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**ORIGINAL ARTICLE**

# Expanding current guidelines for management of COVID-19 focusing on low- and middle-income countries

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Abstract

Within a short time, Coronavirus disease 2019 (COVID-19) has evolved into a pandemic spreading at a speed and scale that has been able to overwhelm even the most advanced health care systems quickly. Multiple guidelines published by organizations such as the WHO and US' CDC address the response to COVID-19 at the international, national, and local levels. Although these guidelines are meant to be globally accessible, implementing them is a challenge given the variability in the health care systems worldwide between low- and middle-income countries (LMIC) and high-income countries and even amongst different regions within each LMIC. We have chosen to evaluate the current guidelines focusing on LMIC and expand on the guidelines as necessary.

Keywords: COVID19, management, low-resource settings, low-middle-income countries.



## INTRODUCTION

Within a short time, Coronavirus disease 2019 (COVID-19) has evolved into a pandemic spreading at a speed and scale that has been able to overwhelm even the most advanced health care systems quickly.[1,2] As of May 25, 2022, there are currently 522,970,476 confirmed cases and 6,277,407deaths, with a mortality rate of 1%.[3] Twenty percent of the cases are severe or critical with older people and those with underlying conditions such as cardiovascular and respiratory conditions having the worst outcomes.[4] Multiple guidelines published by organizations such as the World Health Organization (WHO) and the United States' Center for Disease Control and Prevention (CDC) address the response to COVID-19 at the international, national, and local levels. Although these guidelines are meant to be globally accessible, implementing them is a challenge given the variability in the health care systems worldwide between low- and middle-income countries (LMIC) and high-income countries (HIC) and even amongst different regions within each LMIC. We have chosen to evaluate the

current guidelines focusing on LMIC and expand on the guidelines as necessary.

Two indicators can be used to evaluate the country's functional ability to respond to a health emergency. One is the State Party Self-Assessment Annual Reporting (SPAR) developed by the WHO, which evaluates each country based on multiple capacities, including legislative, surveillance, human resource, national health emergency framework, and points of entry.[5] Another indicator developed by the RAND Corporation is the infectious disease vulnerability index (IDVI) which expands to include demographics, socioeconomic, environmental and political conditions (Table 1).[6] Both SPAR and the IDVI allow the international community and organizations to focus on more vulnerable countries. It is important to note that the African continent is especially susceptible because 24 of the most vulnerable countries per the IDVI create a near-continuous belt from the West of Africa to the horn of Africa.[6]

Per the current available data, it appears that many LMIC have been spared the worst of the pandemic with the WHO's African Region having only about 2% of the total cases with a crude mortality rate of 3%.[3] It is not clear if this is due to a lack of adequate testing capacity and/or under-reporting of death versus a decrease in the spread of the virus because of a lack of urbanization and warmer weather.[7] However, the overall burden from COVID-19 in the WHO's African Region is significant with a total of 8.5 million cases and 171,386 deaths since the start of the pandemic.[8]Most recently the region is seeing an upward trend in cases with a weekly increase in COVID-19 cases as high as 69% and in the number of COVID-19 deaths as high as 136%.[50] This upward trend in cases could lead to a collapse of many health care systems in LMIC, which are already stretched during regular times and have limited capacity to deal with a surge in demand resulting from this kind of pandemic. The limited baseline capacity is due to limitations in the number of beds, especially Intensive Care Unit (ICU) beds, the availability of a trained workforce, and critical supplies and equipment. A recent article shows that the number of ICU beds in low-income counties averages around 0.97 beds per 100,000 population while Germany and the USA have 29.2 and 34.7 beds per 100,000 population respectively. [9] Looking at the total healthcare workforce in the WHO African Region and the Eastern Mediterranean, there are 2.3 and 4.0 healthcare workers per 1000 population respectively. In comparison, European and American healthcare workforces have 18.9 and 24.8 members per 1000 population.[10]

Another challenge that LMIC health care systems will face is that non-communicable diseases, such as diabetes mellitus (DM) and hypertension (HTN), disproportionately affect populations in LMIC with three-quarters of global non-communicable disease (NCD) deaths occurring in LMIC.[11] Non-communicable diseases are associated with worse outcomes in COVID-19, with the majority of deaths occurring in patients with comorbidities.[12] Additionally, acute lower respiratory infections (ALRI), which is a significant complication in COVID-19, is the leading cause of mortality in low-income countries.[13] The additional burden of ALRI imposed by the COVID-19 pandemic will be untenable in many health care systems.

