>
<td>Chest X-ray: Bilateral lung infiltrates involving ≥50% of lung fields</td>
<td>Sepsis and septic shock</td>
</tr>
<tr>
<td></td>
<td>RR ≥24/min</td>
<td>RR ≥30/min</td>
<td>Multi-organ dysfunction (MODS)</td>
</tr>
<tr>
<td></td>
<td>SpO₂ &lt;94% on room air</td>
<td>SpO₂ &lt;90% on room air</td>
<td>Altered mental status</td>
</tr>
</tbody>
</table>

Clinical Features

Asymptomatic Infection

This has been well documented in several studies to an approximate magnitude of 30–40% across the globe but not systematically studied.¹³ Objective findings on HRCT chest are seen even with asymptomatic infection. Several of them develop symptoms (they are pre-symptomatic) over the period of 3–7 days.¹⁴

Spectrum of Illness (Table 2)

It ranges from mild to severe and critical illness. The overall case fatality rate is 2.3% with no fatality in mild cases.¹⁵ High case fatality has been documented in those with multiple underlying comorbidities.

Clinical Signs and Symptoms (Table 3)

IP is 14 days¹⁶ (median IP is 5.1–5.2 days) with interquartile time (IQT) of 2–7 days implying dispersion of 50% cases in this period.¹⁷ Though predominantly a respiratory pathogen SARS-CoV-2 has myriad extra-pulmonary manifestations.

Clinical course of COVID-19: Patients infected by the SARS-CoV-2 virus develop symptoms usually after a mean IP of 5.1–5.2 days (14 days) and majority (80%) recover without further progression or complications. Amongst the hospitalized patients 40% progress to develop dyspnea after 7 days of symptom onset and yet a minority (14%) and (5%) progress to develop severe and critical illness respectively after approximately 10 days of symptom onset (Fig. 1).²⁰

Laboratory findings (Table 4):²¹ Most common lab findings in COVID-19 are severe lymphopenia, elevated aminotransferases, CPK, Troponin T, and elevated inflammatory markers like CRP, serum LDH, Ferritin, IL-6, and D-dimer. They are associated with worse prognosis and mortality.
Imaging:
- Chest X-ray: During early or mild phase of the illness chest radiographs are normal. Common abnormal findings are consolidation and ground glass opacities in bilateral, peripheral lower lung fields with a peak in severity 10–12 days post-symptom onset.²²
- HRCT Chest: In a systematic review by Bao et al.²³ of 2,700 patients of COVID-19 most common abnormalities were ground-glass opacifications (83%), ground-glass opacifications with mixed consolidation (83%), ground-glass opacifications with mixed consolidation (58%) and adjacent pleural thickening (52%) followed by interlobular septal thickening (48%) and air bronchograms (46%). Less common findings are crazy paving pattern, bronchiectasis, pleural effusion, pericardial effusion, and lymphadenopathy (Figs. 2A and B).

**Risk factors for severe disease (Table 5):** These include epidemiological, clinical, and laboratory factors. Age is a major factor impacting case fatality; with mortality rate being 8% and 15% amongst those aged 70–79 years and ≥80 years respectively according to a report from the Chinese Centre for Disease Control and Prevention. Other factors are:²⁴

**Complications of COVID-19:** Major complications of COVID-19 are ARDS in almost 17–29% cases developing at a median of 8 days post-symptom onset in most cases;²⁵ acute kidney injury, cardiac complications
like cardiomyopathy (33%), arrhythmias (17%), acute cardiac injury (7%), and shock (9%); thromboembolic complications such as pulmonary thromboembolism and acute cor pulmonale, acute stroke; inflammatory syndromes such as cytokine release syndrome and multisystem inflammatory syndrome; secondary bacterial and fungal infections (8%); sepsis, septic shock, MODS, and DIC; coagulopathy; and APLA and CNS encephalitis. Cytokine release syndrome (CRS) is the most devastating complication characterized by increased levels of inflammatory cytokines such as IL-6, TNF-α, and IL-10 and activation of T lymphocytes, macrophages, and endothelial cells leading to fever and multi-organ dysfunction. Severe form of CRS needs rapid intervention with steroids and immunomodulators such as Tocilizumab (anti IL-6 antibody).

**Differential Diagnosis**

COVID-19 pneumonitis must be differentiated from other respiratory infections like bacterial, fungal, and viral pneumonias (influenza, parainfluenza, rhinovirus, other coronavirus, human metapneumovirus, adenovirus, etc.). Most of these have similar clinical and laboratory features and only molecular test can clinch the diagnosis.

### TABLE 5

<table>
<thead>
<tr>
<th>Epidemiological category 1</th>
<th>Vital signs category 2</th>
<th>Labs category 3</th>
</tr>
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<tbody>
<tr>
<td>Age ≥65 years</td>
<td>Heart rate &gt;125/min</td>
<td>Admission absolute lymphocyte count &lt;0.8 × 10^9/L</td>
</tr>
<tr>
<td>Pre-existing pulmonary disease</td>
<td>Respiratory rate &gt;24/min</td>
<td>LDH &gt;245 U/L</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>PaO2/FiO2 &lt;300 mm Hg</td>
<td>CRP &gt;100</td>
</tr>
<tr>
<td>Diabetes with HbA1c &gt;7.6%</td>
<td>SpO2 ≤94% on room air</td>
<td>CPK &gt;Twice the ULN</td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
<td>Elevated troponin T</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td></td>
<td>D-dimer &gt;1,000 ng/mL</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td></td>
<td>Ferritin &gt;500 µg/L</td>
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<tr>
<td>Use of biologicals</td>
<td></td>
<td></td>
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<tr>
<td>History of transplant or other immunosuppressive medications</td>
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<td></td>
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<tr>
<td>Uncontrolled HIV (Viremic or CD4 &lt;200)</td>
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Figs. 2A and B: HRCT images showing bilateral ground glass opacities (GGO’s) in peripheral lower lung zones
CHAPTER 2
COVID-19: An Overview

**Diagnosis**

COVID-19 cannot be definitively distinguished from other respiratory viral illnesses based merely on clinical symptoms and laboratory findings. A high clinical suspicion in people presenting with respiratory tract symptoms as well as those who have had close contact with a suspected or confirmed case must be subjected to testing (Table 6). Tests currently approved by the FDA are molecular tests such as RT-PCR which are confirmatory and serological tests have been approved under emergency usage. Viral cultures are not recommended. Rapid antigen tests though easy to perform are not recommended due to high false positive and negative rates.

*RT-PCR* of nasopharyngeal swab specimens has a sensitivity of ~63%, depending on assay used, sample procurement method and stage of illness.\(^{29}\) False-negative rates\(^{30}\) have ranged from <5% to 40%. Hence, negative results must be correlated clinically and if suspicion is high the test may be repeated after 24–48 hours after the initial negative result. Lower respiratory tract samples such as BAL yield better results. The test yield of RT-PCR is maximum from day 1–3 of symptom onset.

The reliability of *serological tests* depends on the duration of illness, seroprevalence and specific assay. According to a study, serological response in the form of IgM occurs after median of 5 days and IgG after 14 days of symptom onset.\(^{31}\) Useful when patient presents after 2 weeks into the illness, when RT-PCR is negative. A positive test for IgM and IgG is diagnostic for COVID-19, but a negative result does not rule out the disease. False positive results may be obtained due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as HKU1, NL63, OC43, or 229E. Thus, serological tests should not be used as confirmative tests and must be interpreted with caution.

**Management of COVID-19 (Fig. 3)**

**Outpatient**

Suspected and mild cases can be managed on an outdoor basis by telemedicine and home isolation along with good hand and respiratory hygiene. Since, 80% cases are asymptomatic or have mild to moderate illness which can be managed on an outpatient basis, thereby reducing the burden on our already pummeling health system. Home isolation is recommended for 10–14 days post-symptom onset and post-positive test result in symptomatic and asymptomatic individuals respectively.

**Hospitalized Patients**

- General measures include oxygenation, hemodynamic resuscitation, and awake prone positioning. Empirical antibiotics are not recommended unless there is evidence of coexisting bacterial or fungal infection. Statins and ACEI and ARBs to be continued if already prescribed. Prophylaxis for thromboembolic complication is mandatory. Steroids to be used in patients who need supplemental oxygen early in the course of illness.
- **Specific treatment:** Include *Antivirals and Immunomodulators*. None of them are a recommended specific therapy though and are under trials. Like influenza antivirals if effective need to be initiated early in the course of illness. Drugs are as follows:

  - **Hydroxychloroquine/Chloroquine:** Prevents binding to ACE-2 receptors, interferes with cellular acidification in the phagolysosome and blocks endosomal transport.
Management protocol team of department of medicine, SMS Medical college Jaipur

Stratification of patients according to severity of illness of COVID-19

**Mild**
- Fever and/or uncomplicated upper respiratory tract infection without dyspnea or hypoxemia

**Moderate**
- Pneumonia with signs of severe disease
- Chest X-ray: Bilateral lung infiltrates involving <50% of lung fields
- RR >24/min
- SpO₂ <94% on room air

**Severe**
- Severe respiratory distress requiring mechanical ventilation (invasive or non-invasive)
- Chest X-ray: Bilateral lung infiltrates involving ≥50% of lung fields
- RR >30/min
- SpO₂ <90% on room air

**Critically ill**
- Rapidly progressive type 1 respiratory failure
- Septic shock
- Multi-organ dysfunction (MODS)
- Altered mental status

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**Admit in ward**
- Oxygen supplementation: Initiated to target SpO₂ ≥92-96% (in COPD target SpO₂ 88-92%), use non-rebreathing face mask preferably or HFNC
- Prose positioning for awake spontaneously breathing patients, if no contraindication
- Dexamethasone 6 mg IV OD for 3-5 days
- Antivirals:
  - A) Tab. HCQ: 400 mg BD x 1 day, fbs 200 mg BD 4 days
  - B) Tab. Lopinavir/Ritonavir: 200/50 mg 2 tablets BD x 7-10 days
  - C) Inj. Remdesivir: 200 mg IV over 30-120 mins. 1 fbs 100 mg IV OD days 2-5
- Convalescent plasma therapy (4-13mL/kg or 200 mL slowly over 2 hrs).
- Second dose of 200 mL if required.
- Pao2/FiO2 >200-300
- Inj. Tocilizumab: 8 mg/kg iv once (Max dose: 800 mg usual dose 400 mg), Raised IL-6
- Anticoagulation: Prophylactic dose, LMWH/UFH, if no contraindications especially in patients with D-dimer >1000 mg/mL
- Cautious observation fluid therapy with crystalloids guided by dynamic parameters
- MDI preferred over Nebulization
- Continue ACEI/ARB and Statins if already prescribed
- Monitor plus watch for worsening in those with high risk factors
- Refer to ICU if RR >30/mm; SpO₂ <90% on room air

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**Admit in ICU**
- Oxygen supplementation: target SpO₂ ≥92-96% (in COPD target SpO₂ 88-92%), use HFNC or NIV such as CPAP or BiPAP. If not responding then consider intubation with Lung protective ventilation strategy
- Empirical antibiotics if bacterial pneumonia is suspected (MRSA/MDR)
- Septic shock: Vasopressor Nor adreneric drug of choice fbs vasopressin, maintain MAP >60 mmHg
- Corticosteroids**: Dexamethasone 6 mg IV OD or Hydrocortisone 50 mg IV QID if refractory septic shock for 3-5 days
- Antivirals** as per moderate cases
- Convalescent plasma therapy
- Inj. Tocilizumab
- Anticoagulation**: Prophylactic dose LMWH/UFH, if no contraindications especially in patients with D-dimer ≥1000 ng/mL
- Full therapeutic dose (0.5 mg/kg BW SC BD) for those in ICU
- Cautious conservative fluid therapy with crystalloids guided by dynamic parameters
- Monitor** plus watch for signs of rapidly progressive respiratory failure, sepsis and refractory septic shock, MOIDS and altered mental status

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**Fig. 3:** Management of COVID-19: Institutional protocol

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a. Monitor QT interval 2-3 hours after second dose of HCQ & twice daily thereafter (if QTc increases by >9 ms or is >500 ms, reduce the dose or consider discontinuing)
b. Contraindications to prone positioning in awake spontaneously breathing patient: Seizure or chest wall instability, facial or pelvic fracture, uncontrolled intracranial pressure
c. Dynamic parameters includes capillary refill time, serum lactate levels, pulse pressure variation, stroke volume variation
d. To be initiated early (within 48 hours) in those on supplementary oxygen

e. Inj. Enoxaparin 40 mg SC OD (Prophylactic dose), modify as per creatinine clearance, Obese dose is 40mg SC BD. Assess risk of bleeding
f. Use according to discretion of treatment protocol team (institutional protocol to be followed)
g. Monitor Transaminases and eGFR (Discontinue if ALT >5 times the ULN, or eGFR <30 mL/min)

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Very low quality evidence for treatment of COVID-19. May cause QT prolongation and needs monitoring. A large multicentre study concluded that use of a regimen containing hydroxychloroquine (HCQ) or chloroquine (with or without a macrolide) was associated with no evidence of benefit, but instead was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for inhospital death with COVID-19. As per ICMR recommendations, it should be used in moderate to severe and critically ill and in mild cases associated with comorbidities like elderly, DM, hypertension, CKD, and others mentioned earlier in this chapter. About 821 individuals were randomly assigned to HCQ or placebo folate within 4 days of a household or occupational exposure to SARS-CoV-2 in a double-blind trial, HCQ did not reduce the rate of RT-PCR confirmed COVID-19 or consistent symptoms within 14 days (11.8 vs. 14.3% with placebo).

**Lopinavir-ritonavir:** A randomized controlled trial in hospitalized adults who also received other medications yielded no benefit but was given relatively late in the disease course. May be considered in moderate to severe cases, especially in those with multiple comorbidities and HIV patients.

**Remdesivir:** It was used in treatment of Ebola. It is a nucleotide analogue that inhibits viral RNA polymerase with in vitro activity against SARS-CoV-2 and MERS. A placebo-controlled, double-blind, randomized trial of IV Remdesivir in hospitalized adults with COVID-19 pneumonitis concluded that Remdesivir was better compared to placebo in shortening the time to recovery in patients with COVID-19 pneumonitis. It is recommended that if available it should be used in severe and critical cases of COVID-19. Combination with HCQ is not advisable due to adverse drug interaction.

**Favipiravir:** Anti-influenza drug, RNA polymerase inhibitor which is available in India for treatment of mild COVID-19. In a study use of Favipiravir in patients with mild disease was associated with rapid rates of viral clearance and radiographic improvement as compared to Lopinavir-ritonavir.

**Interferon beta:** In one open-label randomized trial from Hong Kong, in 127 adults hospitalized with nonsevere COVID-19 use of INF-β within 7 days of symptom onset along with Ribavirin and Lopinavir-ritonavir was associated with early recovery and viral clearance. It needs further study, and is currently under evaluation in the WHO “SOLIDARITY” trial.

**Immunomodulators (Tocilizumab):** An FDA approved anti-IL6 agent for CAR-T cell cytokine release syndrome. It is more effective if used early in ARDS before more advanced lung and multi-organ dysfunction sets in. An unpublished study from China of 21 severe and critically ill patients concluded that use of Tocilizumab was associated with improved oxygenation, better CT findings, and survival in 1 week. Other immunomodulators under study are Sarilumab, Anakinra, and Siltuximab.

**Convalescent plasma therapy:** FDA approved for use in severe and critical COVID-19 cases. Early usage in treatment within 5–6 days of symptom onset is advocated before patients own antibodies form. Eligibility of donor includes age ≥18 years, male or nulliparous female >55 kg weight, prior RT-PCR documented diagnosis, and complete resolution of symptoms at least 28 days prior to donation or 14 days prior to donation with two negative RT-PCT results 24 hours apart. A randomized controlled trial among patients with severe and critical COVID-19 convalescent plasma therapy added to standard therapy versus standard therapy alone did not result in a statistically significant improvement in time to clinical improvement within 28 days. Adverse events include pathogen transmission, allergic reactions, transfusion-related acute lung injury, and circulatory overload. To be avoided in those with IgA deficiency and immunoglobulin allergy.

**Intravenous immunoglobulin (IVIg):** Pooled IVIg reduces inflammation via multiple mechanisms such as lessening interrupting complement cascade and reducing activated CD4+ and CD8+ T-cells. It has been proposed in viral mediated lung injury or ARDS due to disordered regulatory T-cell hyperimmune response. It needs further studies.

