COVID-19 Management: What We Need to Know?

Introduction

The world is plagued by the COVID-19 pandemic. This is an unprecedented situation in the modern era wherein we do not know our enemy in detail. In fact, we hardly know anything. We have just started to learn about COVID-19; the management guidelines are evolving and are mostly consensus based at present, rather than randomized data. In this article, we will briefly review some important updates and evolving research in the management of COVID-19.

Testing

Diagnostic testing

Nasopharyngeal swab by real-time reverse transcription-polymerase chain reaction (rRT-PCR) is the recommended testing method for COVID-19.[1] RT-PCR has a high specificity and does not cross-react with other human coronaviruses and respiratory pathogens.[2]

Antibody-based rapid testing in the blood is not recommended by the World Health Organization as results are dependent on age, nutritional status, the severity of illness, concurrent medications, and immunosuppression like human immunodeficiency virus (HIV).

Indications for testing (Indian Council of Medical Research Guidelines)

1. All symptomatic individuals who have undertaken international travel in the past 14 days
2. All symptomatic contacts of laboratory COVID-19 confirmed cases
3. All symptomatic health-care workers
4. All patients with severe acute respiratory illness (fever and cough and/or shortness of breath)
5. Asymptomatic direct and high-risk contacts of a confirmed case should be tested once between day 5 and day 14 of coming in his/her contact
6. All symptomatic influenza-like illness with fever, cough, sore throat, and/or runny nose (in hotspots/cluster and large migration gatherings/evacuees canters):
   a. Within 7 days of illness – rRT-PCR
   b. After 7 days of illness – Antibody test (if negative, confirmed by rRT-PCR).[3]

Treatment

The current standard of care for COVID-19 infection is symptomatic supportive care. The potential investigational therapies include antivirals, antibodies, cell-based therapy, ribonucleic acid (RNA)-based therapy, and others. Surviving sepsis management guidelines in mentioned in Table 1.

Investigational therapies

Remdesivir

Remdesivir, a nucleotide analog prodrug that inhibits viral RNA polymerases and has shown *in vitro* activity against severe acute respiratory syndrome coronavirus 2.[4]

In a study of 53 patients with severe COVID-19 (oxygen saturation of <94% in room air or who receiving oxygen support), the patients received remdesivir on a compassionate basis for 10 days (200 mg intravenously on day 1, followed by 100 mg daily for 9 days). At baseline, 57% patients received mechanical ventilation and 8% received extracorporeal membrane oxygenation. This study showed that 68% had an improvement in oxygen support, 57% of ventilated patients were extubated, 47% discharged, and 13% died. The limitations of this study are small numbers, short duration of follow-up (18 days), nonrandomized design, late initiation of treatment (remdesivir was started 12 days from the start of symptoms), different duration of remdesivir treatment, and no data on viral load.[5]

Lopinavir-Ritonavir

Lopinavir/ritonavir combination showed *in vitro* activity against other novel coronaviruses through inhibition of 3-chymotrypsin-like protease.[4] It is Food and Drug Administration (FDA) approved for the treatment for HIV.

A randomized controlled, open-label trial was done in adult hospitalized Chinese patients with severe COVID-19 (oxygen saturation of <94% in room air or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen of <300 mmHg). Patients were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. A total of 199 patients were randomized, and mortality at 28 days was similar in the lopinavir–ritonavir group and the standard care group (19.2% vs. 25.0%; difference: −5.8% points; 95% confidence interval [CI]: −17.3–5.7). This study showed that there was no benefit (clinical improvement, reduction in mortality, or reduction in viral RNA load) when treated with antiviral drugs (lopinavir–ritonavir combination) as compared to standard of care treatment.[6] Currently, this is the only published phase 3 randomized controlled trial (RCT) for the management of COVID-19 infection.