These challenges create particularly difficult conditions for hospitals in LMICs to take care of patients with COVID-19.[11–13] Our article focuses on providing practical suggestions to health care workers in hospitals in LMIC to deal with the current pandemic.

## INFECTION PREVENTION AND CONTROL AND TRIAGING

As governments are creating and implementing policies to curve the impact of the pandemic, so should individual health care systems. One of the significant goals of hospitals must be to prevent harm to health care workers (HCW) and patients; consequently, infection prevention and control (IPC) must

**Supplementary information** The online version of this article (Tables/Figures) contains supplementary material, which is available to authorized users.

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be a priority. However, IPC is a significant struggle in low-resource settings with one-third of hospitals lacking running water and a global shortage of personnel protective equipment (PPE).[14] However, using the WHO's Guidelines on Core Components of Infection Prevention and Control Programs and the CDC's Comprehensive Hospital Preparedness Checklist there are multiple steps that hospitals in LMIC countries should be able to implement to optimize IPC.[15,16] Initially, hospitals should set up an IPC multidisciplinary team to facilitate the implementation and adherence to the steps necessary to ensure adequate infection prevention (Table 2). Communication of policies to the staff should be prompt with proper education of successful implementation.

In addition to the creation of an IPC team, hospitals must also create a surge capacity plan early with a focus on increasing bed capacity, an increasing number of staff available for direct patient care, optimizing care of COVID-19 and non-COVID-19 by possible transfer to other facilities to optimize acute care resources for critically ill, and cancelation of elective admissions and surgeries.

With the surge plan, the rationing of equipment also needs to be discussed to allow community involvement and a transparent process. Currently, the CDC or WHO have no recommendations regarding the rationing of equipment; however, there have been multiple countries that have adopted a Multiprinciple Allocation Framework for the allocation of ventilators. This framework allows all patients that would usually be candidates for ICU admission and treatments to the eligible; however, priority score is assigned based on (1) likelihood of survival to discharge and (2) presence or absence of comorbid conditions. Additionally, health care workers and younger patients have a higher priority.[24,25]

## CLINICAL PRESENTATION

As hospitals prepare for a surge in COVID-19 patients, it is important for HCW to understand the clinical presentation, course, and complication of these patients to foresee and understand the necessary tests, medications, and equipment that will need to be available. A report from China found that in patients that presented with COVID-19, 81% of cases were mild, 14% were severe, and 5% were considered critical. The fatality rate in this report was 2.3%.[26] Most clinical presentations have a respiratory component to them. In mild cases, patients present with fever, cough, dyspnea, and/or vomiting and diarrhea.[26,27] In moderate and severe presentations, patients have pneumonia, but the difference is the presence of hypoxemia.[28,29] Critically ill patients present with hypoxemic respiratory failure secondary to acute respiratory distress syndrome (ARDS), along with other complications.[28,29] The most common complications secondary to COVID-19 are venous thromboembolism (VTE) presenting with extensive deep vein thrombosis (DVT), pulmonary embolism (PE), and/or acute ischemic strokes.[30] Studies report a prevalence of VTE in COVID-19 patients ranging from 20% to 85%.[31] Cardiovascular compromise per case series is seen in 7-20% of COVID-19 patients, and if present on admission is associated with a higher risk of mortality with a reported mortality rate as high as 22%.[31–33] Another major complication in hospitalized COVID-19 patients is acute kidney injury (AKI) with a report from the USA showing a prevalence of 36.6%.[34] Neurologic complications are seen in about 36% of patients, and it is thought to be secondary to direct viral invasion. Presentations can vary from altered mental status, seizures, meningitis, and Guillen-Barre syndrome.[32] Recently, multisystem inflammatory syndrome (MIS), a hyperinflammatory syndrome characterized by significant elevation of proinflammatory cytokines and multiorgan failure, has received increasing attention.[35] It is a rare condition with a higher prevalence in pediatric patients (MIS-C). [51] Patients present with persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions, and, in severe cases, hypotension and shock. [51,52]