**Prevention**

Numerous vaccines are being evaluated including viral-vector vaccines, nucleic acid-based (DNA and mRNA) vaccines and inactivated or recombinant protein vaccines. Impact of BCG immunization on COVID-19 is unknown; hence, its use in COVID-19 is not recommended by WHO.
Prognosis

Recovery from the illness and its long-term sequelae depend on age, underlying comorbidities, and severity of illness. According to WHO, mild cases recover in 2 weeks and severe cases recover in 3–6 weeks. The overall global mortality of COVID-19 is 3.4% as of March 3rd, 2020. The mortality rate attributed to SARS-CoV-2 is less than that commonly ascribed to community acquired pneumonia (12–15%), but more than seasonal influenza (~0.1%). Critically ill COVID-19 cases face the perils of post-intensive care syndrome (persistent impairments in mental health, physical function, and cognition), although the incidence is unknown.

Conclusion

Escalated globalization, expanding human population, increasing human-animal interactions, altered ecosystems clubbed with viral genetic recombination, mutation, and reassortment have led to emergence of several novel pathogens that have wreaked havoc on not just the global economy but on the very existence of a healthy life. The emergence of global pandemic of COVID-19 exposed the Achilles heel of our preparedness toward unanticipated epidemics and pandemics despite use of spatial epidemiology or mathematical models to predict such emerging and re-emerging pathogens. In an era of universal distrust and rising global tension with overload of information it becomes imminent that we as medical fraternity understand the true trajectory of this pandemic. The only bastion of defense in this conundrum is worldwide dissemination of truthful and accurate scientific data. The knowledge of the disease is changing so fast that what seems true today, might not be so in the future.

References

CHAPTER 3

Hydroxychloroquine for Cytokine Storms: Pros and Cons

Daya Kishore Hazra, Padmamalika Khanna nee Hazra, Ratnamalika Kumar, Suratwant Hazra

Abstract

Hydroxychloroquine is a most economic therapeutic agent with a proven track record in rheumatoid arthritis, systemic lupus erythematosus, and for the last 6 years in Diabetes Mellitus. Its clinical value in abating or preventing the cytokine storm in COVID-19 is a subject of controversy: in India we continue to use this agent both for prevention and for management albeit Western reports on arrhythmias have installed a caution in its use if there is QT prolongation. Possible mechanisms of its action in correcting inflammation and hyperglycemia are discussed. Like corticosteroids and ivermectin, hydroxychloroquine is likely to remain a part of the low cost anti COVID-19 strategies.

Introduction

One of the most keenly argued facets in the context of Coronavirus Disease 2019 (COVID-19) is the use of hydroxychloroquine (HCQ/HYQ) for management or prophylaxis, and this is evidenced by sharp swings in WHO/FDA recommendations as well as the marked divergence between advisories and regimes in different countries.\(^1\)\(^\text{-}\)\(^\text{15}\) ICMR continues to approve the prophylactic use of this in asymptomatic healthcare workers/surveillance workers and asymptomatic contacts of laboratory confirmed cases.\(^2\) It has been in use since 1955 in rheumatoid arthritis and lupus, and figures in the WHO Essential List of Medicines. The Central Drugs Standard Control Organization approved its use in rheumatoid arthritis in 2001, polymorphic light eruptions in 2006, lupus erythematosus in 2008 and diabetes mellitus in 2014. Its action was regarded as anti-inflammatory. When the COVID-19 pandemic emerged it was suggested as of being of possible benefit both for prophylaxis as well as for treatment.

However, some reports suggested that it predisposes to cardiac arrhythmia by causing QTc prolongation and even Torsades de Pointes—a dangerous disorder. This led to various recommendations for prior QT assessment before instituting chloroquine/HCQ demarcating green/orange/red zones for use analogous to traffic signals.\(^16\)\(^\text{-}\)\(^\text{18}\) Because HCQ had often been used with azithromycin in COVID-19, and azithromycin had itself been incriminated for sometimes causing QT prolongation, the combined use of these two was especially controversial.

But HCQ had been used in rheumatoid arthritis for 65 years, and in diabetes for the last decade and had not been cited for causing rhythm disorders. The anti HYQ article in the Lancet which led to the WHO initially suspending the HCQ arm of the solidarity anti COVID trials was discovered to be based on dubious data by Surgisphere, and was subsequently retracted. The WHO resumed this arm after this retraction, but again suspended this arm after UK reports about the lack of benefit by HCQ. Some of the anti HCQ comments were allegedly related to pressure by the makers of more expensive anti COVID
Hydroxychloroquine for Cytokine Storms: Pros and Cons

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drugs as well as the political controversies aroused by the endorsement of HCQ by the US President! The recent FDA withdrawal of permission for the use of HYQ was based on a randomized trial on postexposure prophylaxis, showing lack of benefit, but not cardiac rhythm disorders.

We have suggested that a detailed analysis of the experience of persons on prior HCQ use for diabetes or rheumatoid arthritis during the pandemic should be rewarding.

Chloroquine has an even longer history of use as an antirheumatoid and antimalarial drug as compared to hydroxychloroquine, but HYQ has overshadowed it as its hydroxyl group limits the crossing of the blood retinal barrier and further, HCQ clears faster from the retinal pigment cells and accumulates less than chloroquine. An ophthalmological cohort of 526 patients showed no retinopathy in the first 6 years, and 0.5% after 8.7 years.

HCQ as an Anti-inflammatory Reagent

The anti-inflammatory action of HCQ has been attributed to inhibiting the formation of the cytokines IL1, IL6, and TNF alpha, reducing C reactive protein, inhibition of leukocyte migration, and activation, as well as of prostaglandin synthesis and an antiplatelet effect.

It also inhibits nitric oxide and extracellular oxidant production from neutrophils and macrophages.

The cardiovascular effects of HCQ in the diabetes context, which include lowering of cholesterol both total and LDL, lowering of triglycerides, and antiplatelet, anti-thrombotic, and antihypertensive effects are worth recalling in the context of its alleged cardiovascular deleterious effects in COVID-19.

Postulated Mechanisms of Action of HYQ in COVID-19

HYQ causes alkalization of the intracellular milieu. This inactivates the insulin degrading enzymes making it released from the cell ready to act again.

Patients with diabetes, elevated BMI, high cortisol levels have a higher mortality rate in COVID! Diabetes is the most prevalent comorbidity in COVID-19, second only to obesity!

Hyperglycemia Worsens Viral Respiratory Diseases

Hyperglycemia increases glucose content of airway secretions, increases influenza virus infection in vitro in pulmonary epithelial cells, increases vascular permeability, and a collapsed alveolar epithelium in the lungs, and may suppress the antiviral immune response.

The role of anti-inflammatory agents including HCQ in management of diabetes type 2 has been recently reviewed.

Postulated mechanisms of action of HYQ in COVID-19 other than anti-hyperglycemia action are also related to its rendering the cytosol alkaline. The increased pH of the endosomes and lysosomes inhibits endolysosome function prevents the fusion of virus with the host cells and subsequent replication. HCQ also enters the antigen presenting cells and prevents autoantigen presentation to T cells. It attenuates the possibility of the cytokine storm by inhibiting the transcription of pro inflammatory genes.

The beneficial actions of HCQ in human disease according to a Pub Med search through MESH is multifaceted including diabetes mellitus, dyslipidemias, coagulopathies, infectious diseases, and malignancies may have multiple mechanisms, including altered signaling through cellular receptors, post-glycosylation modifications of infectious agents, changes in levels of inflammatory mediators, and inhibition of autophagy.

Since COVID-19 behaves like an infectious agent induced inflammatory coagulopathy with hyperglycemia and cytokine release, several of these actions can be involved!

Dosage

Hydroxychloroquine dosage recommended has varied. The ICMR national task force on 22/5/2020 suggested 400 mg twice daily on Day 1, followed by 400 mg once weekly for next 7 weeks to be taken with meals for asymptomatic health-care workers involved in care of suspected or confirmed COVID cases. The same regime was advised for asymptomatic household contacts of laboratory confirmed cases. This also can be used weekly beyond 8 weeks with strict monitoring of clinical and EKG parameters under medical supervision.
For patients the AIIMS COVID-19 preparedness Document Version 1.3 dated 10th June, 2020, suggests 400 mg BD × 1 day followed by 400 mg OD × 4 days for high-risk cases testing positive. For moderate disease, AIIMS suggests to consider 400 mg BD for 1 day, then 400 OD × 4 days. Exclusions/contraindications include retinopathy/hypersensitivity/G6PD deficiency/preexisting cardiomyopathy and cardiac rhythm disorders. Rarely the drug causes a self limiting blurring of vision which improves on discontinuation of the drug.

**Role of HCQ in Cytokine Storm**

Whether HCQ is of value in the prevention or control of cytokine storms in COVID is most important to consider! The jury is still out!

A number of agents are now in use in the prevention and/or treatment of the cytokine storm. Corticosteroids are the sheet anchor of therapy and prevention, and a dropping pO₂ measured by a pulse oximeter is an early indicator of silent hypoxia. Other acute phase reactants that are looked for include elevated Trop T, C reactive protein, ferritin, D dimer, neutrophil/lymphocyte ratios. High resolution chest CT has now been supplemented by chest X-ray to diagnose lung involvement, and artificial intelligence is being explored to enable remote diagnosis on the chest X-ray (Shukla AK: Personal Communication).

Since immunosuppressive drugs are of value in therapy, but also can promote infections there was an initial apprehension that during prophylaxis HCQ immunosuppressive action may even promote infection?

However, today in India HYQ is being used for immunoprophylaxis, except in subjects with contraindications such as cardiac arrhythmias or QT prolongation.

Whether HCQ can prevent cytokine storms is moot as evident from the variety of opinions. Since immunosuppressive drugs are of value in therapy, but also can promote infections there was an initial apprehension that during prophylaxis HCQ immunosuppressive action may even promote infection?

Whether HCQ can prevent cytokine storms is moot as evident from the variety of opinions.

BOX 1 Changing clinical pictures and multi-system features

Observing the changing clinical picture of the COVID pandemic, from a flu-like lung illness to a multisystem picture, one is reminded of Lorraine Daston’s historical perspective:

To quote her, Historically:

- It’s natural to cast about for answers at the dawn of a pandemic
- “At moments of extreme scientific uncertainty”
- “Observation, usually treated as the poor relation of experiment and statistics in science, comes into its own”
- Confronting a new disease, doctors have no choice but to turn to “suggestive single cases, striking anomalies, partial patterns”
- Slowly, as our ideas about “what works and what doesn’t” help tell us “what to test, what to count,” the picture clarifies
- Until then, “we are back in the seventeenth century, the age of ground-zero empiricism, and observing as if our lives depended on it”

One patient at a time, we have to work our way into the present!

Cytokine production by inflammatory macrophages. Remdesivir and Favipiravir are all under evaluation both for the cytokine storm, and even more important, for reducing viral RNA production.

Another approach is extracorporeal adsorption of cytokines using cartridges such as CYTOSORB/DEPURPO and OXIRIS: these are expensive but Indian analogues patented by our group for endotoxin removal need to be developed. These can be used in series with ECMO-extracorporeal membrane oxygenators.

Other agents being evaluated are herbs such as Turmeric, Tinospora cordifolia (Giloy), Ashwagandha (Withania somnifera), Cinnamon, and Boswellia.

Ultraviolet blood irradiation biophotonic therapy, rapamycin, low dose lung irradiation, nicotine, electroacupuncture, Cox 2 inhibitors, ibuprofen are other approaches that have been suggested!

The hypotension is managed by inotropes: noradrenaline being preferred to dopamine.

Azithromycin and doxycycline are antibiotics that have been used.

There are Australian and Bangladesh reports on the use of ivermectin to prevent or treat COVID infection.

Convalescent serum and injectable hyaluronidase and niacin are beneficial in anecdotal cases.
Conclusion

The value of HCQ in preventing and treating COVID-19 is being extensively evaluated, ever since the French report and the US Presidents advocacy.

India which produces the majority of the world’s HCQ was recently extolled and thanked for making it available to countries around the world, including the USA, Brazil, and African countries.

Its inexpensive character suggests that, like corticosteroids, it will play an important role in the COVID pandemic, albeit with care, prudence, and cautious medical supervision including periodic QT measurement from ECG or monitors.

The changing clinical picture especially the multisystem involvement including: gastrointestinal, neurological, renal, endocrine, and dermatological presentations is discussed in Box 1.

References


**Abstract**

COVID-19 disease has prominent manifestations on the hematopoietic system. Complete blood count parameters that may assess the worsening of COVID-19 infection are: absolute neutrophilia, absolute decrease in lymphocyte count, absolute decrease in monocyte count, and an increase in neutrophil to lymphocyte ratio (NLR). In addition, the coagulation system needs to be evaluated by regularly monitoring of hemostatic markers—D-Dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19. Risk stratification for venous thromboembolism should be performed for all inpatients with COVID-19. In the absence of contraindications, the vast majority of inpatients, including with severe COVID-19 should receive prophylactic anticoagulation. Delay in recognizing the hematological manifestations may have a negative impact on the clinical conditions and outcomes of patients, especially those with more aggressive diseases.

**Introduction**

On 11th March 2020, Dr Tedros Adhanom Ghebreyesus, WHO Director-General, declared COVID-19 as a pandemic. As we stand today, COVID-19 has spread globally. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses named the etiologic agent of COVID-19 as “Severe Acute Respiratory Syndrome related Coronavirus 2”, or SARS-CoV-2.1

The lungs are the initial target organ for COVID-19. However, the infection has a significant impact on the hematopoietic system and hemostasis. The involvement of hematopoietic system in patients with novel coronavirus pneumonia was brought to light by Guan et al.2 This was followed by a series of case reports and papers further highlighting the involvement of hematopoietic system in the pathogenesis of COVID-19.

It is very important to analyze the hematological parameters critically to pick up the essential diagnostic and prognostic information. The effect on each lineage and the various hemostatic mechanisms is discussed here.

**Effect on Neutrophils**

Neutrophilia has been described in most of the COVID-19 patients. The median peak absolute neutrophil count (ANC) impacts the possibility of ICU admission (11.6 × 10⁹/L in ICU patients as compared to 3.5 × 10⁹/L in the non-ICU group (P value < .001).3 Rather, than the absolute neutrophil count; an elevated neutrophil to lymphocyte ratio (NLR) correlates more with pneumonia progression.4 In addition, the myeloid series shows a left shift, which is manifested in the peripheral blood as a leukoerythroblastic picture.5

**Effect on Lymphocytes**

Earlier in the course of the disease (1-4 days), peripheral blood leukocyte and lymphocyte counts are normal or slightly reduced. Lymphocytopenia sets in 83.2% infected patients around 7–14 days after the incubation period.2 Nadir of lymphocytes counted on day 7 from symptom onset followed by its restoration serves an important
prognostic marker. Therefore, instead of a single value of lymphocyte count, it is the serial assessment which may be predictive of outcome. In particular, two readings are given importance. If the percentage of lymphocytes is less than 20 at days 10–12 from the onset of symptoms and less than 5 at days 17–19, it depicts as the worst prognosis.6 Hence, repletion of lymphocytes plays a role in recovery.7

The activated lymphocytes are seen morphologically as lymphoplasmacytoid cells (69%).8 However, there is no change in the CD4+/CD8+ lymphocyte ratio as depicted by immunophenotyping. Functionally though, impairment of the function of CD4+ helper and regulatory T-cells occurs which promotes an initial hyperactivation of cytotoxic CD8+ T-cells followed by its rapid exhaustion.9

Why does Lymphopenia Ensue?
- Expression of the ACE2 receptor on lymphocytes surface causes SARS-CoV-2 to directly infect these cells and causes their lysis.
- Cytokine storm, which sets in later in the disease course, may promote lymphocyte apoptosis and atrophy of lymphoid organs and spleen impacting lymphocyte turnover tremendously.
- Coexisting lactic acid acidosis, in debilitating conditions like cancer puts these patients at an increased risk for complications from COVID-19 by inhibiting the lymphocyte proliferation.10

Effect of COVID on Platelets
Thrombocytopenia is not uncommon and has been shown to be present in 36.2% COVID positive patients.2 A meta-analysis of nine studies has suggested that thrombocytopenia is significantly associated with the severity of the COVID-19.11 Those presenting with a peak in the platelet count during the disease course also had poorer prognosis. But what has emerged as a stronger parameter than the absolute platelet counts is the platelet to lymphocyte ratio at the time of platelet peak as this may give a reflection of the ensuing cytokine storm.12

Coagulation Anomalies in COVID Patients
COVID-19-associated coagulopathy (CAC) is common in patients with COVID-19. CAC manifests as elevated levels of D-dimer (46.4%) and fibrin degradation products, reflecting a highly prothrombotic state.2 The prothrombin time (PT) and activated partial thromboplastin time (aPTT) are only mildly prolonged. Later, if progressive consumptive coagulopathy continues, there is a decrease in antithrombin III, a rise in PT and aPTT, and further increase of D-dimer (>15.0 μg/mL). Fibrinogen levels are usually high in the initial phase, but returns to normal and decreases further in non-survivors. One study has reported disseminated intravascular coagulation (DIC) in 15 out of 21 non-survivors (8% of the total cohort).13

Table 1 summarizes the risk of various complications at different D-dimer levels.
Autoimmune Thrombotic Thrombocytopenic Purpura-Like Syndrome Associated with COVID-19

COVID-19 associated acute respiratory distress syndrome (ARDS) probably results from endotheliopathy-associated vascular microthrombotic disease (EA-VMTD). This could be secondary to an imbalance between low ADAMTS13 and excessive exocytosis of ultra large von Willebrand factor multimers (ULVWF) from Weibel-Palade bodies present on endothelial cells. Endothelial derived ULVWF multimers bound to the endothelial surface of the vascular wall recruit platelets and might initiate microthrombogenesis thus leading to large microthrombi composed of platelet and eULVWF complexes. Platelets adhered to eULVWF strings get activated resulting in platelet aggregation and recruitment of leukocytes dependant on P-selectin. The aggregates grow further and ultimately enter circulation. Numerous circulating complexes of endothelial derived ULVWF and platelet microthrombi result in the genesis of EA-VMTD triggering complement activation and resulting in a thrombocytopenic purpura (TTP)-like syndrome. This would require a recombinant Anti-CD59, recombinant ADAMTS13, Glycoprotein IIb/IIia receptor blocker, therapeutic plasma exchange, and anticomplement therapy.

