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Pragmatic Recommendations for Therapeutics of Hospitalized COVID-19 Patients in Low- and Middle-Income Countries

Varun U. Shetty,[1] Brian Jason Brotherton,[1,2] Andrew Achilleos,[3] Kevan M. Akrami,[4,5,6] Lia M. Barros,[7] William Checkley,[8,9] Natalie Cobb,[10] Stephanie Maximous,[11] David Misango,[12] Casey Park,[13] Shaurya Taran,[13] and Burton W. Lee[11,14]* for the COVID-LMIC Task Force and the Mahidol-Oxford Research Unit (MORU)

[1]*Critical Care Medicine Department, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania;* [2]*Department of Internal Medicine, Kijabe Medical Center, Kijabe, Kenya;* [3]*Department of Critical Care, Sunnybrook Health Sciences Center, Toronto, Canada;* [4]*Faculdade de Medicina, Universidade Federal da Bahia, Salvador, Brazil;* [5]*Divisions of Infectious Disease, University of California San Diego, San Diego, California;* [6]*Critical Care Medicine, University of California San Diego, San Diego, California;* [7]*Department of Cardiology, University of Washington Medical Center, Seattle, Washington;* [8]*Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, Maryland;* [9]*Center for Global Non-Communicable Disease Research and Training, School of Medicine, Johns Hopkins University, Baltimore, Maryland;* [10]*Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington Medical Center, Seattle, Washington;* [11]*Division of Pulmonary Allergy Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania;* [12]*Department of Anaesthesiology and Critical Care Medicine, Aga Khan University Hospital, Nairobi, Kenya;* [13]*Department of Medicine, Interdepartmental Division of Critical Care Medicine, Toronto, Canada;* [14]*Critical Care Medicine Department, National Institutes of Health, Bethesda, Maryland*

Abstract. The therapeutic options for COVID-19 patients are currently limited, but numerous randomized controlled trials are being completed, and many are on the way. For COVID-19 patients in low- and middle-income countries (LMICs), we recommend against using remdesivir outside of a clinical trial. We recommend against using hydroxychloroquine ± azithromycin or lopinavir–ritonavir. We suggest empiric antimicrobial treatment for likely coinfecting pathogens if an alternative infectious cause is likely. We suggest close monitoring without additional empiric antimicrobials if there are no clinical or laboratory signs of other infections. We recommend using oral or intravenous low-dose dexamethasone in adults with COVID-19 disease who require oxygen or mechanical ventilation. We recommend against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen. We recommend using alternate equivalent doses of steroids in the event that dexamethasone is unavailable. We also recommend using low-dose corticosteroids in patients with refractory shock requiring vasopressor support. We recommend against the use of convalescent plasma and interleukin-6 inhibitors, such as tocilizumab, for the treatment of COVID-19 in LMICs outside of clinical trials.

INTRODUCTION

Therapeutic recommendations for COVID-19 patients in low- and middle-income countries (LMICs) should ideally be based on high-quality evidence such as well-designed randomized controlled trials in patients from LMICs who are infected with SARS-CoV-2. However, such evidence is uncommon, and we must often extrapolate from studies conducted in high-income countries (HICs), non–COVID-19 patients, studies of suboptimal quality, or some combinations of the aforementioned. Nevertheless, given the widespread pandemic with millions affected, we offer a set of pragmatic recommendations for therapeutics of COVID-19 patients in LMICs based on a review of the available literature and international guidelines.[1–3]

This study focuses on management of patients hospitalized with COVID-19. Although most patients with COVID-19 will not be hospitalized, evidence regarding management of patients in the outpatient setting is scarce, and this subset of patients does not burden healthcare systems as much as those severely ill with COVID-19. Therefore, our focus is on therapeutics of hospitalized patients with emphasis on shortening the duration of hospitalization or reducing mortality.