## TESTING

When available, suspected COVID-19 patients should receive a nasal swab reverse-transcriptase polymerase chain reaction (RT-PCR) test or other

nucleic acid amplification test (NAAT) for the diagnosis of COVID-19.[53] In case of deficiency of tests, HCW can use medical history, clinical and diagnostic data to support a diagnosis of COVID-19 and triage patients. We understand that there might be a limitation on which tests can be performed in many LMIC countries and how often. One recommendation, in this case, would be to reserve initial testing for patients that are at high risk for complications of COVID-19, i.e., older than 65 and with comorbidities and patients presenting with a severe or critical illness. Guide repeat labs based on the severity of initial presentation, abnormality in labs, and worsening clinical status (Figure 1).

Additionally, the recommended imaging will be an anterior-posterior chest radiograph.[40,42] The chest radiography in patients with mild disease may appear normal or show interstitial peripheral infiltrates. Patients with a more severe condition, such as ARDS, most commonly show a ground-glass opacification with or without consolidations.

## CASE MANAGEMENT

COVID-19 being a multi-organ disease, HCW will assess multiple parameters to determine to admit or discharge a COVID-19 patient. Most patients with COVID-19 do not require hospitalization. Discharge patients home if they have a mild infection with normal saturations (>92%), no increased work of breathing, and can adequately isolate themselves at home.[37] Management of these patients should focus on close monitoring for clinical deterioration, re-evaluation and hospitalization as appropriate. On discharge, it should be stressed to these patients the importance of prevention measures when in contact with any other person and strict self-isolation. Per the CDC guidelines, if testing is not available, then home isolation should be discontinued only when there has been no fever for 72 hours, symptoms have improved, and at least five days have passed since the first symptoms.[38]

Some patients have severe disease that warrants hospital care. Management of such patients consists of ensuring appropriate infection control, providing timely supportive care, and when available and indicated timely treatment. Most COVID-19 patients require respiratory support, with reports stating that approximately 14% will require oxygen therapy, and 5% mechanical ventilation.[37,39] For patients that present with pneumonia and hypoxemia but no respiratory distress, a nasal cannula (NC) is enough support to provide oxygen to maintain saturations between 92-96%.[27] For patients with respiratory distress, attempt a trial of non-invasive ventilation through HFNC or BIPAP if available.[37]However, they must be used with caution in patients with COVID-19 because they are aerosol-generating and can put HCW at increased risk for acquiring the virus if proper PPE and isolation precautions are not used.[39] Despite the risk, non-invasive support is recommended because it prevents endotracheal intubation in 70% of patients.[37] If intubation is an option, patients should be monitored closely and cared for in a setting where intubation can be performed in the event of no improvement after a short trial (about two hours).[37]Avoid emergency intubations given that intubation in an uncontrolled setting increases the risk of nosocomial infection of healthcare providers.[27] The recommendation is to intubate patients with worsening respiratory distress, high concentration of oxygen (>60%) with persistent hypoxemia, or hemodynamic instability.[37] The Surviving Sepsis Campaign guidelines recommend a lung-protective strategy for patients with moderate and severe ARDS secondary to COVID-19 (Figure 2).[37] A treatment that is easily implemented and requires minimal supplies is placing a patient in a prone position, which is beneficial for both non-intubated and intubated patients. The theoretical benefits are that the prone position makes ventilation more homogeneous, reduces lung compression, and improves perfusion. There are only a few case series regarding a prone position in COVID-19 patients. Still, those showed an improvement in oxygenation and a decrease in respiratory rate while in the prone position.[39] There have been, however, large randomized clinical trials in patients with ARDS patients, one showing that prone positioning for at least 16 hours with protective mechanical ventilation reduced 90-day mortality.[39,40]Consequently, we recommend placing patients in the prone position early in their

admission and for 12-16 hours or as tolerated if awake; however, use medications to allow patients to tolerate this position for a longer length of time.