Pathogenesis of CAC

The few proposed pathways are as follows:

- Immune deregulation and endothelial dysfunction
- Prolonged immobilization, dehydration, coexisting comorbidities, presence of cardiovascular disease, previous history of VTE and genetic predisposition such as heterozygous Factor V Leiden mutation may increase VTE risk.
- Activation of ACE2 receptor in the endothelium could result in endothelial cell activation/damage due to the virus binding.
- The release of a large amount of inflammatory mediators may lead to an increased blood viscosity may cause further hypercoagulability.
- Interventions like mechanical ventilation, central venous catheterization, and surgery may induce additional vascular endothelial damage and activation of coagulation system.

Management of CAC

Risk assessment models (RAM) such as IMPROVE-VTE/modified IMPROVE-VTE RAM should be used to identify high VTE risk patients requiring thromboprophylaxis. Dynamic D-dimer evaluation and ultrasound venous echo-Doppler or bedside echocardiography can further risk stratify the patients for VTE. If there are no contraindications, all patients with severe COVID-19 should receive prophylactic anticoagulation. Low molecular weight heparins (LMWH), or unfractionated heparin (UFH) should be preferred over direct oral anticoagulants (DOACs) as drug-drug interactions with concomitant antiviral (especially anti-HIV protease inhibitors such as ritonavir) and antibacterial (such as azithromycin) treatment is a risk. Such treatments interfering with CYP3A4 and/or P-gp pathways can augment the bleeding risk or reduce the antithrombotic effect.

Cytokine Release Syndrome in COVID-19

Cytokine release syndrome (CRS) also known as cytokine storm syndrome, macrophage activation syndrome, and haemophagocytic lymphohistiocytosis are the terms used for the frequently fatal hyperinflammatory conditions seen in COVID-19. The most accepted pathophysiological pathways that result in CRS is the defective lymphocyte
killing via the perforin pathway. Homozygous defects in perforin pathway genes cause familial hemophagocytic lymphohistiocytosis, and heterozygous mutations are associated with secondary hemophagocytic lymphohistiocytosis. However, the role of similar or novel genetic defects in the severity of COVID-19-associated CRS is unknown. Perhaps, genomic sequencing of patients with COVID-19-associated CRS would provide an insight. Elevated proinflammatory cytokines (IL-1, IL-6, and interferon-γ) produced by a dysregulated host immune response sets the soil for CRS. COVID-19-associated CRS, however, has early acute respiratory distress syndrome and clotting and surprisingly higher serum ferritins and lower IL-6 concentration. Hyperferritinemia and high LDH levels are common. Usually, low fibrinogen levels and cytopenias of more than two cell lineages by hemophagocytosis are not reported in COVID-19 in contrast to CRS associated with other causes. So, the pathophysiology of COVID-19 overlaps with low-grade HLH. Anticytokine management should be used for treating COVID-19-associated CRS. Ruxolitinib, a JAK1/2 inhibitor, tyrosine kinase inhibitors (TKIs), and the anti-CD26 antibody begelomab have proved efficacious in inhibiting cytokine release. IL-1 blockade with anakinra (a recombinant CD26 antibody begelomab have proved efficacious in treating COVID-19-associated CRS. Ruxolitinib, a JAK1/2 inhibitor, tyrosine kinase inhibitors (TKIs), and the anti-CD26 antibody begelomab have proved efficacious in inhibiting cytokine release. IL-1 blockade with anakinra (a recombinant human IL-1 receptor antagonist) notably improved survival.

Conclusion

The pathogenetic pathways discussed are evolving as our understanding of this disease is becoming clearer day by day. There is still much to be learned about the manifestations of COVID-19, and hence the literature is adding up new information. There is still a long way before we demystify this organism and are well acquainted by its effects. Whether there will be any chronic conditions or whether any further mutation in the virus would bring in some more acute complications, only time will tell.

References


CHAPTER 5

Effect of COVID-19 on Health-care Workers

KC Shashidhara, Spoorthy Raj

Abstract

COVID-19 (Corona virus disease 2019) is a respiratory viral infection, caused by SARS-CoV-2 (Severe acute respiratory syndrome Corona virus 2) that has spread across the world and has assumed a pandemic status. With ever increasing case load, lack of efficient treatment and vaccine for prevention, there is increased demand on health-care workers, in terms of work hours, and also, they are faced by, increased risk of infection, physical stress, and associated physical illness due to use of personal protection equipment, mental health issues, and social issues.

Thorough understanding of the impact of the ongoing pandemic on health-care work force is pivotal in appropriate management of the pandemic, as well as in ensuring the physical and mental well-being of health-care workers and prevent attrition of health-care work force.

Introduction

COVID-19 (Corona Virus Disease 2019) is a viral respiratory illness caused by novel corona virus, SARS-CoV-2. It is an RNA virus, belonging to the subgenus Sarbecovirus of the genus beta coronavirus of the family coronaviridae. The virus was first detected, while investigating the cause of cluster of pneumonia cases in Wuhan, Hubei province, China. Since then the virus has spread exponentially all around the world. Human to human transmission has found to be via respiratory droplets. COVID-19 was declared as pandemic by WHO on February 11th, 2020.

Health-care Workers (HCWs): All people serving in health-care settings, either paid or unpaid, who are at risk of getting exposed, either directly or indirectly to infectious materials, contaminated medical equipment, hospital surfaces, or contaminated air are considered as health-care workers. This includes doctors, nursing staff, technicians, pharmacists, students, trainees, administrative personnel, and engineering and facilities management staff.

HCWs work in contaminated environment and stay in close contact with virus infected individuals, and hence face higher risk of getting infected. Also, excess work load, risky working environment, social stigma exert deleterious effects on their mental health.

Problem Statement

COVID-19 is a rampantly spreading pandemic. Globally, total number of cases (as on 24 July) were 15,659,529 with 6,36,599 deaths. India is burdened with 12,91,623 cases with 30,658 deaths. The exact statistics pertaining to infection and deaths among HCWs is not available; however, as per CDC reports, there are more than 71,000 cases and 375 deaths among US health professionals as on June 2020. In India, according to the study published in IJMR, the incidence rate of COVID-19, among HCWs was 0.8%. The number of deaths is estimated to be 104 among doctors, 10 among nurses, and 15 among other health-care workers; however, the exact numbers are suspected to be much higher.
Effect of COVID-19 on Health-care Workers

COVID-19 is a fast spreading pandemic and currently there is enormous ongoing research to understand the disease dynamics and develop safe and effective vaccine and treatment strategy. However, in the absence of such vaccine and clear treatment guidelines there is increased pressure on global health-care work force (Fig. 1). This occurs in two forms:

- Overwhelming case load
- Loss of health-care work force due to adverse effects on health of HCWs

The effects on health-care workers can be conceptualized as follows:

- Risk of hospital acquired infection
- Effects on physical health due to demanding work environment
- Effects on mental health
- Social issues

Risk of Hospital-acquired Infection

HCWs are at increased risk of hospital acquired infection due to following reasons:

- Work environment, demanding close contact with infected patients
- Longer duration of exposure due to long working hours
- Inadequate supply of personal protection equipment
- Inadequate training, preparedness, and motivation regarding use of personal protection equipment.

Effects on Physical Health due to Demanding Work Environment

It is mandatory for HCWs to use proper PPE for prevention of nosocomial spread of infection. However, prolonged use of PPE is associated with side effects like:

- PPE (N95 mask and protective eye wear) associated de-novo headache as well as worsening of pre-existing primary headache syndromes like migraine, which affect the work efficiency and sleep quality.5
- PPE associated dermatosis like: Heat stress, dehydration, Acne, skin irritation, irritant contact dermatitis, allergic contact dermatitis, contact urticarial dermatitis, pigmentation, and frictional erosions.6

Effects on Mental Health

Health-care workers work in demanding work environments during times of crisis, like the present COVID-19 pandemic. Due to increased work load and stress they face increased risk of mental health disorders like depression, generalized anxiety disorder, obsessive compulsive disorder, panic attacks, post-traumatic stress disorder, insomnia, and a wide array of somatic symptoms.

Features responsible for mental health problems among HCWs include:7

- Speculations about unforeseen modes of transmission of disease
- Rapidity of spread
- Spread from asymptomatic patients
- Lack of definitive treatment protocol and non-availability of vaccines
- Widespread global connectivity and extensive media coverage resulting in catastrophic reactions to outbreak
- Complete uncertainty
- Unprepared health infrastructure

According to the study conducted by Chatterjee et al.,8 the prevalence of depressive symptoms among HCWs, during COVID-19 was 35%. The prevalence of symptoms related to stress and anxiety was 39.5% and 33%, respectively. Similarly, Korean study showed the prevalence of depressive symptoms among doctors to be 26.6%,9 and a study conducted in Singapore showed the prevalence of anxiety, depression, stress, and post-traumatic disorder to be 14.5%, 8.9%, 6.6%, and 7.7%, respectively.10
With further loss of health-care work force due to acquisition of nosocomial infection, the work load on prevailing work force will manifold by several times and further worsens their mental health status. Mental health issues are more prevalent among HCWs working in emergency, ICUs, and infectious diseases wards.

**Social Problems**
- Violence on doctors
- Concern regarding being source of spread to family members especially among those caring for elderly and children
- Social stigma

**Measures to Safeguard Health and Safety of HCWs**

**Measures to Reduce Infection among HCWs**

CDC recommendations include:

- Recommendations for routine health-care delivery
- Recommendations for care of suspected and confirmed cases of COVID-19
- Recommendations for routine health-care delivery include:
  - Use of telehealth and nurse directed triage protocols *(Flowchart 1)*. It is advised to schedule appointments for routine medical care through phone call. At the time of scheduling such appointments for routine health-care delivery, care should be taken to prevent crowding of patients in waiting areas.
  - All patients and visitors entering a health-care facility are to be screened for signs and symptoms of COVID-19.
  - Visual alerts, regarding use of face mask, hand hygiene practices and cough and sneeze etiquette are to be posted at entrance and strategic places to ensure compliance for the same.
  - Provision of alcohol-based hand sanitizers and face masks to patients entering health-care facility.
  - Patients waiting for consultation should be placed in such rooms, which allow for adequate social distancing, are well ventilated and have easy access to respiratory hygiene supplies.
  - Provision of a separate area at the health-care facility for provision of services to patients with symptoms of COVID-19.
  - Admitted patients are to be revaluated every day for development of signs and symptoms of COVID-19.
  - Application of source control measure such as use of cloth face covering or face mask to all patients and visitors, considering the potential for transmission from asymptomatic and pre-symptomatic patients.

![Flowchart 1: Algorithm for use of telehealth and nurse directed triage protocol](image-url)
- Health-care workers to maintain adequate physical distancing whenever possible.
- Health-care workers to practice source control measures and physical distancing even in non-patient care areas so as to prevent transmission from unprotected exposures to asymptomatic or presymptomatic coworkers.
- HCWs to be provided with break areas, which allow scope for maintaining adequate social distancing.
- HCWs to be advised to wear protective eye wear in addition to facemask during patient care encounters.
- HCWs are advised to use N95 or equivalent or higher-level respirator while aerosol producing procedures like intubation.
- It is advisable to perform targeted SARS-CoV-2 testing for asymptomatic patients to further reduce the transmission risk in health-care setting.
- Engineering controls are to be optimized to reduce or eliminate exposures to HCWs and other patients from infected individuals. For example, use of physical barriers and dedicated pathways to guide symptomatic patients through triage areas.  
  Traffic control bundle: It begins with outdoor triage. Patients are grouped into three categories at the triage station which is established at the entry to healthcare facility.  
  Hot zone: Patients with symptoms and consistent for COVID-19 or who are already tested positive for COVID-19 are directed to individual isolation rooms for further care.  
  Intermediate zone: Patients with atypical symptoms and inconclusive SARS-CoV-2 test results are directed to quarantine ward and observed for the extent of their incubation period.  
  Clean zone: patients without symptoms or signs consistent of COVID-19 are placed in clean zone. Patients designated to hot zone and intermediate zone are provided separate paths so that they do not cross the paths of health-care workers or patients moving to clean zone. HCWs while transiting from clean zone to intermediate and hot zones are instructed to follow appropriate hand hygiene and use personal protection equipment. Also while moving from hot zone to clean zone they are advised to de-gown and practice hand hygiene. Each transition zone is to be clearly labeled and necessary personal protection measures to be followed is to be clearly mentioned to ensure compliance (Flowchart 2).11
- Air handling systems to be optimized.
- Portable solutions like HEPA filtration units can be added to augment air quality.
- Each health-care facility to be equipped with designated staff to address health-care related exposures among HCWs.

Recommendations for care of suspected or confirmed cases of COVID-19:
- Assess for the need for hospitalization. If deemed necessary, it is advisable to give separate rooms with door and dedicated bathroom to each patient. If not feasible then all COVID-19 patients are to be placed in one room which is equipped with enough facilities to maintain physical distancing and source control precautions.
- Patients on whom aerosol generating procedures are planned are to be placed in airborne infection isolation room.
- There should be dedicated HCW assigned for care of COVID-19 patients and same HCW should not be used to provide care to other patients during the same duty shift.
All HCWs providing care to COVID-19 patients should use personal protection equipment, which includes protective eyewear, NIOSH approved N95 or equivalent or higher respirator, clean non-sterile gloves and isolation gown.

Health-care workers are advised to practice hand hygiene measures like washing hands with soap and water for at least 20 seconds or using alcohol-based hand sanitizer with 60–95% alcohol, before and after patient contact, contact with potentially infectious material, and before putting on and after removing PPE, including gloves. Hand hygiene supplies are to be made easily available to all health-care personnel at every care location.

HCWs are advised to monitor themselves for signs and symptoms of COVID-19 and report promptly to the designated team in the health-care facility and refrain from providing patient care during the period of infectious symptoms.

It is advised to minimize the movement of COVID-19 patients outside their designated wards. Whenever moving the patient is necessary, the information regarding the same should be communicated to respective departments and necessary precautions are to be taken before transferring the patient.

It is advised to refrain HCWs from entering the patient rooms soon after discharging or transferring the patient. Sufficient time should be provided for adequate number of air exchanges and then should be appropriately cleaned and surface disinfection to be carried out before returning it back to routine use.

It is advised to minimize the number of visitors to health-care facility. Alternative measures like video calls can be encouraged to ensure patient visitor interactions.

Use of dedicated medical equipment for provision of care to COVID-19 patients.

It is advised to follow routine cleaning and disinfection of all non-dedicated medical equipment.

It is advised to follow cleaning and disinfection of the environment consistently.

Routine standards are to be maintained while handling laundry, medical waste, and food services.

It is advised to redeploy health-care workers who have medical conditions which predispose them to severe infection or death, if infected with SARS-CoV-2, away from high-risk sites.