Hydroxychloroquine/chloroquine and azithromycin

Chloroquine and hydroxychloroquine are used in the treatment of malaria, discoid/systemic lupus erythematosus, and rheumatoid arthritis. These drugs

Table 1: Surviving sepsis guidelines: management of critically ill adults with COVID-19[19]

Recommendation	Level of evidence
Health-care workers performing aerosol-generating procedures should use N95 respirators in addition to other personal protective equipment (gloves, gown, and face shield/goggles) in a negative pressure room	Best practice
The most experienced person with airway management should intubate and use video-guided laryngoscopy (if available) to minimize the number of attempts and risk of transmission	Best practice
Supplemental oxygen should be started if the peripheral SPO_2 is <92%	Weak
For patients with acute hypoxemic respiratory failure on oxygen, SpO_2 be maintained not higher than 96%	Strong
For patients with hypoxemia despite conventional oxygen, HFNC/NIPPV can be used with close monitoring of the respiratory status. If worsening is suspected, early intubation in a controlled environment is advised	Best practice
For intubated patients with suspicion of COVID-19 infection, the endotracheal aspirate is the preferred specimen for COVID-19 testing	Weak
In mechanically ventilated patients with ARDS, low tidal volume ventilation (4-8 mL/kg of predicted body weight) and targeting plateau pressures of <30 cm H_2O	Strong
For patients with moderate-to-severe ARDS, target a higher PEEP >10 cm H_2O with monitoring for barotrauma	Strong
For patients with moderate-to-severe ARDS, prone ventilation for 12-16 h with judicious use of neuromuscular blocking agents (intermittent bolus or continuous infusion) can be done	Weak
For patients with refractory hypoxemia, venovenous ECMO can be done	Weak
For mechanically ventilated patients with ARDS, systemic corticosteroid (methylprednisolone 1-2 mg/kg/day for 5-7 days) can be used	Weak
In mechanically ventilated patients with respiratory failure, empiric antibacterial agents can be used	Weak
For patients with shock, initial resuscitation should be a conservative fluid strategy with a buffered/balanced crystalloid solution. Avoid starches, dextrans, gelatins, and albumin	Weak
For patients with shock, norepinephrine is the preferred first-line vasoactive agent and vasopressin the second-line agent	Weak
For patients with cardiogenic shock, dobutamine is the preferred first-line vasoactive agent	Weak
For patients with shock on vasopressor support, a MAP of 60-65 mmHg should be targeted	Weak
For critically ill patients, paracetamol can be used to control fever	Weak
For critically ill patients, treatment options including lopinavir/ritonavir, convalescent plasma, immunoglobulins, interferons, chloroquine/hydroxychloroquine, and tocilizumab are not recommended[19]	Weak

MAP: Mean arterial pressure, SPO_2: Oxygen saturation, ARDS: Acute respiratory distress syndrome, PEEP: Positive end-expiratory pressure, ECMO: Extracorporeal membrane oxygenation, HFNC: High-flow nasal cannula, NIPPV: Noninvasive positive-pressure ventilation

have immunomodulatory effects and block the viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification.[4]

A French study included twenty patients with COVID-19 infection who were treated with oral hydroxychloroquine sulfate 200 mg, 3 times/day with or without azithromycin for 10 days and were compared to controls. There was a reduction in viral loads on day 6 as compared to the controls. The limitations of this study are small sample size, nonrandomized design, and mortality not being the endpoint.[7] Another French study with 11 patients with severe COVID-19 infection treated with hydroxychloroquine (600 mg/day for 10 days) and azithromycin (500 mg on day 1 and 250 mg from day 2 to day 5) showed no evidence of rapid antiviral clearance or clinical benefit.[8] Moreover, severe side effects of chloroquine can include psychiatric manifestations, arrhythmias, and sudden death.[9]

Inhalational plasminogen therapy

Plasminogen is a key regulator in fibrin degradation, wound healing, and infection.[10]

A study from China with 13 patients who had moderate-to-severe COVID-19 infection were treated with atomization inhalation of free-dried plasminogen (10 mg OD for moderate and 10 mg BD for severe infection). Six patients with severe infection had improvement in oxygen saturation, five patients with moderate infection had radiological improvement of pneumonia, and two critical patients with hypoxemia had improvement in saturation within an hour.[10] The limitations of this study are the small sample size, nonrandomized design, and mortality not being evaluated as an endpoint.