Per the International Society on Thrombosis and Haemostasis, venous thromboembolism (VTE) prophylaxis is appropriate in all hospitalized patients with COVID-19 given the hypercoagulable state with low-molecular-weight heparin (LMWH) unless there is a contraindication to anticoagulation (i.e., active or severe bleeding).[31] Consider full anticoagulation for patients that have confirmed VTE such as DVT or PE.[31] If confirmatory testing is not possible, treat patients empirically based on the clinical condition, for example, a sudden deterioration in respiratory status in an intubated patient consistent with pulmonary embolism or physical findings consistent with thrombosis, i.e., superficial thrombophlebitis.[31]

Another focus in the management of COVID-19 patients is the treatment of AKI, which occurs in about 40% of all patients and 90% of mechanically ventilated patients.[32] The management is mainly supportive. A good resource is the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines; however, it is important to note that their recommendations have not been validated to reduce the occurrence and severity of AKI in COVID-19 patients.[41] One of their important recommendations is to restore normal volume status since many of these patients present with hypovolemia secondary to fever and decrease intake while avoiding volume overload and thus reducing the risk of pulmonary edema, right ventricular overload, congestion, and subsequent AKI.[41] If conservative management fails, consider renal replacement therapy (RRT) in patients with volume overload, especially those with refractory hypoxemia where available.[41] In patients with COVID-19 and AKI, early initiation of RRT seems to provide adequate organ support and prevent the progression of disease severity. Continuous RRT (CRRT) is the preferred modality in hemodynamically unstable patients with COVID-19.[41] Given the possible need for resource-intense therapy in COVID-19 patients ranging from a high level of monitoring in both nursing and labs and high technological therapies such as ventilation and CRRT, it is essential for hospitals in LMIC to create a model such as the Multi-principle Allocation Framework to decide a priori how to allocate the limited resources.[24,25]

## PREVENTION

### Vaccination

Vaccines are critical in controlling the spread of the COVID-19 pandemic and preventing serious illness.[59]Controlling both spread and decreasing critical illness are essential in LMIC where the health care system has limited capacity to deal with a surge in demand. The goal for vaccination should be the immunization of 70% of the country's population.[60]

However, per the WHO website as of May 2022, almost one billion people in lower-income countries remain unvaccinated.[59]The reasons are multifactorial from vaccine supplies, lack of political commitment, and vaccine hesitancy.[59,60,62]To address, vaccine supplies and improve political commitment, WHO has released documents to aid countries in both addressing the allocation and prioritization of populations to receive COVID-19 vaccines and to ensure that successful COVID-19 vaccines and treatments are shared equitably across all countries.[61] Vaccine acceptance is variable in LMIC but broadly high with a median acceptance of 75%.[63]The most common reason for vaccine refusal was side effects possibly reflecting the rapid pace of vaccine development.[63]Given the high acceptance rate in LMIC, although clear and timely information at a grass root level will be important, minimizing access barriers and creating reminders and primes to encourage the populations to act on their will to be vaccinated will be more beneficial.[63]

## OTHER POSSIBLE THERAPY OPTIONS

### Corticosteroids

Steroids are not recommended for routine treatment in patients with COVID-19 because of no survival benefits and possible harms such as delayed viral clearance.[27] However, there is a role for use of low-dose dexamethasone in patients with respiratory symptoms requiring oxygen because it has

been shown to decrease mortality.[54] Additionally, its use should be in the early stages of the disease because it has been shown to improve clinical outcomes and prevent disease progression.[54,55] Another patient population that steroids are indicated in is patients with MIS both adults and pediatrics.[51,56,57] Other therapeutic options are intravenous immunoglobulin, IL-1 blockage (anakinra), IL-6 blockade (tocilizumab), Janus kinase (JAK) inhibition.[35]