Measures to improve mental health among HCWs:

- Prompt screening for presence of mental health concerns.
- Use of proper duty roster to reduce long working hours.
- Educational interventions targeting nonmedical health-care workers enabling them to understand and use infection control measures.
- Psychological support including counseling services and development of support systems among colleagues.
- Provision of enough scope for rest breaks, food breaks, and decompression time for health-care workers and ensuring adequate communication and feedback sessions with local managers to help HCWs maintain compliance with personal safety measures and stay focused on provision of care.

Measures to improve social health of HCWs:

- Improving awareness among public to reduce social stigma and marginalization of those involved in care of COVID-19 patients.
- Strengthening social support systems to provide care for elderly and children.
- Provision of adequate information and practical solutions for health-care workers to improve environmental safety at home and prevent transmission to family members. For example, changing from hospital scrubs to personal clothing during return to home from work, showering on return to home, separation of living spaces, and bathrooms.

Conclusion

Health-care workers are the main personnel involved in the management of this raging pandemic; however, as individuals they are faced with increased risk of infection, physical and psychological stress. They are also constantly worried by the concern about family transmission, specifically to elderly members with chronic medical conditions, and immunocompromised which needs to addressed in a better way. It is therefore essential to promptly address physical, mental, and social health concerns affecting the health-care workers and take appropriate measures to improve the same.
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CHAPTER 6

Diabetes and COVID-19: What Is the Connection?

Viswanathan Mohan

Abstract

Diabetes and COVID-19 have a lot of interactions. Uncontrolled diabetes can make outcomes and prognosis in a person with COVID-19 worse. Conversely, COVID-19 can precipitate diabetes or worsen pre-existing diabetes in several ways. This article discusses the relation between Diabetes and COVID-19. It also deals with the treatment of diabetes in a person with COVID-19. Finally, it talks about how COVID-19 and the lockdown changed the way diabetes is treated and led to the growth of Telemedicine in India.

Introduction

The COVID-19 pandemic is one of the most unprecedented in the recent history of mankind. Already, millions have been affected in all continents of the world (except Antarctica) and hundreds of thousands have died due to COVID-19. There is convincing evidence that uncontrolled diabetes and hypertension and cardiovascular disease are associated more severe outcomes and higher mortality in COVID-19.

This article will deal with the connection between diabetes and COVID-19 and will try to answer the following questions:

- Are people with diabetes more prone to COVID-19?
- Are those with diabetes likely to have worse outcomes compared to those without diabetes?
- How does diabetes worsen COVID-19?
- Are any changes to treatment of diabetes to be made if they develop COVID-19?
- How did COVID-19 and lockdown change the practice of diabetes?

Are People with Diabetes more Prone to COVID-19?

It is well known that individuals with diabetes are more susceptible to viral, bacterial, and fungal infections as compared to those without diabetes. This is mainly because those with diabetes (especially uncontrolled diabetes) have less robust immune function. Moreover, glucose can serve as a medium for microorganisms to grow. With respect to respiratory infections, it has been recognized that while individuals with diabetes have less robust immune function. Moreover, glucose can serve as a medium for microorganisms to grow. With respect to respiratory infections, it has been recognized that while individuals with diabetes are more likely to get lower respiratory infection, no such increased predisposition when it comes to upper respiratory infection such as rhinitis, sinusitis, and pharyngitis. Therefore, it is probably not surprising that there is no evidence to suggest that people with diabetes are actually more prone to COVID-19, which starts off as an upper respiratory infection in most cases. The American Diabetes Association (ADA) has also issued a statement that people with diabetes are not more prone to COVID-19 than the general population.
Are People with Diabetes Likely to Get more Severe Form of the Disease and are Outcomes Worse in those with Diabetes?

If those with diabetes do contract COVID-19, they are indeed likely to develop more severe form of the disease particularly if the diabetes is uncontrolled. Data from Wuhan, China, confirms that approximately 20% of severe cases of COVID-19 do show diabetes, as comorbidity. Data from Italy also showed similar findings in that more than two-thirds of those who died due to COVID-19 had diabetes. Another retrospective study from Wuhan revealed that out of 41 COVID-19 patients, 32% of them had an underlying disease among which 20% was accounted for by diabetes. A retrospective study focusing on outpatients at Fujian Provincial Hospital, China, included 135 elderly patients and concluded that those with type 2 diabetes (T2D) had worse outcomes. According to reports from India, of the first 125 deaths on COVID-19, 56% had diabetes, 47% had hypertension, and over a third had both diabetes and hypertension.

A large observational report from China including showed that of the 173 patients with severe COVID-19, comorbidities like hypertension, diabetes, or cardiovascular disease were seen frequently. In another study of 140 COVID-19 inpatient admission, hypertension and diabetes were present in 30% and 12%, respectively.

Of the 72,314 COVID-19 cases reported from China, the overall fatality rate was 2.3% but this increased to 10.5% if CVD was present and to 7.3% and 6%, respectively, if diabetes or hypertension were present.

Another worrying finding is that people with diabetes potentially have milder early symptoms of COVID-19, which makes the subsequent rapid deterioration much more difficult to predict and prevent.

What are the Mechanisms by which Diabetes Worsens COVID-19?

An important feature of T2D is low-grade inflammation. There is long-term immune system imbalance, metabolic syndrome, or nutrient excess associated with obesity. Also, in individuals with diabetes, there is an exaggeration of proinflammatory responses, especially interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNFα). This may be further worsened in those with severe COVID-19. Prolonged hyperglycemia alters the host immune system. Dysfunctions in leukocytes, monocyte and macrophage chemotaxis and phagocytosis, and damaged specific immunity have also been reported in subjects with diabetes. Moreover, diabetes shares the common features promoting disease progression with infectious disorders such as the proinflammatory state and endothelial dysfunction.

Role of ACE2 in Diabetes and COVID-19

The role of ACE2 has been discussed in earlier articles and hence is not dealt with in detail here. Drugs like ACE inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) are widely used in diabetes since hypertension and albuminuria are common in people with diabetes. ACE2 is the receptor to which the Spike (S1) protein of the virus binds to gain entry into the respiratory tract epithelial cells. It is believed that ACE2 receptor stimulation might ease the entry of SARS-CoV-2 into the pneumocytes and thus result in worse outcomes in diabetic patients.

One study from China by Chen et al. claimed that viral clearance is delayed by diabetes, hypertension in males and in old people, which may worsen the prognosis of COVID-19 infection, likely due to the increased expression of ACE2. The authors recommended that the use of ACE1 inhibitors be carefully considered in such population, as it may lead to upregulation of ACE2. However, there is another school of thought that ACE2 overexpression may in fact help as it converts angiotensin-2 into angiotensin 1-7, which has effects exactly opposite to that of angiotensin-2, meaning that it can balance angiotensin-2 in the body so that it is potentially useful or protect against ARDS and the cytokine storm. Therefore, ACE2 seems to attract the virus into the pneumocytes, but on the other hand, perhaps also equips the cells against a cytokine storm. Thus, some authors have contended that blockage of the renin angiotensin aldosterone system (RAAS) by ACEi/ARBs can actually be beneficial in protecting against COVID-19. Current evidence does not support the discontinuation of ACE inhibitor treatment due to concerns regarding Coronavirus infection. Moreover, the European Society of Cardiology, Council on Hypertension; ACC/AHA/HFSA (American College of Cardiology, the American Heart
Association and the Heart Failure Society of America) and the American Society of Hypertension have stated that patients should continue treatment with their usual antihypertensive therapy because there is lack of scientific evidence to incriminate ACE inhibitors or angiotensin receptor blockers in COVID-19 infection.

Other drugs like pioglitazone and liraglutide can also lead to upregulation of the ACE2 in animals.\(^{19,20}\) It is not clear whether these drugs should be discontinued in COVID-19 but pioglitazone is not favored in COVID due to the chances of fluid retention.

**Management of Diabetes: What Changes Need to be Made?**

Glycemic control is the first and foremost factor in diabetes management; otherwise, complications associated with long-term hyperglycemia are not only frequent causes of premature mortality but also virtual drivers of indirect costs. Some studies have shown that the glucose concentration in the airway secretion is directly proportional to the blood glucose concentration.\(^{21}\)

**Can all Anti-diabetic Drugs be Continued?**\(^{22}\)

There is as yet no direct evidence on the effects of the various categories of antidiabetic medications on the risk of developing COVID-19 infection or the adverse outcomes of the same.

**In those with Mild or Well-controlled Diabetes**

In general, patients with T2D, who have mild symptoms of COVID-19 and asymptomatic patients, can continue their usual dose of medications, with appropriate titration if necessary so as to maintain good glycemic control. If the control is inadequate, addition of insulin would be warranted. There is no data on whether use of metformin, sulfonylurea, DPP4 inhibitors alpha-glucosidase inhibitors or insulin influences outcomes of COVID-19 over and above their effects on glycemic control.\(^{16}\) As regards the other classes of antidiabetic agents:

- SGLT2 inhibitors are best avoided in severely symptomatic and hospitalized COVID-19 patients, primarily on account of the risk of dehydration and diabetic ketoacidosis. Also, these agents are known to upregulate renal ACE2, although the implications of this upregulation in the context of COVID-19 are unknown.
- Hydroxychloroquine (HCQ), approved and used as a third-line antidiabetic agent in India, also seems to have beneficial effects in COVID-19, and in India has been approved for prophylaxis of COVID-19 among health-care professionals treating COVID-19 patients and for asymptomatic close contacts of such patients. However, issues related to QT prolonged must be kept in mind. Also recent reports suggest that HCQ may not be beneficial in COVID-19 management and HCQ use remains a contention issue.\(^{23-25}\)
- Many patients with COVID-19 infection report loss of taste and smell sensation, and hence have poor appetite. Many also have GI symptoms such as nausea, diarrhea, and vomiting. The antidiabetic drug regimen should be closely titrated so as to account for fluctuations in food intake caused by these symptoms.

**Role of Anti-diabetic Drugs in COVID-19**

Table 1 shows the role of anti-diabetic drugs in COVID-19.\(^{26}\)

**If Diabetes is Severe or in Hospitalized Patients and those in ICU**

Severe COVID-19 infection can lead to deterioration of glycemic control and some patient could develop diabetic ketoacidosis on account of the excessive outpouring of counter regulatory (stress) hormones. In all such severe cases or in hospitalized patients, insulin would be the antidiabetic agent of choice. Treatment with basal-bolus insulin regimens or IV insulin infusion will usually be needed in such cases. However, the treatment has to be individualized on a case to case basis.

**How did COVID-19 and Lockdown Change the Practice of Diabetes?**

Following the COVID-19 pandemic many countries introduced a total lockdown and did not permit movement of people outside of their houses. This means that routine in person diabetic clinics applicants were not possible.

In India, the lockdown was introduced on March 25th 2020 initially for a period of 21 days but this was extended thrice and as of now the lockdown is in force till May 17th. With India’s population currently at 1.366 billion, this is probably the largest lockdown in human history.
### TABLE 1  Role of anti-diabetic drugs in COVID-19\textsuperscript{26}

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Benefits</th>
</tr>
</thead>
</table>
| Metformin | • Has anti-proliferative and immunomodulatory effects—Protective\textsuperscript{27}  
• Decreased mortality in lower respiratory infections\textsuperscript{29}  
• Risk of lactic acidosis |
| Thiazolidinediones (TZDs) | • Seen to increase risk of pneumonia compared to sulphonylureas\textsuperscript{19}  
• Increase ACE2 expression\textsuperscript{30}  
• Therefore avoid in COVID-19 |
| Glucagon like peptide-1 receptor agonists (GLP-1 RAs) [Liraglutide] | • Also increases ACE2 expression in lungs\textsuperscript{31}  
• Best avoid |
| DPP 4 inhibitors | • In MERS—COV: Reduced viral entry  
• Increased upper respiratory infection with DPP 4 inhibitors known, but no increased risk of pneumonia  
• No evidence for or against use of DPP 4i in COVID-19 |
| SGLT2 inhibitors | • Better to discontinue because of risk of dehydration and euglycemic ketosis |
| Sulphonylureas and insulin | • Dose may have to be adjusted based on blood glucose levels |

**Fig. 1:** Interaction of the person with diabetes and health-care providers using technologies.
Telemedicine which was not legally permit until the COVID-19 set in was rapidly legalized by the Board of Directors of the National Medical Council of India and guidelines for the same were rapidly drawn. With this, telemedicine for diabetes too off in India. Many government and private hospitals and clinics rapidly adopted telemedicine in India.

In a study conducted by us currently, it was seen that 82% of patients who availed the teleconsultation were happy with it. However, only 58.1% stated that they would be keen to continue it in the future.

It is reasonable to assume that if the COVID-19 or similar pandemic arise in the future, telemedicine will become a most accepted method of diabetes treatment.

In the future, we could see the integration of the person with diabetes and the health-care provider (doctor/nurse/educator/dietitian), thanks to using technologies as shown in Figure 1.

Glycemic Control during COVID-19

There have been several predictions regarding the diabetes control during COVID-19. One school of thought believes that due to disruption of lifestyle (diet/exercise), there could be disastrous effects on glycemic control. There were even predictions that A1c could be worsen from around 8% to 12% or even 16%. In a study of 2,500 persons with diabetes in India, it was seen that the reverse is also true. It was seen that glycemic control actually improved from 8.2% to 7.7% in this set of individuals. Reduced frequency of eating out (and eating healthier home meals), timing meals, less stress, better sleep, possibly lower exposure to pollution (because of working from home), and reduced smoking and alcohol (because of non-availability) could be some of the factors which contributed to the improved diabetes control in this study.

Conclusion

In conclusion, the COVID-19 has taught us many things about diabetes. The worse outcomes and increased mortality points to the obviously need for tighter diabetes control. On the other hand, as a silver lining to the difficulties due to the lockdown, many people’s health and lifestyle seem to have improved, resulting in better diabetes control and to the birth of telemedicine.

References

CHAPTER 7

COVID-19-associated Renal Injury

Shashidhar Shree Niwas, Ramya Vedula, Prateek Kumar, Madhuri, Shashank Jain

Abstract

SARS-CoV-2 related renal disease is common in severe cases. Common presentations are proteinuria, hematuria, oliguria, and renal dysfunction. Emerging data from case reports and autopsy series of COVID-19 suggests that it causes acute kidney injury (AKI). Intrinsic renal pathology including viral mediated tubular cell injury, thrombotic vascular processes, and glomerulonephritis. Predominant pathways of renal injury are due to hemodynamic changes, direct cytopathic effect, and cytokine storm syndrome. The indications for RRT in AKI largely remain the same regardless of the COVID-19 status of any given patient.

Introduction

The Corona Virus Disease (COVID-19) pandemic which is rapidly evolving and expanding has infected a population of more than 77 million across the globe and around 10 Million in India as of 25th December, 2020. This virus was first recognized in December 2019 in Wuhan of China when pneumonia of unknown origin came into limelight. It was identified as COVID-19, a neovirus causing severe pneumonia that rapidly led to a major health crisis with devastating consequences not only in India but also in major developed countries of the world.

Initially data from China and Italy, which was identified as caused by COVID-19, shows that death rate worsens in persons with increasing age more than 50 years and also leads to higher risk due to comorbidities like hypertension (HTN), cardiac disease, diabetes mellitus, chronic renal disease, cancer, etc.

Diagnosis

The diagnosis of COVID-19 is mainly based on epidemiological factors (history of contact), clinical manifestations, laboratory examination (hemogram), chest computed tomography, and virological investigations. Incubation period varies between 4–15 days. The virus is highly contagious and mode of transmission is respiratory droplet, contact, aerosol.

Infection has been reported in all ages, but lesser in children. The majority of infections are mild, presenting with a flu-like illness. The common clinical presentations of COVID-19 are fever (98%), cough (76%), myalgia and fatigue (18% each), loss of smell and taste, accompanying leukopenia (25%), and lymphopenia (63%). About 16–20% cases have been classified as severe which includes pneumonia, multiorgan dysfunction, and cytokine storm syndrome.