METHODS

A full description of the methods is provided in the Appendix. An international team of clinicians with significant experience in resource-limited settings appraised a list of questions pertinent to therapeutics of COVID-19 patients by reviewing the literature. These were reviewed for content and clarity by the heads from other subgroups. After their approval, we split up, each seeking evidence for recommendations regarding the questions posed, seeking help from other subgroup members in identifying relevant publications, where necessary.

A literature search was performed in a minimum of one general database (i.e., MEDLINE and EMBASE) and the Cochrane Library. Furthermore, we identified investigations from LMICs and searched for unpublished study results. We also reviewed existing guidelines from the World Health Organization, U.S. National Institutes of Health, and Surviving Sepsis Campaign COVID-19.

We selected relevant publications, appraised the evidence, and classified the quality of evidence as high, moderate, low, or very low. Recommendations were rated as strong or weak, depending on the quality of evidence, magnitude of effect, and several other factors such as availability, affordability, safety, and feasibility in LMICs. A strong recommendation was worded as "we recommend. . ." and a weak recommendation as "we suggest. . .," followed by the quality of evidence. A number of recommendations could remain "ungraded," when, in the opinion of the subgroup members, such recommendations were not conducive for the process described previously (Appendix Table 2). The recommendations were reviewed by the subgroup in an iterative process and were later reviewed by the entire task force in two rounds. In the absence of high-quality evidence from COVID-19 patients, or specifically from LMIC settings, we extrapolated from available studies from HICs or non–COVID-19 patients or both.

* Address correspondence to Burton W. Lee, Critical Care Medicine Department, National Institutes of Health, 10 Center Dr., Rm. 2C145, Bethesda, MD 20892-1662. E-mail: leebw@nih.gov

QUESTIONS

We formulated seven questions, as listed in the following. For hospitalized COVID-19 patients in LMICs, the following questions were formulated:

1. Should remdesivir be given?
2. Should hydroxychloroquine ± azithromycin be given?
3. Should lopinavir–ritonavir be given?
4. Should broad-spectrum antimicrobial therapy be given empirically for potential coinfections?
5. Should corticosteroids be given?
6. Should convalescent plasma be transfused?
7. Should interleukin-6 (IL-6) inhibitors, such as tocilizumab, be given?

Table 1 shows a summary of our recommendations and suggestions.

1. For hospitalized COVID-19 patients in LMICs, should remdesivir be given? *Rationale.* The U.S. Food and Drug Administration (FDA) has approved remdesivir for the management of hospitalized patients infected with SARS-CoV-2 and severe disease.[4,5] It is important to consider whether this should be the standard care for similar patients in LMICs.

Recommendations from other guidelines. *NIH COVID-19 treatment guidelines.*[2]. For patients with COVID-19 who are not hospitalized or who are hospitalized with moderate disease but do not require supplemental oxygen.

Recommendations: There are insufficient data for the Panel to recommend either for or against the use of remdesivir for the treatment of COVID-19.

For hospitalized patients with COVID-19 who require supplemental oxygen but who do not require delivery of oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or Extracorporeal Membrane Oxygenation (ECMO).

Recommendations: The options given next are listed in order of preference; however, all these options are considered acceptable.

1. Remdesivir 200 mg intravenously (IV) for 1 day, followed by remdesivir 100 mg IV for 4 days or until hospital discharge, whichever comes first (AI); or
2. a combination of remdesivir (dose and duration as aforementioned) plus dexamethasone 6 mg IV or orally for up to 10 days or until hospital discharge (BIII); or
3. if remdesivir cannot be used, dexamethasone may be used instead (BIII). (See Remdesivir for more information.)

For hospitalized patients with COVID-19 who require delivery of oxygen through a high-flow device or noninvasive ventilation but not invasive mechanical ventilation or ECMO.

Recommendations: The following options are listed in order of preference; however, both options are considered acceptable.

1. A combination of dexamethasone plus remdesivir at the doses and durations discussed above (AIII); or
2. dexamethasone alone at the dose and duration discussed earlier (AI).

For hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO.

Recommendations: The options below are listed in order of preference; however, both options are considered acceptable.

1. Dexamethasone at the dose and duration discussed earlier (AI); or

TABLE 1
Recommendations and suggestions for therapeutics of COVID-19 patients in low- and middle-income countries

1. Should remdesivir be given?	We recommend against using remdesivir for COVID-19 patients outside of a clinical trial (strong recommendation, moderate quality of evidence)
2. Should hydroxychloroquine ± azithromycin be given?	We recommend against using hydroxychloroquine ± azithromycin (strong recommendation, high quality of evidence)
3. Should lopinavir–ritonavir be given?	We recommend against using lopinavir–ritonavir (strong recommendation, high quality of evidence)
4. Should broad-spectrum antimicrobial therapy be given empirically for potential coinfections?	We suggest close monitoring without additional empiric antimicrobials if there are no clinical or laboratory signs of other infections (weak recommendation, very low quality of evidence) We suggest empiric antimicrobial treatment for likely coinfecting pathogens if an alternative infectious cause is likely (weak recommendation, very low quality of evidence)
5. Should corticosteroids be given?	We recommend using oral or intravenous low-dose dexamethasone in adults with COVID-19 disease who require oxygen or mechanical ventilation (strong recommendation, high quality of evidence) We recommend the use of alternate equivalent doses of corticosteroids in the event that dexamethasone is unavailable (strong recommendation, low quality of evidence) We recommend against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (strong recommendation, high quality of evidence). We recommend using low-dose corticosteroids in adults with COVID-19 disease and shock requiring vasopressor support (strong recommendation, moderate quality of evidence)
6. Should convalescent plasma be transfused?	We recommend against the use of convalescent plasma in LMICs, except in the context of a clinical trial (strong recommendation, low quality of evidence)
7. Should IL-6 inhibitors, such as tocilizumab, be given?	We recommend against the use of IL-6 inhibitors, such as tocilizumab, for the treatment of COVID-19 in LMICs outside of clinical trials (strong recommendation, low quality of evidence)

IL-6 = interleukin-6; LMICs = low- and middle-income countries. For hospitalized COVID-19 patients in LMICs.

2. dexamethasone plus remdesivir for patients who have recently been intubated at the doses and durations discussed above (CIII).

WHO COVID-19 guidelines[1]: We suggest against administering remdesivir in addition to standard care.

Search strategy and Medical Subject Headings terms. PubMed was searched for following MeSH terms and its equivalents through November 12, 2020: "remdesivir and COVID 19," and "remdesivir and COVID 19 and LMIC." This search yielded 795 studies; six were clinical trials and/or randomized clinical trials; 25 were meta-analyses, reviews, and/or systematic reviews; 200 were from LMICs.