Convalescent plasma therapy

Passive immunization for the treatment of human infectious diseases can be traced back to the 20th century when antibodies were used from the serum of stimulated animals, especially rabbits and horses.[11]

A study has been reported from China, in which ten patients who had severe COVID-19 infection received one dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:640 in addition to supportive care, antiviral agents, and steroids. The clinical symptoms were significantly improved along with an increase in oxygen saturation within 3 days.

Table 2: Ongoing phase 3 clinical trials

Type	Mechanism	Developer/researcher	Sample size
Sarilumab	Interleukin-6 antagonist	Sanofi/Regeneron	400
Remdesivir	Antiviral	Gilead	2400
CD24Fc	Nonviral immunomodulator		230
Tocilizumab	Humanized anti-interleukin-6 receptor monoclonal antibody	Roche	330
Chloroquine/	Antimalarial	Washington University School of Medicine	55000
Hydroxychloroquine	Antirheumatic		
BCG vaccine	Antituberculosis	Murdoch Children's Research Institute	4170
Enoxaparin	Anticoagulant	University hospital, Geneva	200
Hydroxychloroquine/oseltamivir/ azithromycin	Antirheumatic	Shehnoor Azhar, Lahore	500
	Antiviral against H1N1		
	Antibiotic		
Anakinra, Siltuximab, Tocilizumab	Anti-interleukin	University hospital, Ghent	342
Hyperbaric oxygen	Free radical	Karolinska University Hospital	200
Colchicine	Inhibits microtubules	Montreal Heart Institute	6000
Naproxen	Anti-inflammatory	Assistance Publique - Hôpitaux de Paris	584
Hydroxychloroquine	Antirheumatic	Centre Hospitalier Universitaire de Saint Etienne	1200
Ritonavir/lopinavir	Antiviral		
Darunavir/cobicistat + chloroquine	Antiretroviral	Fundacio Lluita Contra la Sida	3040
	Antimalarial		
Nitazoxanide	Antiprotozoal	Romark	330
Natural honey	Anti-inflammatory, Immunomodulatory	Misr University for Science and Technology	1000
Convalescent plasma	Artificially acquired passive immunization	Thomas Benfield	1500
Sarilumab	Interleukin-6 antagonist		
Baricitinib	Janus kinase inhibitor		
Hydroxychloroquine	Antirheumatic		
Cholecalciferol	Vitamin D3	University hospital, Angers	260
Pyridostigmine bromide	Acetylcholinesterase inhibitor	Salvador Zubiran	436

Table 3: Anticancer clinical trials for COVID-19 infection

Type	Mechanism	Developer/researcher	Sample size
Bevacizumab	Vascular endothelial growth factor antagonist	Qilu Hospital of Shandong University	140
Imatinib	Tyrosine kinase inhibitor	Hospital Universitario de Fuenlabrada	165

Radiological examinations showed varying degrees of resolution of lung lesions within 7 days. The viral load was undetectable after transfusion in seven patients who had previous viremia. The limitations of this study are a small number, nonrandomized design, confounding use of antiviral therapy and steroids, and nonassessment of cytokine changes. This study also does not answer the question of an optimal concentration of neutralizing antibodies and treatment schedule.[12] In another uncontrolled case series of five critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) from China, the administration of CP containing neutralizing antibody was followed by an improvement in clinical status.[13]

The Indian Council of Medical Research (ICMR) is planning to do a randomized controlled, open-label trial of CP therapy versus conventional therapy in COVID-19-infected patients.[14]

Tocilizumab

Tocilizumab is a novel monoclonal antibody that competitively inhibits the binding of interleukin-6 (IL-6) to its receptor. It is FDA approved for the treatment of rheumatoid arthritis and cytokine release syndrome.[4]

A study from China reported 15 moderate-to-seriously ill COVID-19-infected patients treated with injection tocilizumab (80–600 mg) with or without

methylprednisolone. This study showed a reduction of C-reactive protein and IL-6 in patients who received tocilizumab. The limitations of this study are small sample size, nonrandomized design, and again, mortality was not an endpoint.[15]

Methylprednisolone

A retrospective cohort study from China evaluated 201 COVID-19-infected patients with ARDS who were treated with methylprednisolone and reported a lower risk of death (hazard ratio: 0.38; 95% CI: 0.20–0.72).[16] The Chinese thoracic society recommends methylprednisolone 0.5–1 mg/kg for <7 days in selected patients after assessing the risks and benefits.[17] The limitations include the retrospective study design and the potential adverse effects of steroids.