**Convalescent plasma**

Immune (i.e., convalescent) plasma refers to plasma collected from individuals following the resolution of infection. It has been used emergently in epidemics where there is insufficient time or resources to generate immunoglobulin preparations.[43,44] Convalescent plasma is a potential therapy that may provide immunity from COVID-19 specific antibodies, and it is a safe therapy. [37.] The prior use for viral infections offers a strong precedent for such an approach.[43,44]

**Hydroxychloroquine (HCQ)**

Antimalaria agents have demonstrated antiviral effects on COVID-19 in vitro.[37]Early studies evaluating its effect in the treatment in COVID-19 patients have come under some scrutiny causing the use for the treatment of COVID-19 to be banned in many countries.[46,47] Most recently, a systematic review and meta-analysis of HCQ published in 2021 concluded that given moderate-quality evidence showing that HCQ generated virological cure and radiological cure with no difference in mortality, there was an option for its use in a judicious and monitored use in the treatment of COVID-19 infection in low to middle-income countries. Safety concerns like QT prolongation prevent random use, especially in high-risk populations.[58]

**Remdesivir**

A randomized study between Remdesivir and placebo found that Remdesivir was superior to placebo in shortening the time to recovery in patients with COVID-19 from median recovery time of 15 days to 11 days. Additionally, patients also had a decrease in lower respiratory tract infections.[48] Remdesivir is not currently readily available in most countries; however, there are current plans to increase production and distribution.[49]

**Antimicrobials**

Because symptoms of bacterial co-infection or superinfection in patients with COVID-19 can be similar to the underlying viral infection there is a challenge in identifying them. The Surviving Sepsis Campaign recommendation is to use empiric antibiotics in mechanically ventilated COVID-19 patients given that superinfection is common in this population, and it leads to an increase in mortality.[37] They do acknowledge that this a weak recommendation with low-quality evidence, coming from critically ill patients with MERS and influenza. Additionally, they recommend daily assessment and de-escalation based on microbiology results and clinical status. Limiting the length of treatment is important, given that more than 90% of COVID-19 patients receive antibiotics.[37] Antibiotic stewardship must still be practiced preventing antibiotic resistance in settings where there is limited availability to a wide range of antibiotics.

## CONCLUSIONS

Since the first case of COVID-19 in late 2019 in Wuhan, China, there has been a rapid worldwide spread of the virus leading to a global pandemic. Most COVID-19 cases are found in two WHO regions, Europe and America, with 83% of the cases.[3] However, over the last few months, there has been a steady increase in the number of COVID-19 cases in LMIC.[3] Multiple challenges in LMIC, such as a limited baseline capacity and a high-risk population, create particularly difficult conditions for hospitals in these settings to take care of the surge in patients secondary to the pandemic.[11−13] Our article provides practical suggestions for the leadership and HCW of hospitals in LMIC in how to deal with the current pandemic. Although LMIC hospitals might have limited resources, there are multiple steps that they can take to manage IPC and adequately treat COVID-19 patients.