Evidence. After initially receiving emergency approval for use in COVID-19 patients who are hypoxemic ($SpO_2 \leq 94\%$ on room air, requiring supplemental oxygen, mechanical ventilation, or ECMO),[4] remdesivir is now FDA-approved for treatment of patients older than 12 years, at least 40 kg and requiring hospitalization.[5] However, the WHO's position had always been to not use remdesivir outside the context of clinical trials.[6] The WHO guidelines, released after the results of the SOLIDARITY trial, make a weak recommendation against using remdesivir in any form of COVID-19.[1] The FDA approval is based on three randomized controlled trials. The Adaptive COVID-19 Treatment trial compared remdesivir versus placebo in 1,063 hospitalized COVID-19 patients with lower respiratory tract involvement.[7] The trial was stopped early after interim analysis demonstrated that remdesivir significantly reduced the primary outcome of time to recovery from 15 to 11 days (rate ratio: 1.32; 95% CI: 1.12–1.55; $P < 0.001$). Although some[2] have suggested that the benefit was primarily observed in the subgroup requiring oxygen but not high flow oxygen, mechanical ventilation, or ECMO, the authors of the randomized trial clearly state that the test of interaction for the subgroup analysis was not statistically significant.[8,9] There was no significant difference in mortality (hazard ratio: 0.73; 95% CI: 0.52–1.03) between the two groups, but it is possible that a survival benefit would have been demonstrated if the study had not been stopped early.[10] An industry-funded multicenter randomized controlled trial, which compared 5 days versus 10 days of remdesivir among 397 patients with severe COVID-19,[11] found no difference in clinical outcomes. However, patients receiving mechanical ventilation, ECMO, or multi-organ failure were excluded. Another open-label, multicenter trial funded by Gilead randomized patients to either 5-day or 10-day treatment with remdesivir and compared it with the control group.[12] The 5-day group demonstrated improved clinical scores as compared with the standard of care, but the 10-day arm did not. A smaller randomized placebo-controlled trial from China found no mortality benefit with remdesivir, but the study may have been underpowered to detect such a benefit.[13] The largest and the most recent trial is the pragmatic SOLIDARITY trial funded by the WHO which evaluated the effects of four repurposed antiviral agents against SARS-CoV-2: remdesivir, hydroxychloroquine, lopinavir–ritonavir, and interferon-beta 1a (β1a). The remdesivir portion of the study randomized 2,750 and 2,725 COVID-19 patients to remdesivir and control, respectively.[14] The primary outcome was in-hospital mortality, and the study subjects were enrolled from 30 countries, many of them from LMICs. This trial found no significant mortality benefit with remdesivir. The study also did not find any benefit for secondary outcomes such as initiation of ventilation or duration of hospitalization. The SOLIDARITY authors also included a meta-analysis of all available trials and found no mortality benefit with remdesivir. It is notable that ACTT-1 and both industry-sponsored multicenter trials had less than 25% of patients receiving steroids, whereas SOLIDARITY had 48% of its patients receiving steroids in both arms. Considering the modest efficacy of remdesivir on patients requiring oxygen and its lack of mortality benefit, it is unclear whether remdesivir will continue to be effective in the presence of consistent use of steroids. Based on the available evidence, the efficacy of remdesivir appears to be limited at best.

Availability, feasibility, affordability, and safety. Remdesivir should not be part of standard care for SARS-CoV-2 in LMICs, given lack of demonstrated mortality benefit and concerns over its availability and cost-effectiveness. For example, remdesivir may be available for as low as $64 (rupees 4,800) for a 100-mg vial in India ($704 for a 10-day course),[15] but it may still be cost-prohibitive for many patients because 45% of Indians earn less than $133/month (Rs. 10,000).[16] Thus, the available evidence does not justify using remdesivir in resource-limited areas where more effective therapies such as oxygen and dexamethasone should be prioritized.

Recommendation for LMICs. We recommend against using remdesivir for COVID-19 patients outside of a clinical trial (strong recommendation, moderate quality of evidence).

2. For hospitalized COVID-19 patients in LMICs, should hydroxychloroquine ± azithromycin be given? *Rationale.* Numerous antimicrobial drugs are being evaluated for management of COVID-19 patients, including chloroquine or hydroxychloroquine ± azithromycin.

Recommendations from other guidelines. NIH COVID-19 Treatment Guidelines[2]: The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients (AI). In nonhospitalized patients, the Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (AI). The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI).

Surviving Sepsis COVID Guidelines[3]: There is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19 (no recommendation).

WHO COVID-19 Guidelines[6]: We recommend that chloroquine or hydroxychloroquine (± azithromycin) not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials.

Search strategy and MeSH terms. PubMed was searched for following terms through November 12, 2020: "hydroxychloroquine," "hydroxychloroquine and azithromycin," "azithromycin," and COVID-19. This search yielded 1,844 results; 30 were clinical trials and/or randomized clinical trials; 69

were meta-analyses, reviews, and/or systematic reviews; 465 were from LMICs.