Renal Manifestations of COVID-19

Data indicates SARS-CoV-2 has particular organotropism beyond the respiratory tract, including the kidneys, liver, heart, and brain, and this influences the course of COVID-19 disease and, possibly, aggravates preexisting conditions. Emerging data from case reports and
autopsy series of COVID-19 suggests that it causes acute kidney injury (AKI). Intrinsic renal pathology including viral mediated tubular cell injury, thrombotic vascular processes, and glomerulonephritis have been reported. AKI also resulted from extrinsic factors such as fluid depletion, multiorgan failure, and rhabdomyolysis.\(^7,8\) Clinical reports have emerged of proximal tubular injury, in association of Fanconi syndrome that manifests as hypokalemia, hypophosphatemia. It also has features of normal anion gap metabolic acidosis, hypovolemia due to salt wasting manifestation. The USA, France, and China reported incidence of AKI that varies from 3% to 37% of patients in retrospective, observational.\(^8-11\)

**Pathogenesis of Renal Injury**

The incidence of renal manifestations and impact and outcome of COVID-19 on kidney is not completely known. Studies describe the clinical manifestations, associated risk factors, and course of acute renal injury in hospitalized patients with COVID-19.\(^7-12\) The largest available published data was in 13 New York metropolitan city hospitals.\(^9\) Total 5,449 patients got admission in these centers with COVID-19, AKI was diagnosed in 36.6% cases. Out of them, 14.3% needed kidney replacement therapy (KRT). Acute renal injury was mostly observed in conditions with respiratory failure. Renal injury was more common (89.7%) of patients on mechanical ventilation as compared to those of non-ventilated patients (21.7%). Surprisingly 96.8% of patients requiring renal replacement therapy were on ventilators. The onset of AKI was observed within 24 hours of intubation in 52.2% of those who needed mechanical ventilation. Major factors for AKI were higher age, diabetes mellitus, cardiac disease, black race, HTN, and requirement of mechanical ventilation and inotropic agents.\(^6\) Out of them 35% died, 26% discharged among all patients with AKI but 39% were still hospitalized. This study clearly shows AKI occurs early in course, and is in temporal association with respiratory failure and have a poor prognosis. Hematuria (46%) and proteinuria (42%) were documented which are mostly part of glomerulonephritis, AKI, thrombotic microangiopathy.

There are predominantly three pathways of renal injury:
- Renal impairment due to hemodynamic changes,
- direct cytotoxic effect, and
- cytokine storm syndrome.\(^9\)

Expression of viral receptor ACE2 on tubular epithelial cells might suggest direct cytopathic effect in renal injury. There may be a role of immunological and prothrombotic factors, which may be triggered by infection. Angiotensin converting enzyme (ACE) both expressed on renal tubular cells was identified as binding partners for SARS-CoV.\(^9\) Viral RNA has been identified in kidney tissue in infected persons. Higher plasma cytokine levels granulocyte-colony stimulating factor were present in patients requiring intensive care unit admission.\(^9\)

**Histopathology**

Largest series of 26 cases of postmortem renal biopsy samples were studied by light microscopy described proximal tubule injury, non-isometric vacuolar degeneration, and even frank tubular necrosis was observed.\(^13\) There were red blood cells accumulation obstructing the capillary lumen in absence of platelets and fibrinoid material. There was no evidence of vasculitis, interstitial inflammation or hemorrhage (Figs. 1A to C).

**Assessment of Renal Injury in Suspected or Confirmed COVID-19**

In patients with COVID-19, AKI is quite common except in mild cases especially with high risk factors. Its incidence increases as severity increases further. Up to 31% on ventilators and 4% not on ventilator needed renal replacement therapy (RRT). AKI is an independent predictor of mortality.\(^9,12\) Common causes may include volume depletion, hemodynamic changes, viral infection leading directly to kidney tubular injury, overzealous diuretics, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis. In management of COVID-19, maintaining euvoemia is critical in prevention and management of AKI, overzealous diuretics, hyperpyrexia, and increased respiratory rate increases insensible fluid loss and hypovolemia may also increase risk of coagulopathy. Assessment of hemodynamics, volume status, monitoring intake output charts, identifying risk factors for AKI, history of pre-existing comorbidities in all patients is essential.

**Patients with Dialysis-requiring AKI**

COVID-19 infection presents particular challenges for patients on dialysis. The indications for RRT in AKI largely
Figs. 1A to C: (A) Clinical information of 1-26 patients affecting different organs. (B) SARS-CoV-2 RNA copies in different organs. (C) Expression of SARS-CoV nucleoprotein in renal tubules.

remain the same regardless of the COVID-19 status of any given patient. Continuous variant of renal replacement therapy (CRRT) is modality of choice in providing dialysis wherever this facility is available among seriously ill patients with AKI.\textsuperscript{14,15} Sustained low-efficiency dialysis or SLED may be performed in hemodynamically stable patients to rapidly changing hemodynamics, deteriorating clinical condition, multiorgan dysfunction, hyperkalemia, metabolic acidosis, shock, inotropic, and ventilator support, which depends upon facility and skilled staff.\textsuperscript{14-16}

In resource constrained situation there are strategies to reduce cost and better utilization of available resources like: colocalization of desired dialysis patients on same floor/ICU and time, SLED instead of CRRT, extended tubing and putting dialysis machine outside of room.

\textbf{Figure 2} shows a simple overview of continuous venovenous filtration (CVVH), which is a most commonly used form of CRRT.\textsuperscript{17} A dialysis filter, which is used as a permeable membrane that filters patient's blood, and then the ultra-filtrate is removed, resulting in clearance of nitrogenous waste products; however, blood cellular components and large proteins like albumin are not removed. Isotonic fluid is used as replacement volume and provides base equivalents like bicarbonate or citrate. The replacement fluid is commonly given prefilter than postfilter to avoid hemoconcentration which can lead to clotting of the membrane.\textsuperscript{15} To increase clearance of waste products during intermittent hemodialysis the rate of replacement fluid and filtrate turnover is increased.\textsuperscript{16}
Studies have suggested that circuit thrombosis is more common in COVID-19 than noncovid patients. In the absence of major contraindications, patients with COVID-19 should receive anticoagulation during RRT. If available, remote monitoring with audio and video streams should be used to troubleshoot alarms.

When resource constrained setting or overburdened hemodialysis centers due to increasing COVID cases, peritoneal dialysis is a good alternative in AKI cases. Patients with AKI who are treated with peritoneal dialysis have similar rates of all-cause mortality, kidney function recovery, and infectious complications compared with patients treated with other modalities.

Pharmacological Agents for COVID-19

High-quality evidence showing the effectiveness of treatments for COVID-19 is scarce, but over 400 studies are now registered in ClinicalTrials.gov testing a range of therapies. Given the abundance of scientific research and clinical, clinicians require accurate evidence for effective medical treatment of COVID-19 infection.

Antiviral Agents

- **Remdesivir**: It is an enzyme inhibitor of RNA polymerase which acts against SARS-CoV-2. Randomized controlled trial has been performed of IV Remdesivir in patients admitted with COVID-19 with evidence of pneumonia. It has shown superior effect in reducing the time to recovery in admitted patients with COVID-19 and pneumonia.

- **Hydroxychloroquine**: It has shown in vitro activity against SARS-CoV-2, an immunomodulatory benefit. However, several clinical trials have not shown very convincing data against COVID-19.

- **Ivermectin**: This has been recently approved by FDA in COVID-19 infection. It also shows antiparasitic activity previously shown to have broad-spectrum antiviral activity in vitro. It is an inhibitor of the causative virus (SARS-CoV-2). Ivermectin therefore warrants further investigation for possible benefits in humans.

- **Tocilizumab**: Disproportionate and excessive immune response to infection with the SARS-CoV-2 virus has been found to be part of cytokine storm in the ARDS and multiorgan failure in some patients. Cytokine IL-6 inhibitor, tocilizumab is part of several randomized, double-blind, placebo-controlled phase 3 clinical trials as well as uncontrolled trials to evaluate the safety and efficacy of tocilizumab plus standard of care in hospitalized adult patients with severe COVID-19 pneumonia with some promising initial results.

- **Plasma therapy (convalescent plasma)**: It is a type of passive antibody therapy in which blood plasma is isolated from people who have recovered from the COVID-19 infection and is administered to those with the disease to suppress viremia and improve clinical symptoms.

- **ICMR has regularly updated the clinical management of COVID-19 in India. Recently it has included the role of remdesivir, favipiravir, tocilizumab, and convalescent plasma on selected group of patients. The document states, “Remdesivir (under Emergency Use Authorization) may be considered in patients with moderate disease (those on oxygen)... tocilizumab (Off Label) may be considered in patients with moderate disease with progressively increasing oxygen requirements and in mechanically ventilated patients not improving despite the use of steroids. Long-term safety data in COVID-19 remains largely unknown... Convalescent plasma (Off Label) may be considered in patients with moderate disease who are not improving (oxygen requirement is progressively increasing) despite the use of steroids.” Though the revised protocols allow hydroxychloroquine to be prescribed to patients in the early course of the disease, evidence for its use “remains limited.”
Conclusion

The COVID-19 pandemic has posted major challenges around the globe. Renal clinical presentation ranging from mild proteinuria, hematuria to progressive AKI necessitating renal replacement therapy (RRT), thrombotic microangiopathy, and rhabdomyolysis. International collaboration and interdisciplinary research is needed to obtain adequate evidence to support current clinical approaches and to develop new approaches to management. Multiple pathways might play role in AKI including direct renal injury. AKI is independent predictor of mortality in COVID-19. Strategies to enhance the antiviral potency of antiviral agents, vaccine, and ways to mitigate immunopathological host responses contributing to COVID-19 severity require further research in patients of COVID-19.

References

CHAPTER 8

Sahaja Yoga Meditation for Reduction of Stress during the Present Corona Pandemic

Sandeep Rai, Devdutt Rai, Madhur Rai

Abstract

The world is fighting against the COVID-19 outbreak, which is now spread to more than 200 countries worldwide. There has been a huge loss of life, drastic changes in our way of life, disrupted plans due to travel restrictions and social distancing. Health experts say, during this time of heightened stress, anxiety, and fear, finding ways to cope up and to create stability is the key to maintaining a healthy body and mind. Pandemic-related stressors may be difficult to change; nevertheless, an enhancement in one’s coping abilities to combat the deleterious effects of stress on the body and mind can be definitely brought about. In fact, new studies have now revealed that by practicing only 15–20 minutes of Sahaja Yoga meditation daily, you can remain stress-free.

Introduction

When stress does not let up and is paired with the feeling that we have very little or absolutely no control over the circumstances that are creating it, that’s called chronic stress. Chronic stress zaps brain power by damaging neural pathways and hampering judgment. It damages the immune system and many other organs including the heart and the brain. Presently robust evidence exists for the Mind-Body medicine practices like meditation and yoga for improving one’s psychological and physical health.

Sahaja Yoga is indeed a very unique meditation developed by Dr. Nirmala Devi Srivastava, popularly known as H.H. Shri Mataji Nirmala Devi in 1970. This meditation causes a transformation inside a person by which one becomes balanced and de-stressed. It offers a practically easy method of understanding one’s own energy systems and harnessing the innate powerful energy, present in all human beings, for improving one’s own health. Scientific researches have now clearly shown that Sahaja Yoga meditation acts by reducing the activity of the sympathetic system (Stress) and increasing the parasympathetic activity (Relaxation) in an individual.

Sahaja Yoga meditation practice for 12–16 weeks, in subjects who had never practiced any form of meditation before, has shown a slowing of the heart rate, decrease in the respiratory rate, decrease in both BP and in the production of urinary vanillymandelic acid (VMA), which is a breakdown product of stress hormone adrenalin and an increase of Galvanic Skin resistance. Changes in all these parameters reflect a de-stressed state of body. These parameters indicate activation of a deep parasympathetic state, which in turn indicates a physiologically relaxed state of the body and mind, and this may play a very big role in the prevention of stress-related diseases.

Electrophysiological studies (EEG) and analysis, on SY meditators, have shown specific brain activation patterns, which indicate a relaxed state of mind, a subjective feeling of happiness, and an enhanced interconnectivity of different brain regions. In an interesting study examining emotional reactions of Sahaja Yoga meditators compared to non meditators, a decreased electrophysiological,
physiological, and psychological reactions were seen in meditators when exposed to stressful stimuli, compared to non-meditators, thus showing for probably the first time in the world, the neurophysiologic proof, to support the hypothesis, that Sahaja Yoga meditation leads to development of greater resilience in an individual to deal with stressful life events. Many other randomized trials on Sahaja Yoga meditation have demonstrated beneficial effects on depression and work-related stress.

In other researches conducted on Sahaja Yoga meditation, very good results were achieved in patients suffering from anxiety and depression, enhancing QOL and significant improvement in psychological health of a mixed population consisting of subjects from different countries and of age groups (Fig 1). Encouraging results have also been recorded in patients with hypertension, asthma, and perceived stress, after a couple of weeks of Sahaja Yoga meditation practice. SY meditation practice also showed a significant reduction in epilepsy attacks, attacks of bronchial asthma, and improvements in the control of diabetes and blood pressure.

Chronic stress is known to increase cortisol levels in body which in turn decreases immunity and consequently impairs a person’s ability to fight infections. Two randomly controlled studies conducted in the Dept. of Medicine & the Dept. of Physiology at the MGM Institute of Health Sciences, Navi Mumbai by the authors of this article, on effects of Sahaja Yoga on perceived stress and serum cortisol levels recorded a very robust reduction in perceived stress and serum cortisol levels in Sahaja Yoga meditation practitioners as compared to non-meditating healthy population. More over an exciting new research has shown that practice of Sahaja Yoga resulted in increase in gray matter volume of brain, in many cortical and sub-cortical brain regions of the right hemisphere. These regions are associated with self-control, compassion, and stress modulation.

Modern medicine’s understanding of the human immunosystem, as a complex multidimensional interaction among different organ systems, is slowly expanding, throwing its light on new facets like neuroendocrine and psychoemotional aspects governing its effective functioning. Chronic stress, although mental in origin, has many detrimental effects on the body as well as on the immunity by creating an imbalance in the neuroendocrine pathways. These chronic stressors overwhelm the immune system of our body thus weakening the immune system’s ability to activate a strong immunological response to an infectious organism and thus making the individual susceptible to life threatening medical consequences. It is now amply proven that practice of meditation establishes moderation in the person’s psychological and emotional spheres and corrects the imbalance in the neuroendocrine pathways.

Both health and yoga experts now firmly believe that meditating on a regular basis can help to improve the immunity of the body, thus creating a shield in a fight against the highly infectious diseases, like COVID-19. Scientific research has already shown that meditation produces remarkable effects on the brain and immune system.
functions.\textsuperscript{19-21} Recent studies have now shown that the relaxation produced after meditation reduces the levels of IL-6, a proinflammatory cytokine which plays a major role in the pathophysiology of several diseases including COVID-19.\textsuperscript{22}

Meditation has shown to increase the telomerase activity of chromosomes and lengthens telomeres and thus promotes immune cell longevity.\textsuperscript{23} Meditation has shown to reduce the activity of nuclear factor-kB (NF-kB), which is a known mediator in the pathogenesis of inflammation and in generating C-reactive protein which increases in inflammatory conditions including COVID-19.\textsuperscript{24,25} Meditation has shown to boost the levels of salivary immunoglobulin A, which is an immune mediator at mucosal surfaces such as GI tract, respiratory tract, and genitourinary tract.\textsuperscript{24,25} Meditation has also shown to increase the levels of antibody titer against influenza virus thus increasing immunity against some of the common viral infections.\textsuperscript{23,28} Regular meditation practice has also shown an increase in the absolute lymphocyte count which is an important predictor of the risk of opportunistic infections and is now increasingly used to grade the severity of COVID-19 infections.\textsuperscript{27} A very recent review analyzing various studies, for the effects of meditation and yoga on immune system has found the evidence of enhancement of immunity in an individual, by the practicing some forms of yoga and meditation.\textsuperscript{28}

**How Sahaja Yoga Meditation Reduces Stress?**

*The Possible Mechanisms:* Mammals, including humans, have over millions of years evolved the ability to deal quickly and reflexively with perceived threats to their survival and this ability has conferred a robust survival advantage to this group of animals. In humans however, the same stress response can be triggered in situations which, while they do not necessarily threaten survival but occur fairly frequently over a prolonged period of time. Such a typical situation is in the present day stress of Corona pandemic which we all are facing on a daily basis. Repeated activation of the stress response is thought to result in dysregulation of the immune system which hampers the body’s own survival mechanisms and this in turn damages health. The changes in mind and body achieved by Sahaja Yoga meditation are characterized by the relaxation response. Psychophysiological studies on Sahaja Yoga meditation, suggest that indeed it elicits a relaxation response. The hypothesis is that the innate energy, called Kundalini energy, described in detail in the ancient Indian scriptures, actualizes in limbic area of the brain and modulates the stress response of an individual through the limbic system (Fig. 2). The limbic system has intricate connections with hypothalamus and via hypothalamus the autonomic nervous system is modulated. The limbic system by its action on the HPA axis modulates the release of various important hormones including cortisol which is secreted in response to stress. Practicing Sahaja Yoga meditation balances the energy systems of the body for its optimum functioning.