## INFORMATION

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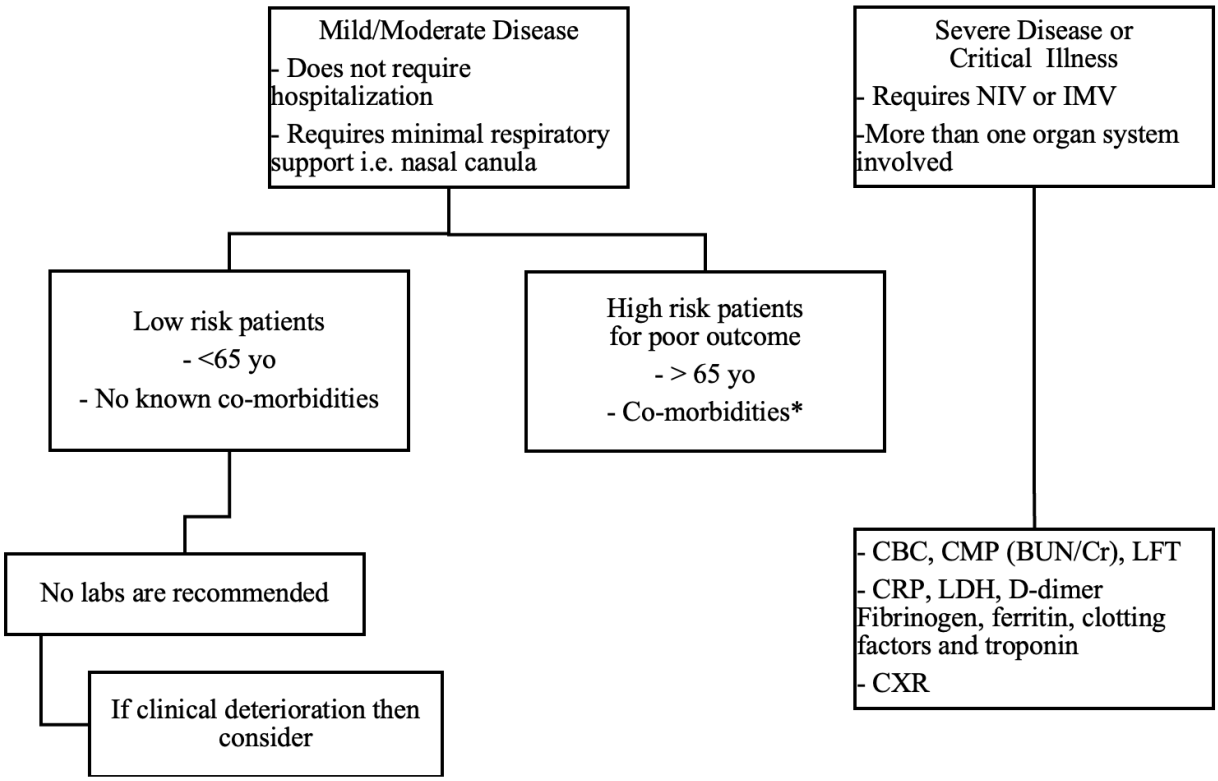


**FIGURE 1:** Recommended Laboratory and Imaging for COVID-19Patient Based on Clinical Presentation (36).

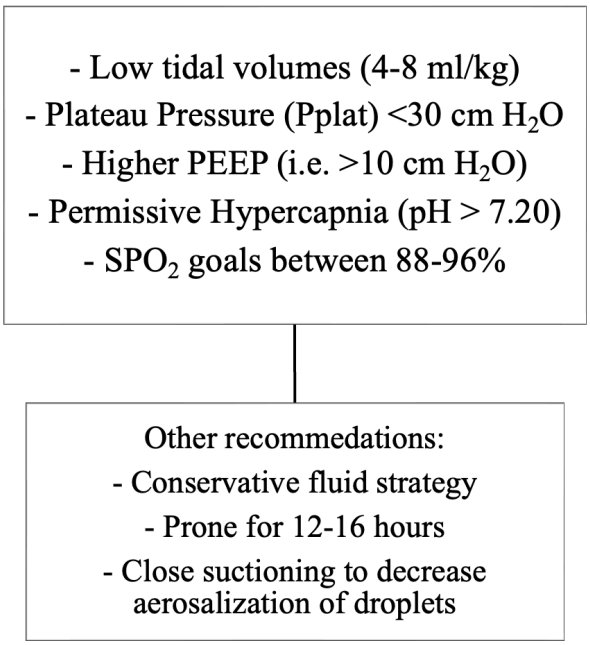


**FIGURE 2:** Surviving Sepsis Recommendations for Lung-Protective Ventilation in COVID-19 Patients (37).

| WHO Region | SPAR (average in %, range) | IDVI (average, range) |
|---|---|---|
| African | 44 (17-80) | 0.30 (0-0.7) |
| Southeast Asia | 61 (34-85) | 0.48 (0.31-0.71) |
| Eastern Mediterranean | 66 (32-96) | 0.49 (0-0.78) |
| Americans | 71 (48-99) | 0.61 (0.15-0.97) |
| European | 75 (35-99) | 0.77 (0.52-1) |

Chart 1: SPAR and IDIV per WHO Region (5,6).