Low-molecular-weight heparin

A study from China evaluated the use of low-molecular-weight heparin in patients with severe COVID-19. This study enrolled 449 patients, and among them, 99 patients received heparin for 7 or more days. There was no difference in mortality between patients who used heparin and those who did not (30.3% vs. 29.7%, P = 0.910). However, the mortality was reduced in patients who used heparin with sepsis-induced coagulopathy score >4 (40.0% vs. 64.2%, P = 0.029) or D-dimer >6-fold of upper limit of normal (32.8% vs. 52.4%, P = 0.017).[18] The limitations of this study are retrospective design and the influence of confounding variables (other therapies).

Infectious Disease Society of America Guidelines

The Infectious Disease Society of America does not recommend the use of hydroxychloroquine/chloroquine ± azithromycin, lopinavir/ritonavir, corticosteroids, tocilizumab, and CP as a treatment for COVID-19 infection outside the context of a clinical trial.

Prophylaxis (Indian Council of Medical Research National taskforce recommendation)

1. Asymptomatic health-care workers involved in the care of suspected or confirmed cases of COVID-19:
   tablet hydroxychloroquine 400 mg twice a day on day 1, followed by 400 mg once weekly for the next 7 weeks
2. Asymptomatic household contacts of laboratory-confirmed cases:
   tablet hydroxychloroquine 400 mg twice a day on day 1, followed by 400 mg once weekly for the next 3 weeks[20]

Contraindications

Hydroxychloroquine is contraindicated in children below 6 years and patients with preexisting retinopathy.

Monitoring

A baseline electrocardiogram should be done to rule out congenital/acquired long QT syndrome and second- or third-degree atrioventricular blocks. Electrolyte imbalances (hypokalemia/hypomagnesemia/hypocalcemia) must be corrected before starting hydroxychloroquine.

Side effects

Hydroxychloroquine can cause hypoglycemia,[21] QTc prolongation, and torsades de pointes that can lead to fatal ventricular arrhythmia[22] or cardiomyopathy.[23]

Is there evidence to support hydroxychloroquine prophylaxis?

An *in vitro* study showed hydroxychloroquine to be more potent than chloroquine in inhibiting COVID-19 infection.[24] A phase 3 RCT from Columbia University comparing hydroxychloroquine prophylaxis with placebo for household contacts of index cases with an estimated sample size of 1600 is planned.[25] The hydroxychloroquine prophylaxis is debatable given the inadequate evidence to support, potentially fatal side effects due to QTc prolongation, risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency, and a possible shortage of hydroxychloroquine for patients with malaria, rheumatoid arthritis, and systemic lupus erythematosus.[26]

Prevention

Vaccine

Vaccines are a crucial component for COVID-19 prevention as there is rapid clinical deterioration and no effective treatment. Currently, m-RNA and nucleic acid-based vaccine clinical trials against COVID-19 infection are ongoing.[27]

World Health Organization – Solidarity trial

This trial randomizes patients with COVID-19 infection to either local standard of care or local standard of care plus one of the four experimental therapies (remdesivir, chloroquine or hydroxychloroquine, lopinavir + ritonavir, lopinavir + ritonavir + interferon beta-1a). Currently, the Canadian arm is recruiting patients for the treatment with lopinavir + ritonavir, and Norwegian arm is recruiting patients for the treatment with remdesivir or hydroxychloroquine.

Conclusion

Currently, the appropriate prevention, prophylaxis, and treatment of COVID-19 infection are largely unknown. Symptomatic supportive care with active participation in clinical trials is encouraged. We await the results of many ongoing RCTs to guide us in the prevention and management of COVID-19 infection [Tables 2 and 3].

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