Sahaja Yoga is now a practiced in many corporate offices and is an integral part of wellness programs. It is also increasingly being incorporated in many youth development programs around the world. In this ongoing Corona pandemic, technology has enabled to teach and conduct online Sahaja Yoga collective meditation programs for lakhs of people in India and across the world, and these online programs have become hugely popular.

The Harvard Medical School also, in its latest health guideline released on COVID-19 pandemic, has said that, Yoga and meditation are “some tried and true ways to relax and to remain stress free in these difficult times.” There have been numerous medical researches conducted in India and abroad on Sahaja Yoga. Sahaja Yoga is now available free of charge, on the various online platforms, to learn and practice, and it is also taught free at all the Centers of Sahaja Yoga which are present today in more than 150 countries of the world.

H.H. Shri Mataji Nirmala Devi ji has received numerous Prizes and recognitions from all over the world for her significant contribution to the understanding of subtle energy systems of the human body. She was conferred with the Honorary membership to the prestigious Presidium of Petroyska’s Academy of Art and Science, Russia (Einstein being one of the members). She has been conferred the United Nations Peace Prize and had been nominated for Nobel Peace Prize, twice. For any further information on Sahaja Yoga you may visit www.freemeditation.com or write to doctorsandeeprai@gmail.com.

**Acknowledgments:** We sincerely owe our gratitude to the Medical Director, Dr. S. N. Kadam, Respected Dean & Heads of Dept. Med. & Physio., MGIHS, Mumbai;
Dr. Vishesh Agarwal, Consultant Physician, Nanavati Hospital, Mumbai; Dr. Yashoda Kattamani, Associate Prof. Physiology, MGMHKS; Dr. R. Manocha, Asst. Prof., Sydney Med School; Dr. Sheng Chia, Epidemiologist, London; Dr. Sergio Elias Hernandez, University de La Laguna, Tenerife, Spain; Prof. U. Panjwani, DIRDO, New Delhi; Dr. D. Chug, Neurologist, USA; Prof. K. Rubia, Kings College London; and all the doctors and subjects who participated voluntarily in research projects for their active participation, cooperation, and valuable contribution.

Conclusion

The world is fighting the COVID-19 pandemic and people are desperately looking for ways to cope up with this unrelenting stress. Chronic stress zaps brainpower by damaging neural pathways, compromises the immune system besides taxing many other organs of the body. It may not be an easy task to change the present day stressors, but coping abilities to combat negative effects of stress on health and disease can definitely be enhanced. In fact, new research reveals that simple 20 minutes of Sahaja Yoga meditation a day can keep stress away.

By practicing this meditation, an inner transformation takes place by which one becomes energized and de-stressed. Studies show that Sahaja Yoga meditation acts by reducing sympathetic activity (Stress) and enhancing the parasympathetic activity (Relaxation). Rigorous researches on Sahaja Yoga meditation have demonstrated significant benefits on depressive mood, anxiety, and work stress and have shown improvement in Psychological health, Perceived Stress levels, and overall Quality of life. Sahaja Yoga meditation is taught free of charge in more than 150 countries around the world. The simple technique of Sahaja Yoga can be learnt free from internet and through online meditation programs also. For learning Sahaja Yoga meditation or for any more information please visit site -www.freemeditation.com or www.sahajayoga.org.in

Fig. 2: The subtle system and chakras
References

Abstract
The current pandemic caused by SARS-CoV-2 (COVID-19) began in China and has taken over 4,00,000 lives, putting every country to a standstill. Its manifestations range from mild symptoms to respiratory failure and multi-organ damage in those with risk factors. Spreading mainly by person-to-person transmission, it reached every part of the world within 3 months. Management of the disease is based on case severity and symptomatic treatment. While several new drugs are being developed, many drugs have been repurposed for the same. Other than low dose steroids, no drug has shown proven benefit in preventing severe disease so far. As of now, prevention is the best strategy against this disease. There are universal preventive measures for everyone including health-care workers to be followed even outside health-care facilities. Certain vaccines are being developed all around the world, but that might be a long road ahead. Even after development of a specific drug/vaccine, this new disease is here to stay. Past experiences have taught us to learn to live with it and adjust our lifestyle accordingly.

Introduction
In 2019, a novel coronavirus disease 2019 (COVID-19) began in Wuhan, China, and spread worldwide and was declared a pandemic by WHO. It is caused by severe acute respiratory syndrome-coronavirus-2 also called as—SARS-CoV-2. As of the first week of June, 7 million reported cases and 400,000 deaths in more than 200 countries. In India, there is 250,000 reported case with approximately 6,000 deaths. This is a Betacoronavirus and is similar to Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV).

Clinical Features and Transmission
The spectrum of disease ranges from mild to critical:\n- Mild (no or mild pneumonia)—81%
- Severe disease (dyspnea, hypoxia, or >50% lung involvement on X-ray)—14%
- Critical disease (respiratory failure, shock, or multiorgan dysfunction)—5%

The median incubation period is 4 days (2-14 days). However, about half of the population seems to be asymptomatic. Clinical presentation is mostly of upper respiratory illness (Table 1). There are certain risk factors and laboratory parameters, which predispose to severe or critical disease (Box 1 and Table 2).

Transmission
There are two main modes.

Person to Person
It is the predominant method that occurs via respiratory droplets spread through close-contacts. These respiratory droplets do not travel more than 6 feet. Although airborne precautions are recommended, the transmission via
### TABLE 1  
**Clinical features**

<table>
<thead>
<tr>
<th>Typical clinical features</th>
<th>Atypical clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry cough</td>
<td>Nausea &amp; vomiting</td>
</tr>
<tr>
<td>Fever*</td>
<td>Nasal congestion</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Sputum</td>
<td>Tonsillar enlargement</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Conjunctival congestion</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
</tr>
</tbody>
</table>

*Low grade, about 88% developed during hospitalization. Some patients also reported of anosmia and dysgeusia.

### BOX 1  
**Risk factors for severe disease**

- Age >65 years
- History of hypertension
- History of cardiovascular disease
- Diabetes mellitus
- Obesity (BMI ≥30)
- Biologics (eg, TNF inhibitors, interleukin inhibitors, anti-B cell agents)
- History of immunosuppression (eg, Transplant)
- CD4 cell count <200 cells/microL (eg, HIV)

### BOX 2  
**List of Aerosol generating procedures**

- Open suctioning of airway
- Sputum induction
- Tracheal intubation
- Noninvasive ventilation
- Tracheostomy
- Cardiopulmonary resuscitation
- Manual ventilation before intubation
- Bronchoscopy

This route is still unclear. Airborne precautions are recommended when high-risk aerosol-generating procedures are in place (Box 2).

SARS-CoV-2 has been detected in other specimens as well, including stool, tear film, blood, semen. However, the role of these sites in the transmission is still not known. No feco-oral transmission has been detected as of yet.

### Period of Infectivity

It can be transmitted 2–3 days before the onset of symptoms and then throughout the disease. Maximum transmission has been reported in the first 7 days. Infectivity peaks 1 day before the onset of symptoms.3

### Environmental Contamination

If susceptible individuals come in contact with contaminated surfaces, then it serves as a potential source of contamination. The survival time of viral particles has been demonstrated to be different on different surfaces.

### Diagnosis

Given the high transmission and prevalence of COVID-19, an efficacious strategy for quick diagnosis and prompt response is the need of the hour. An overview of the strategies is discussed below.

### Whom to Test

In this time of the pandemic, a high clinical suspicion of the COVID-19 case is necessary. It should be suspected in any patient with new symptoms. ICMR has prioritized a certain group of symptomatic individuals to be tested and apart from this, testing of asymptomatic cases may be advocated in special circumstances (Table 3).4,5
TABLE 3  Individuals to be tested

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>International travel in the last 14 days</td>
<td>Involved in public health monitoring, screening or sentinel surveillance</td>
</tr>
<tr>
<td>Contacts of laboratory-confirmed cases</td>
<td>Immunocompromised who are admitted to hospitals</td>
</tr>
<tr>
<td>Health care workers involved in management of COVID-19</td>
<td>Before any immunosuppressive procedures</td>
</tr>
<tr>
<td>All patients of Severe Acute Respiratory Infection (SARI)</td>
<td>Undergoing major surgeries</td>
</tr>
<tr>
<td>All symptomatic Influenza-Like-Illness (ILI)</td>
<td>High-risk contacts of a confirmed case to be tested once between day 5 and day 10 of coming into contact</td>
</tr>
<tr>
<td>All hospitalized patients who develop Ili symptoms</td>
<td>Undergoing an aerosol-generating procedure</td>
</tr>
<tr>
<td>All asymptomatic ILI migrants within 7 days of onset of illness</td>
<td></td>
</tr>
</tbody>
</table>

Testing Methods

There are two main testing methods approved:

**RT-PCR**

It is a confirmatory test based on the detection of unique sequences of virus RNA by NAAT polymerase chain reaction (RT-PCR). The gene targets tested are: spike (S), nucleocapsid (N), envelope (E), and RNA-dependent RNA polymerase (RdRp), and certain regions in the first open reading frame. Specimen: Upper respiratory tract samples are collected usually (most commonly from nasopharynx or oropharynx). Lower respiratory tract specimens have higher viral load but are reserved for patients with initial negative test on an upper respiratory tract specimen but high clinical suspicion. The specificity of most of the RT-PCR tests is about 100%. The yield from these specimens is variable (Table 4).

Timing of testing: In nasopharyngeal specimens, viral load becomes detectable earliest by first day of symptom-onset and peaks within the first 7 days. This positivity starts to decline by week 3 and subsequently becomes undetectable. A “positive” PCR result indicates only the detection of viral RNA and it does not necessarily indicate the presence of viable virus. PCR positivity remains longer in sputum and stool may remain positive even after nasopharyngeal samples; however, it is not related to the clinical severity of the disease.

Truenat testing: Recently ICMR approved Truenat for screening. It was originally developed for the detection of tuberculosis. It has advantages of giving results in 30–60 mins. All positive results are confirmed with RT-PCR.

**Table 4** Detection of COVID-19 in different samples

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoalveolar lavage</td>
<td>93%</td>
</tr>
<tr>
<td>Sputum</td>
<td>72%</td>
</tr>
<tr>
<td>Nasal Swab</td>
<td>63%</td>
</tr>
<tr>
<td>Fibrobronchoscope biopsy</td>
<td>46%</td>
</tr>
<tr>
<td>Pharyngeal Swab</td>
<td>32%</td>
</tr>
<tr>
<td>Feces</td>
<td>29%</td>
</tr>
<tr>
<td>Blood</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Antibody Testing

Antibody against COVID-19 is likely to be reactive in the first several days to weeks of infection, and thus may have less utility for diagnosis in the acute setting. It is used mainly for screening purposes and those who present late, beyond the first 2 weeks of illness onset. There are no data regarding the specificity of these serological tests. Cross-reactivity is a potential concern, and IgM tests are prone to false-positive results.

In India, ICMR has advocated the use of rapid antibody testing in hotspot areas (Flowchart 1).

Management

**Case Severity and Level of Care**

In India, ICMR has advised classifying the cases based on their severity into three groups, and further, the management of each group has been planned at a different level of care known as COVID dedicated facilities (Table 5).

**Treatment of Cases**

Most of the cases of COVID-19 are mild and only a small proportion of them are severe. The management is mainly...
symptomatic. The specific treatment consideration is as follows.15

**Supplemental Oxygenation**

Most of the severe cases require oxygenation. Oxygen can be given by nasal cannula or non-rebreathing mask. The target oxygen saturation is above 94%.16 The use of prone position can improve oxygenation. During prone positioning, there is relative recruitment of nondependent dorsal alveoli and because of a higher density of pulmonary vessels in the dorsal lung region, it results in improved V/Q matching and oxygenation.17

**Specific Pharmacotherapy**

No specific drug therapy has been proven against COVID-19. Several therapies are being evaluated. Some of which are already clinically available for other indications. The potential treatment options in COVID-19 under consideration are given in Table 6.15

“Solidarity Trial” is an international clinical trial launched by the World Health Organization to find an effective treatment of COVID-19. It compares four treatment—chloroquine versus remdesivir versus lopinavir/ritonavir versus interferon beta 1a. Recently, India also became part of this trial.

**Other Specific Issues**

*Hemodynamic stabilization:* Patients with SARI with no evidence of shock should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation. If BP further falls, the use of inotropes and vasopressors should be considered.

*Venous thromboembolism prophylaxis:* COVID-19 is associated with profound inflammation and this can cause endothelial injury and subsequent thrombosis, a phenomenon also termed as thrombo-inflammation.18 It is advised to use pharmacological (UFH, LMWH) in all hospitalized patients with d-dimer more than 1,000 ng/dL unless contraindicated.18

*Steroid:* The recent results from RECOVERY trial has shown remarkable improvements from low dose dexamethasone (6 mg/day), following which the use of same has been
## TABLE 6 Specific pharmacotherapy against COVID-19 under consideration

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Remark</th>
</tr>
</thead>
</table>
| Chloroquine and Hydroxychloroquine (HCQS) | Chloroquine: 600 mg BD × 10 days  
HCQS: 400 mg BD on day 1  
200 mg BD × 4 days | Inhibits endocytosis and blocks viral entry into cell  
HCQS is more effective than chloroquine  
Latest studies have shown no benefit  
Less in-hospital survival observed  
More chances of arrhythmia  
FDA has recommended against the use of this drug in COVID-19 |
| Azithromycin and HCQS               | Azithromycin 500 mg OD × 5 days  
HCQS: 400 mg BD on day 1  
200 mg BD × 4 days | The only drug approved by ICMR for severe cases  
A large multicentre cohort study observed no significant difference in in-hospital mortality  
Both drugs associated with QTc prolongation and combined use may potentiate this.  
American College of Cardiology issued a warning and score-based approach to using these drugs |
| Remdesivir                          | 200 mg i.v on day 1  
100 mg i.v × 10 days (for patients on mechanical ventilation)  
100 mg i.v × 5 days (for other patients) | Nucleotide analogue which inhibits viral RNA dependent RNA polymerase  
Originally developed by company Gilead for EBOLA  
FDA has issued an approval for emergency use for hospitalized patients with severe disease  
Not recommended in:  
• ALT >5x normal  
• eGFR <30 mL/min per 1.73 m²  
• Lactating or pregnant female  
• Children <12 years of age  
However, not available in the Indian market as of now |
| Lopinavir/Ritonavir                  | 400 mg/100 mg BD × 14 days | Inhibits main viral protease  
Administration during early peak of viral replication has proven more efficacious  
Drug-induced transaminitis is a major side effect.  
ICMR has approved off-label emergency use in:  
• Severe patients  
• >60 years  
• With comorbidities |
| Convalescent Plasma                 | 4 to 13 mL/kg (usually 200 mL single dose given slowly over not less than 2 hours) | Contains antibodies from the serum of patient who has recovered from COVID-19  
Clinical trials undergoing (including in India) to prove efficacy  
May be considered in those who are not improving despite steroid therapy  
The early result showed an early time to recovery |
| Tocilizumab                         | 8 mg/kg (up to a maximum of 800 mg per dose). | COVID-19 is characterized by a marked inflammatory response—the cytokine storm  
Markedly elevated inflammatory markers (e.g., D-dimer, ferritin) and elevated pro-inflammatory cytokines (including interleukin IL-6) are associated with poor outcome  
Studies from Wuhan showed clinical benefits and a decrease in C-reactive protein, D-dimer, and ferritin levels |
| Ivermectin + Doxycycline            | Ivermectin – 200 ug/kg on day 1  
Doxycycline– 200 mg stat on day 1  
100 mg BD × 4 days | Both drugs inhibit viral replication and have proven efficacy in in-vitro studies  
Initial case reports from Bangladesh described promising results  
Clinical trials are undergoing to further evaluate the efficacy |
recommended by all major societies including WHO and ICMR.

Use of ACE inhibitors: For patients already taking these drugs, it is advised to continue treatment, if there is no other reason for discontinuation.27

Critical Care and Other Complications

Acute respiratory distress syndrome (ARDS) and critical care: Among those who are critically ill, ARDS is the dominant finding. Age appears to be the major risk factor that predicts progression to ARDS.28

Oxygen target of 94% is preferred. Low flow via nasal cannula is appropriate (i.e., up to 6 L/min). Higher flows (up to 10–20 L/minute) may be administered using a simple face mask, venturi face mask, or non-rebreather mask. However, oxygenation at higher flow is associated with a higher risk of aerosolization.

Refractory hypoxemia is a major issue. Use of high-flow nasal cannula oxygen therapy (HFNO) or noninvasive ventilation (NIV) can be considered. No study is available regarding the comparative efficacy of the two.