| | |
|---|---|
| Policy for the minimum requirement of PPE for essential staff | - The preferred PPE for HCW taking care of patients with either confirmed or suspected COVID-19 are face shield or goggles, N95 or higher respirator, gloves, and isolation gown.<br>- Acceptable alternative, if N95 or higher respirator is not available, is a facemask.<br>- Support staff should be supplied with a facemask and should not have contact with a confirmed or suspected COVID-19 patient.<br>- Care of COVID-19 should be limited to necessary HCW to restrict use of PPE, and they should be less than 65 yo, non-pregnant and not-immune compromise. |
| Baseline assessment of IPC in the hospital | - Availability of PPE for HCW and support staff<br>- Availability of disinfectant gel, soap, running water and single-use towels versus clean reusable towels<br>- Availability of cleaning solution and other cleaning supplies to decontaminate medical devices and patient care equipment<br>- Availability of appropriate waste management given the concern that stool might transmit the virus (17,18) |
| Protocol for triaging patients for COVID-19 testing<br>** If testing is not available, the algorithm for triaging patients could be based on symptoms. | - The requirement that all patients, family, and HCW have a temperature check before entry into the hospitals. HCW or family members that have a fever, but no other symptoms should not be allowed to enter the hospital and instructed to self-quarantine<br>- Patients that have a fever or respiratory symptoms should be directed to a registration desk that is specific for suspected COVID-19 patients.<br>- If available, masks should be provided to patients as soon as they enter the facility. If masks are not available, then patients should cover their nose and mouth with an available piece of clothing<br>- Install barriers (glass or plastic screens) for the registration area to protect staff<br>- Patients should be triaged based on a standardized triage questionnaire to a respiratory waiting area. For an example can refer to the CDC website. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us-settings/sop-triage-prevent-transmission.html) (19)<br>- Adults should have no accompanying family members, and children should be limited to one parent or caretaker. If a patient is thought to be COVID-19 positive, then family members should also be considered positive.<br>- Dedicated personnel should be evaluating patients in the respiratory waiting room with appropriate PPE<br>- If patients are located in an open space, then there should only be one patient per bed with a minimum of one meter but ideally 2.5 meters between beds. Recommend placing plastic barriers between beds (glass or plastic screens).<br>- Patients with high concern for COVID-19 should be quickly triaged for discharge with self-isolation versus admission to an assigned COVID-19 unit. |

Chart 2: Goals for the IPC Team (15,16). Part I.

| | |
|---|---|
| Protocol for reusing equipment including PPE and storing<br>Protocol for cleaning of equipment and spaces | - The CDC has recommendations on how to clean PPE, such as N95, with techniques such as ultraviolet germicidal irradiation (UVGI) or vaporous hydrogen peroxide (VHP). (https://ww.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/decontamination-reuse-respirators.html) (20) |
| Protocol for sick staff | - If testing is available, negative and asymptomatic HCW should go back to work. However, if there is no testing available, then HCW will have to be out of work 72 hours after resolution of symptoms or seven days after the start of symptoms. (21) |
| Determine current and foreseeable gaps in IPC and determine how to address said gaps promptly. | - Tracking distribution and usage of equipment. WHO surge calculator is available for help estimate potential requirement of essential supplies and staff (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/covid-19-critical-items). (22)<br>- Essential to optimize the supply and to adjust the use of PPE based on the current quantity. The CDC provides a document on optimizing PPE supply that depends on if the supply is "stressed, running low or absent." (https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html ) (23) Two of their major points are limiting the number to health care works to essential and extending the life of the PPE to multiple uses. |
| Creation of COVID-19 isolation units both in the general ward and critical care | - Recommend use of negative pressure rooms to contain virus particles; however, if unavailable, then a room with adequate ventilation to prevent transmission of pathogens should be used.<br>- Standardize maximum bed occupancy for the units<br>- If patients are in an open space, only one patient per bed with a minimum of one meter but ideally 2.5 meters between beds. Recommend placing plastic barriers between beds (glass or plastic screens).<br>- There should be an adequate number of nursing and support staff to manage the patient workload safely |

Chart 3: Goals for the IPC Team (15,16). Part II.