The decision to intubate the patient against the risk of salvageability and risk of spread of infection is challenging. A low threshold for intubation in the following patients:

- Rapid progression over hours
- Lack of improvement on high flow oxygen >40 L/minute and FiO₂ >0.6
- Increasing work of breathing or tidal volume, worsening mental status or if developing hypercapnia
- Hemodynamic instability or multiorgan failure

However, given the high risk of aerosol generation, certain precautions must always be practiced (Box 3).29

Septic shock: Sepsis, shock, and multiorgan failure occur but are less common than ARDS. The management of septic shock in COVID-19 is essentially in line with surviving sepsis guidelines.

Acute kidney injury (AKI) and dialysis: AKI among hospitalized patients with COVID-19 ranging from 5% to 23%. It usually manifests during the second week of infection.

Cardiac complications: The most common cardiac complications include myocardial injury leading to myocarditis, arrhythmia, and conduction system abnormalities, acute coronary syndromes, etc.

Coagulopathy: Many studies have described hypercoagulability in COVID-19 and a low risk of bleeding in such patients.

Discharge of the Patients

In contrast to the initial “test-based strategy,” the Govt. of India eventually shifted to “symptom-based strategy” or “time based strategy.” The ICMR laboratory surveillance data also indicated that patients became negative after a mean duration of 10 days (Table 7).

Prevention

Prevention is the best and the only proven strategy that can be adopted against COVID-19. Some of the preventive advises are enlisted in Table 8.

Future Perspective

Future of the COVID-19 management depends mainly on two pillars—discovery of an optimal drug and development of an efficacious vaccine. Many government agencies are funding researches in this field.
TABLE 8 Preventive measure against COVID-19

In healthcare setting
- For all patients/visitors:
  - Screening before entry
  - Universal use of masks
- While dealing with suspect or confirm case:
  - Patient to be kept in a single occupancy room with a separate bathroom and no positive pressure.
  - Healthcare working entering the room should wear PPE comprising at least:
    - Gowns and gloves
    - Respirator or masks
    - Eyes or face mask
  - Maintaining hand hygiene
  - Regularly Clean with sodium hypochlorite (for floor and surfaces) and 70% alcohol for metallic surfaces and doorknobs

Personal preventive measures
- To practice social distancing
- To maintain at least two meters distance
- Proper hand washing
- Respiratory hygiene (e.g., covering while coughing or sneezing)
- Cleaning and disinfecting objects and surfaces

TABLE 9 Potential pharmacological therapies

<table>
<thead>
<tr>
<th>Virus-based</th>
<th>Host-based</th>
<th>Immune-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main protease inhibitor</td>
<td>Lopinavir/ritonavir, Cinanserin, flavonoids</td>
<td>Chloroquine/Hydroxychloroquine</td>
</tr>
<tr>
<td>Papain-like protease (PL2pro) inhibitor</td>
<td>Disulfiram</td>
<td>Camostat mesylate, Nafamostat</td>
</tr>
<tr>
<td>RNA-dependent RNA polymerase inhibitor</td>
<td>Favipiravir, Ribavirin, Remdesivir, Galidesivir</td>
<td>Interferon alpha and interferon beta, Nitazoxanide</td>
</tr>
<tr>
<td>Viral S spike protein inhibitor</td>
<td>Urifennovir</td>
<td>Host Matrix metalloproteinase (MMP) inhibitors</td>
</tr>
<tr>
<td>Viral Nucleic acid inhibitor</td>
<td>Mycophenolic acid</td>
<td>Tetracyclines (doxycycline, minocycline, etc.)</td>
</tr>
<tr>
<td>Other drugs</td>
<td>Loperamide</td>
<td>Convalescent plasma</td>
</tr>
<tr>
<td>Host immunity enhancer</td>
<td>Host protease inhibitor</td>
<td>IL-6 inhibitors Sarilumab, Siltuximab, Tocilizumab</td>
</tr>
<tr>
<td>Host endocytosis inhibitor</td>
<td>Inhibitor of viral nuclear transport</td>
<td>IL-1 inhibitors Anakinra, Anti CD6 monoclonal antibody Itolizumab</td>
</tr>
<tr>
<td>Papain-like protease</td>
<td>Ivermectin</td>
<td>JAK inhibitors Baricitinib, Pacritinib Fedratinib, Ruxolitinib</td>
</tr>
<tr>
<td>RNA-dependent RNA polymerase</td>
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</tbody>
</table>

Potential Pharmacological Therapies

Several treatments are being investigated for COVID-19. Some of these treatments are already available for other indications (repurposed drugs), while many new drugs are being developed specifically for COVID-19 (Table 9).

Among the therapies mentioned in the table, the following are under trial in India:^30

- Disulfiram
- Remdesivir
- Favipiravir
- Loperamide
- Convalescent plasma
- Tocilizumab (IL-6 inhibitor)
- Itolizumab
- Mycobacterium w

Potential Future Vaccines

Several vaccines are under development against COVID-19. As of May 2020, more than 150 vaccine candidates are under development. The majority of these are in the preclinical or exploratory phase. Only a few have entered phase 1. Leading the race for a new vaccine, eight vaccine candidates have already entered human trials across the world (Table 10).

In India, there are at least 30 attempts to develop an effective vaccine against the COVID-19 by six Indian companies. The BCG vaccination has garnered a lot of interest. Studies have suggested that BCG immunization induces a non-specific immune response in the hosts that may have protective effects against non-mycobacterial, including viral, infections. However, more data is needed and this vaccine is under trial as of now.
Conclusion

The development of a vaccine or an efficacious drug is not reality as of now and seems to be a farfetched option. It is impossible to predict when the pandemic would be controlled. The new coronavirus might be here to stay. Moreover, it may take years to build up sufficient levels of immunity. Coronavirus is just another novel disease like HIV, which has not disappeared but measures have been developed by people to live by it. We need to learn to live with coronavirus and adjust ourselves to it.

References


TABLE 10

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<tr>
<th>Name of vaccine</th>
<th>Developing institute</th>
<th>Country</th>
<th>Remark</th>
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<td>mRNA-1273</td>
<td>Moderna</td>
<td>US</td>
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<td>China</td>
<td>Based on engineered replication-defective adenovirus type 5 vector to express the SARS-CoV-2 spike protein</td>
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<td>UK</td>
<td>An engineered adenovirus-based vaccine to express the SARS-CoV-2 spike protein</td>
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<td>Inactivated vaccine</td>
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CHAPTER 10
Clinical Presentation and Systemic Manifestations of COVID-19 (Coronavirus Disease 2019)

Rajib Ratna Chaudhary, Sarda Mukund Shyam

Abstract
COVID-19 (Coronavirus Disease 2019) was reported in December, 2019, and the first case was reported in India on 30th January, 2020, in Kerala. COVID-19 was declared pandemic on 11th March, 2020, due to its rapid spread in the world by World Health Organization (WHO). SARS-CoV-2 virus is a single-stranded RNA virus and is the seventh member of the betacoronavirus family. SARS-CoV-2 virus is an airborne virus, spreads by an infected person on sneezing or coughing small droplets in the air so the person who inhales such droplets or touches the infected surfaces is infected. The incubation period of COVID-19 is 14 days and a median incubation period of 4–5 days (interquartile range 2–7 days). The clinical presentations of COVID-19 are cough, fever, malaise, myalgias, gastrointestinal symptoms, and anosmia or ageusia. COVID-19 diagnosis is based on clinical features and to be confirmed by RT-PCR of nasopharyngeal or oropharyngeal swabs. Management of COVID-19 depends on the severity of disease; with mild disease by home isolation and moderate or severe disease, patients are hospitalized and supportive treatment given. Frequent hand washing with soap and water, face mask, social distancing, testing, and self isolation are important for prevention of COVID-19 until the vaccine becomes available.

Introduction
COVID-19 (Coronavirus Disease 2019) was reported in December 2019 and the first case was reported in India on 30th January, 2020, in Kerala. COVID-19 was declared pandemic on 11th March, 2020, due to its rapid spread in the world by World Health Organization (WHO). India has now more than 88,72,203 infected cases, 4,43,794 active cases with more than 1,32,162 COVID-19 related death (20th November, 2020, MoHF, India).

The common symptoms of COVID-19 in mild cases are fever and cough, in moderate cases, shortness of breath, and in severe cases, the infection can cause pneumonia, multiorgan inflammatory failure, and death.

Frequent handwashing with soap and water, face mask, social distancing, and self-isolation are important for prevention of COVID-19 until the vaccine becomes available.

Transmission
SARS-CoV-2 virus is an airborne virus, spreads by an infected person on sneezing or coughing small droplets in the air so the person who inhales such droplets or touches the infected surfaces is infected.

The transmission is high at the onset of symptom due to high quantity of viral shedding and low over the course of 7–10 days.

SARS-CoV-2 virus has been detected in the stool of COVID-19 patients and consumption of virus-contaminated food may cause infection and transmission is yet not confirmed.
SARS-CoV-2 virus has also been found in semen, but sexual transmission is not yet confirmed.

**Pathogenesis**

SARS-CoV-2 virus is a single-stranded RNA virus and is the seventh member of the betacoronavirus family, subfamily orthocoronavirinae and sarbecovirus subgenus. SARS-CoV-2 virus was isolated from epithelial cells of the human airway and its genome consists of ten open reading frames (ORFs), and consists of four structural proteins, that is, S (spike), E (envelope), M (membrane), and N (nucleocapsid) protein to make complete virus particle. SARS-CoV-2 virus virion is about 70–90 nm in size.4

SARS-CoV-2 virus enters the host target cell receptor, angiotensin-converting enzyme 2 (ACE2) by attaching with the S protein, which is expressed on alveolar epithelial cells type II (AECII), and on other tissues such as endothelium, heart, kidney, and intestine.5 SARS-CoV-2 virus has demonstrated novel glycosylation sites in the spike glycoprotein and the virus may utilize different glycosylation sites to interact with its receptors.6

The pathogenesis associated with hypercoagulability is not clear, but hypoxia and systemic inflammation may activate coagulation pathway due to high levels of inflammatory cytokines in COVID-19.7,8 SARS-CoV-2 virus after entry in human system moves through replicative stage due to direct cytopathic effect and presents with mild symptoms and is followed by a stage of adaptive immunity in which virus level decreases as the immune system takes over and after that there will be sudden clinical deterioration in a stable patient due to tissue destruction because of inflammatory cytokine strom.7,8

**Clinical Presentation and Systemic Manifestations**

The incubation period of COVID-19 is 14 days and a median incubation period of 4–5 days (interquartile range 2–7 days).9 COVID-19 patients reported symptoms in one study within 11.5 days of infection.10 Asymptomatic infection was reported in 50% of the Diamond Princess Cruise ship where out of the 619 people (17%) who were positive for SARS-CoV-2 virus.11

The most common presentation of COVID-19 is fever, headache, muscular pain, running nose, sore throat, breathlessness, tightness of chest, dry cough, hemoptysis, nausea/vomiting, and diarrhea. Loss of taste and smell precedes the onset of respiratory symptom.9 Delayed fever and respiratory symptoms may be atypical presentations in older adults and persons with medical comorbidities.

The systemic manifestations of COVID-19 are bilateral pneumonia (91.1%), which may progress to acute respiratory distress syndrome (ARDS) (3.4%), acute kidney injury (AKI) (0.5%), arrhythmias, heart failure, myocardial infarction, coagulopathy (0.1%), rhabdomyolysis, hyponatremia, acidosis, and septic shock (1.1%).9

**Skin Manifestations**

New onset pernio-like lesions of the feet and/or hands in the absence of any other clear cause (American Association Dermatology guidelines). They are usually asymmetrical. Rashes of COVID-19 could be classified as:12

- Pseudo-chilblains (acral erythema with vesicles or pustules).13 Pseudo-chilblains (COVID toes) occurs in warmer climate and presents with itching, burning, pain, and is more likely to ulcerate where a classic cold-induced chilblain is a benign and self-limited condition presenting with acral erythema of the toes and fingers with swelling.
- Vesicular (chicken pox-like) eruptions occur in middle-aged adults, which typically lasted for 10 days.
- Maculopapular eruptions are perifollicular in distribution and varying degrees of scaling. Some were described as like pityriasis rosea.
- Urticaria.
- Livedo or necrosis. Livedo and necrosis indicate severe illness and poor prognosis.

**Ocular Manifestations**

Nasal cavity and conjunctival sac are anatomically connected through nasolacrimal duct and most of the respiratory organism harbor inside nasal mucosa, so the patient of COVID-19 may present with conjunctivitis and SARS-CoV-2 virus was detected in conjunctival secretions but was absent in those without conjunctivitis. Tears sample may be used for diagnosing COVID-19.14
Hypercoagulability in COVID-19\textsuperscript{15,16}

Hypercoagulable state developed in some patients of COVID-19 and small and large vessels were at increased risk of developing thrombosis. The patients may develop mild thrombocytopenia, prolonged prothrombin time, elevated D-dimer levels, myocardial injury, large vessel strokes, microvascular thrombosis in toes and clotting of catheters.

The high risk of death was strongly associated with elevated D-dimer levels. The thrombotic complications were most frequently reported venous thrombosis and pulmonary embolism.

The major comorbidities associated with COVID-19 are hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, hepatitis B, chronic kidney disease, malignancy, and immunodeficiency, which increase the severity of illness.\textsuperscript{9}

Severity of Illness

The illness may range from mild to moderate, severe, and critical.\textsuperscript{17}

- Mild to moderate 81\% (mild symptoms to mild pneumonia).
- Severe 14\% (shortness of breath, hypoxia, or >50\% lung involvement with pneumonia on imaging).
- Critical 5\% (acute respiratory failure, septic shock, or multiorgan inflammatory failure).

Psychoneural Manifestations

Psychoneural manifestations can be broadly classified in four categories.

Among General Population

The general population may develop fear and helplessness, depressive disorders, somatic symptoms, and even suicidal tendency.\textsuperscript{18}

Among Covid Patients

Quarantined people feel loneliness, depression, insomnia, may cause self-harm, suicidality, and survivors are prone to develop Post Traumatic Stress Disorder (PTSD).\textsuperscript{19,20}

Among Relatives of Covid Patient and Close Contact

Family member and close contact of patient generally develop psychological problem as they are isolated and quarantined. The patient’s family member feels shame, guilt, or stigmatized and may suffer from PTSD.

Among Healthcare Workers

Healthcare workers may develop physical exhaustion, sleep disturbances, and emotional disturbances.\textsuperscript{21,22}

Diagnosis

COVID-19 diagnosis is based on clinical features and to be confirmed by RT-PCR of nasopharyngeal or oropharyngeal swabs.

The RNA of SARS-CoV-2 virus has also been found in stool and blood and may be a marker of severe illness.

The routine investigations demonstrated lymphopenia, neutrophilia, elevated serum aspartate aminotransferase and serum alanine aminotransferase level, elevated lactate dehydrogenase, high C-reactive protein (CRP), and high-ferritin levels, which may be associated with severity of illness.\textsuperscript{9,23}

Lymphopenia and elevated D-dimer indicate high mortality. Procalcitonin was elevated among those admitted in the ICU, but the level was normal at the time of admission.\textsuperscript{24} Potential immune dysregulation was associated with high levels of plasma inflammatory markers.\textsuperscript{23,25}

The X-ray chest and HRCT thorax may demonstrate patchy consolidation, extensive exudative infiltrates, and bilateral peripheral ground-glass opacities (GGOs), but may not be remarkable in the early stage of the disease.

Differential Diagnosis

The differential diagnosis of COVID-19 is another viral pneumonia caused by adenovirus, influenza, human metapneumovirus, parainfluenza, respiratory syncytial virus (RSV), rhinovirus, and bacterial pneumonia.\textsuperscript{24}

Treatment and Prevention

There are investigational treatments for COVID-19 and treatment data is limited on hydroxychloroquine, azithromycin, remdesivir, and favipiravir on the course of disease, severities of illness and hydroxychloroquine as prophylaxis in exposed people.\textsuperscript{26}

Frequent handwashing with soap and water, face mask, social distancing, and self-isolation is important for prevention of COVID-19 until the vaccine becomes available.
Prognosis

The predictors of high mortality are age 80 years and above, hypertension, diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease, malignancy, severe lymphopenia, and elevated level of D-dimer.

Conclusion

- SARS-CoV-2 virus is a single-stranded RNA virus and is the seventh member of the betacoronavirus family, subfamily orthocoronavirinae and subgenus sarbecovirus infecting humans and was isolated from the epithelial cells of human airway.
- The clinical presentations of COVID-19 are cough, fever, malaise, myalgias, gastrointestinal symptoms, and anosmia or ageusia.
- Diagnosis of COVID-19 is usually confirmed on detection of SARS-CoV-2 virus by RT-PCR testing of a nasopharyngeal and oropharyngeal swab.
- Management of COVID-19 depends on the severity of disease; with mild disease by home isolation and moderate or severe COVID-19 patients are hospitalized and supportive treatment given.
- There is investigational treatment available for COVID-19 and so critical patients may be referred for investigational treatment.
- Frequent handwashing with soap and water, face mask, and so critical patients may be referred for investigational treatment.

References

Abstract
Symptoms of acute-COVID-19 illness can persist for more than a couple of weeks, wherein we refer the syndrome as “post-acute COVID-19 syndrome.” It may encompass symptoms localized to a single organ system or multiple organ systems. Post-COVID-19 fatigue, body aches, cough, lung fibrosis, bronchiectasis, myocarditis, coronary ischemia, pulmonary thromboembolism, stroke, microvascular coagulopathy, Guillain-Barré syndrome, cognitive dysfunction, anosmia, ageusia, gastrointestinal upset, psychological distress, depression, sleep disturbances, secondary infections (bacterial and fungal), rash, and asymptomatic liver and/or pancreatic enzyme elevations have been observed. The persistence of symptoms can be witnessed irrespective of the initial severity of COVID-19 illness, though “post-acute COVID-19 syndrome” is commoner subsequent to moderate and severe COVID-19 illness, compared to mild COVID-19 illness; and is commoner in at-risk groups (diabetes, hypertension, obesity, heart disease, and pre-existing pulmonary disease). Persistence of symptoms post-COVID-19 has been reported to be variable and can last for up to 6 months. The exact management is yet not known, but rest, gradual resumption of activity, nutritious diet, and symptomatic management form the mainstay. Specific therapies like steroids, antifibrotic agents (pirfenidone or nintedanib) for pulmonary fibrosis, and anticoagulants for elevated D-dimer levels to prevent coronary and cerebrovascular ischemia and pulmonary thromboembolism (post-ARDS) are being investigated and their role may be discernible in the times to come.

Introduction
COVID-19 is an acute infective illness. It was declared a pandemic in March 2020. Although the world has witnessed pandemics earlier too, but COVID-19 was like none before and it shook human beings out of their comfort levels. Man is a social animal, but the lockdowns, social distancing, wearing face mask, and restrictions on travel and social gatherings disturbed the social fabric of mankind. Managing COVID-19 illness in hospitals and isolation centers, by health-care personnel in personal protective equipment (PPE) or by video or teleconsultation became the order of the day, and resulted in a paradigm shift for the patients, who were so used to the “healing touch” of doctors and nurses. COVID-19 proved to be an acute mental distress to the patients, and also to the family members and the health-care workers involved in imparting care to the ill.

The Genesis and the Pathophysiology
To the patients, COVID-19 was largely asymptomatic in 80–90% of the cases, but 5–15% did have moderate or severe illness. The classification into mild, moderate, and severe illness was based upon the presence of pneumonia manifesting as tachypnea and hypoxia. However, COVID-19 proved to be a respiratory illness, inhalation of droplet nuclei being the primary mode of spread, but with systemic manifestations.
As the pandemic unfolded, several systemic manifestations were observed: 2,3

- High CRP levels and elevated interleukin-6 and serum ferritin indicated a severe inflammatory state.
- Elevated D-dimer levels pointed towards presence of intravascular thrombosis, and this was evident in lungs in post-mortem of COVID-19 patients, and also stroke and coronary ischemia were seen in convalescent COVID-19 patients.
- Elevated liver functions and pancreatic enzymes were witnessed during the acute phase.
- Anosmia and ageusia were also witnessed as atypical manifestations.
- Lung involvement showed diffuse peripheral ground-glass opacities mimicking an acute respiratory distress syndrome (ARDS) like picture.

Most viral illnesses cause a self-limiting acute illness; however, acute COVID-19 illness was associated with significant morbidity and mortality among symptomatic patients, and more importantly, a sizable proportion of these reported delayed recovery and persistent symptoms. Risk factor groups for COVID-19 severity and associated mortality included higher age (>50 years), presence of diabetes, hypertension, obesity and cardiovascular disease, premorbid lung diseases, apart from factors like smoking, alcohol, and patients on immunosuppressive medications or suffering from immune-mediated disorders or cancers. These risk group patients are more prone to moderate and severe COVID-19 illness, and also to greater mortality including sudden deaths. Complications of COVID-19 especially the ARDS with worsening of hypoxia and surge in inflammatory markers akin to the cytokine storm were usually witnessed early in the 2nd week of illness, that is, 8th to 10th day of symptomatic illness. However, the deterioration in the form of respiratory failure was witnessed comparatively earlier, that is, in the latter half of 1st week of illness, in the presence of comorbidities like heart disease and/or diabetes, especially if uncontrolled.

A unique feature of acute COVID-19 illness is being witnessed, with the persistence of symptoms beyond the initial phase of 2 weeks, and at times taking months to resolve. These patients have been variably called as “long-haulers” or suffering from “post-acute COVID-19 illness,” “post-COVID illness,” “long-COVID.” Delayed recovery and greater persistence of symptoms are witnessed primarily in moderate or severe COVID-19 patients, and in those who have any of the aforementioned risk factors for COVID-19. However, this long-COVID syndrome has also been witnessed in mild COVID-19 patients.

The exact pathophysiology of the persistence of symptoms is yet not known. It is possible that some manifestations could be due to direct viral injury, or alternatively due to the systemic inflammatory response generated by the virus. Persistent viremia due to weak or absent antibody response, relapse or reinfection, inflammatory and other immune reactions, deconditioning, and mental factors such as post-traumatic stress singly or together contribute to the post-COVID syndrome. Long-term respiratory, musculoskeletal, and neuropsychiatric sequelae have been described with other coronaviruses (SARS and MERS). Apart from viral infiltration and inflammation, microthrombi and downregulation of ACE-2 receptors may be involved in the pathophysiology of cardiopulmonary complications. 5

The severe inflammatory reaction witnessed in acute COVID-19 illness can lead to a dysregulated innate immune response, ciliary dysfunction, cytokine storm, thrombo-inflammation, microvascular coagulation, and immune exhaustion. This can lead to post-COVID-19 sepsis and predisposition to secondary bacterial and fungal infections, more so in diabetic patients and critically ill patients, who have anyway been administered steroids, anti-interleukin therapies, CRRT/ECMO, prolonged hospital stays with indwelling catheters and emergency procedures, mechanical ventilation, and, at times, breaches in asepsis. Covid-19 associated pulmonary aspergillosis (CAPA) has been reported, and recently, invasive mucormycosis (rhino-orbito-cerebral and pulmonary) has also been brought to the attention of physicians managing COVID-19 and post-acute COVID-19 patients. 6 Tuberculosis has also seen a resurgence in patients afflicted with COVID-19, especially in the post-COVID immunosuppression phase.

The frequency of post-COVID-19 syndrome could vary from as low as 10% to as high as 70%. The exact frequency is difficult to state, as majority of the infections could have passed being asymptomatic, and so the true denominator is not known to calculate the true prevalence.

Clinical Features
Our own experience has shown a spectrum of findings, and Table 1 outlines the manifestations seen in post-

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Post-Acute COVID-19 Syndrome

CHAPTER 11

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Post-Acute COVID-19 Syndrome

1. Post-COVID myalgias, arthralgias, or body aches
2. Post-COVID fatigue
3. Anosmia/ageusia
4. Chronic cough, pulmonary fibrosis, bronchiectasis, and reduction in pulmonary functions
5. Gastrointestinal upset
6. Transaminitis
7. Asymptomatic elevation of pancreatic enzymes
8. Thromboembolic conditions, viz. stroke and myocardial infarction/ischemia
9. Asymptomatic elevation of D-dimer
10. Guillain-Barré syndrome
11. Other neurological syndromes, viz. seizures, encephalitis, PRES, delirium, cognitive dysfunction including difficulty in concentration
12. Myocarditis, pericarditis, dysrhythmias, and pulmonary thromboembolism
13. Metabolic disruption such as poor control of diabetes
14. Psychological distress
15. Psychiatric morbidity—depression
16. Sleep disturbances
17. Weight loss and malnutrition, including sarcopenia in elderly
18. Low-grade fever
19. Skin rashes—vesicular, maculopapular, urticarial or chilblain-like lesions on the extremities (COVID toes)
20. Secondary infections (secondary to viral-illness induced immunosuppression), viz. post-COVID sepsis and mucormycosis
21. Residual renal dysfunction (secondary to acute kidney injury)

acute COVID-19 illness. Post-COVID fatigue with or without myalgias/arthritis is the commonest persistent symptom seen in clinical practice, and is associated with decreased capacity to perform activities of daily living. Many patients of mild COVID-19, who joined back after the mandatory 14–17 day isolation period, were unable to do even 6-hour desk work, and had to be advised rest again. Likewise, few patients did have severe myalgias or arthralgias and headache requiring prescription of potent analgesics to obtain relief. Persistent cough was seen across all severities including mild cases, while persistent dyspnea was more frequently encountered in moderate and severe COVID-19 patients. There were a couple of mild cases past middle-age, who were discharged after the requisite isolation period, but died during sleep around 3rd or 4th week of symptom onset. COVID-19 has been associated with a severe inflammatory process, and sudden cardiac deaths probably due to myocardial infarction or dysrhythmias, triggered by the inflammatory processes in the coronaries/myocardium could be the plausible mechanism. Similarly, most patients lost weight, indicating that COVID-19 is a severe catabolic stress on the body. Inflammatory mediators have taken weeks to months to revert back to normal. Transaminitis, pancreatic enzyme elevations, and D-dimer elevation have persisted for as long as 8–12 weeks, even in mild to moderate cases. Further, atypical symptoms like ageusia and anosmia have also been noted to persist for months together, taking their own sweet time to resolve. Psychological stress and sleep disturbances have been witnessed in many patients, and psychiatric mood disorders may be attributed to the illness, delayed return of normal health, loss of job, and financial losses incurred. Several other associated neurological syndromes are coming to light like headache, loss of concentration, cognitive dysfunction, Guillain-Barré syndrome, posterior reversible encephalopathy syndrome, apart from increase in cases of stroke.4,8-10

In a 6-day outcomes assessment of COVID-19 patients in Michigan, USA,11 488 telephonic contacts could be established, of which 159 patients (32.6%) reported cardiopulmonary symptoms such as cough or dyspnea, 92 (18.8%) of these had new onset cough or worsening of pre-existing cough, while 65 (13.3%) had persistent loss of smell or taste. 58% patients telephonically contacted reported new or worsening difficulty in the conduct of activities of daily living. In the study cohort, 195 patients were employed before hospitalization, 78 (40%) could not return to work because of health issues or loss of jobs. 30 (25.6%) of the remaining 117 who returned to work, reported reduced work hours due to health issues. Out of the 488 surveyed, 238 (48.8%) reported emotional impact, with 28 (5.7%) seeking consultation from mental health practitioner.

In another study12 among 150 noncritical COVID-19 patients, two-thirds of patients had some or the other symptom at day 60 of symptom onset. The proportion of patients who still had asthenia, dyspnea, and anosmia/ageusia at day 30 respectively was 49.3%, 36.7%, and 28% and on day 60 respectively was 40%, 30%, and 23%. In a
telephonic survey among French patients conducted at 3 months, the most common persistent symptoms were—fatigue (55%), dyspnea (42%), memory loss (34%), sleep disorders (30.8%), and difficulty in concentration (28%). 30% of the active workers could not join back because of their health issues. In an Italian study on 143 patients, 87% of patients had persistent symptoms at 60 days after onset of first COVID-19 symptom—32% had 1 or 2 symptoms, while 55% had 3 or more symptoms. Fatigue (53.1%) was the commonest symptom followed by dyspnea (43.4%), arthralgias (27.3%), and chest pain (21.7%), with 44.1% reporting a deterioration in the quality of life.

**Investigations**

It is general consensus that asymptomatic patients may need not be investigated. Blood tests need to be ordered appropriately for specific clinical conditions. Anemia may need to be ruled out in patients having dyspnea, apart from a chest X-ray/CT scan and an echocardiography. C-reactive protein and leucocyte counts may be elevated suggesting infection or ongoing inflammation. Concomitant fever, especially if moderate to high grade should prompt rethink of a concurrent infection. Elevated troponin may suggest myocarditis or ischemia and needs to be correlated with the clinical picture, while elevated natriuretic peptides may indicate heart failure. Although troponin and D-dimer tests may be falsely positive, but negative test results can remove the clinical uncertainty from the minds of treating physicians. Serial chest radiographs and CT scans of the thoraces can aid in picking up pulmonary lesions, but at times indicate disproportionately greater severity compared to what the clinical picture suggests. The exact role will only be clear over a period of time.

**Prognosis**

As already stated, more the number of risk factors present, longer may be the persistence of the symptoms, and more number of symptoms are likely to persist. However, how long will the symptoms persist is difficult to state at the present moment. Some manifestations like stroke and myocardial infarction or sudden cardiac death are catastrophic or considered the end-points, while Guillain-Barré syndrome may go either way depending upon the extent of progression and responsiveness to management strategies. COVID-19 ARDS survivors are at risk of long-term impairment of lung function. Serious interstitial lung disease is rare in patients who are not hypoxic, but it may be too early to comment upon the pulmonary involvement and spontaneous reversibility of fibrosis. However, the experience with influenza-associated pulmonary fibrosis and the previous coronavirus illnesses (SARS and MERS) indicates that residual damage at 1 or 2 years may not be that alarming. What sequelae will post-acute COVID-19 syndrome leave behind are yet not known, but symptoms do improve over time, and presently symptoms have been documented to persist for as long as 6 months.

**Management**

It is evident from the manifestations of COVID-19 and the universality of persistent symptoms, which can be attributable to virtually all the organ systems, that COVID-19 is a systemic illness. There is no definitive management for COVID-19, apart from oxygen therapy, steroids and awake proning in moderate and severe COVID-19 patients. Therefore, to talk about management of the persistent symptoms, that is, post-COVID syndrome is still very difficult. Several drugs are being tested for specific system abnormalities, and there is no specific management.

It was observed that moderate/severe COVID-19 patients, especially those suffering from diabetes, heart disease, or morbid obesity, continued to remain oxygen dependent even after 3–4 weeks of symptom onset. These patients had to be discharged on bed rest and domiciliary oxygen. Home pulse oximetry can be helpful in monitoring these patients with post-COVID lung fibrosis, and rate of oxygen flow may be accordingly adjusted. Prolonged course of steroids and antifibrotic agents like pirfenidone and nintedanib are being tried to reverse lung fibrosis in COVID-19 patients where CT scan has showed fibrotic changes. Deep breathing exercises and steam inhalation help tackle persistent cough in convalescent patients, although cough mixtures (with antitussives) may be prescribed in irritating cough conditions.

Rest, gradual increase in activity and good nutrition including a balanced diet with adequate micronutrient supplementation holds the key to improving fatigue, weight loss, and helps in reversing the catabolic process associated with COVID-19 illness.
Analgesics (non-steroidal anti-inflammatory drugs and paracetamol) can help get rid of body aches, headache, arthralgia, myalgia, and low-grade fever. However, antidepressant medications like amitriptyline, fluoxetine, and duloxetine may be very helpful to overcome depression and the body pain in patients who have associated psychological distress too. Sedatives hypnotics may be used for inducing sleep. Patients with diabetes, obesity, hypertension, and coronary heart disease who have persistent D-dimer elevation can be prescribed aspirin or alternative anticoagulants, although the duration of therapy in these patients is not yet defined.

Psychotherapy and counseling can be very helpful in tiding over the psychological issues related to the post-COVID syndrome. Fungal infections may add to the burden of COVID-19 management and contribute to increased morbidity and mortality. Treatment involves antifungal agents, surgical debridement, control of associated comorbidities, and withdrawing of treatments, which contribute to immune suppression. Amphotericin B is the drug of choice for invasive mucormycosis, but posaconazole or isavuconazole may be used in patients with concomitant renal dysfunction.

Conclusion

Post-acute COVID-19 syndrome requires attention to detail, and treating physicians should actively seek for the varied symptom profile that may be witnessed and comprise this syndrome. Physicians managing COVID-19 and following up these patients post-discharge need to be very attentive and carefully seek symptoms, so as to outline this syndrome and its behavior over time. This will help to determine the progression of individual symptoms and their subsidence over what period of time will be unraveled. Further, management options as part of various clinical trials and also as part of observational studies will guide us to devise management protocols for post-acute COVID-19 syndrome.

References