Evidence. Numerous repurposed agents, ranging from antiparasite to antiretroviral medications, have been shown to reduce replication of SARS-CoV-2 virus in vitro. Some of these agents have been tested clinically, and more studies are underway, but evidence is limited for their broad general use for critically ill patients with COVID-19.[17]

Hydroxychloroquine/chloroquine demonstrated reduction in viral replication in vitro, leading to significant interest to repurpose this FDA-approved medication for treatment of COVID-19.[17] However, there is concern for cardiac side effects with high-dose hydroxychloroquine, especially when combined with azithromycin.[18] The use of hydroxychloroquine with or without azithromycin may compound the evident cardiac toxicity from COVID-19 infection, particularly in LMICs without ready access to continuous cardiac monitoring.[19–21] Although a small study of COVID-19 patients with significant methodological flaws had demonstrated decreased viral nasal carriage in those treated with hydroxychloroquine compared with controls,[22] a large propensity-matched observational study subsequently revealed no difference in intubation or mortality rates with hydroxychloroquine compared with standard care.[23] A multinational registry study had initially reported increased risks of ventricular arrhythmias and death for those using hydroxychloroquine/chloroquine alone or in combination with a macrolide.[24] However, this study was later retracted because of concerns about fabrication of data.[25,26] A recent meta-analysis suggested a trend toward higher mortality in patients treated with hydroxychloroquine, without any improvement in viral clearance.[27] However, most studies in this analysis had used high-dose hydroxychloroquine. The RECOVERY trial, an ongoing adaptive multicenter randomized controlled trial evaluating multiple potential treatments for COVID-19, discontinued the hydroxychloroquine arm of the study because it found no difference in mortality or duration of hospitalization between 1,561 patients on hydroxychloroquine versus 3,155 patients on usual care alone.[28] The multinational WHO SOLIDARITY Trial compared the in-hospital mortality among 947 patients randomized to hydroxychloroquine and 906 to control, many of whom were from LMICs. Although the study has yet to undergo peer review and publication, the preliminary findings show no mortality benefit (95% CI: 0.89–1.59; $P = 0.23$).[14] The ORCHID trial randomized 479 severe COVID-19 patients from 34 U.S. hospitals to hydroxychloroquine (400 mg twice daily for two doses and then 200 mg twice daily for two doses) or placebo. The primary outcome was clinical status at 14 days on an ordinal scale, ranging from one (death) to seven (discharged from the hospital and able to perform normal activities).[29] The trial was stopped early because of futility and the authors reported no significant improvement in the primary outcome (adjusted odds ratio = 1.02; 95% CI: 0.73–1.42). The RECOVERY, SOLIDARITY, ORCHID, and several smaller trials show that hydroxychloroquine is not effective for treatment of COVID-19. The RECOVERY, SOLIDARITY, and ORCHID trials all included hospitalized patients, regardless of oxygen requirement.

The COALITION II Trial was a randomized comparison of azithromycin in addition to standard care versus standard care alone among 447 hospitalized patients in Brazil with suspected COVID-19.[30] Standard care included hydroxychloroquine in both arms, and patients required at least 4 L/minute of oxygen, high-flow nasal cannula, noninvasive mechanical ventilation, or invasive mechanical ventilation. In the modified intention to treat population of 397 patients with confirmed COVID-19, there was no difference in the primary outcome of clinical status at day 15, as assessed by a blinded independent adjudication committee on a six-point ordinal scale. There was also no increase in the incidence of QT prolongation in azithromycin arm when compared with the control arm.

There are also multiple trials studying the role of hydroxychloroquine in the prophylaxis of COVID-19.[31–37] Two randomized controlled trials did not show any benefit to pre- or postexposure prophylaxis with hydroxychloroquine.[38,39] Thus, we do not recommend hydroxychloroquine or azithromycin for this purpose at this time.

Availability, feasibility, affordability, and safety. We recommend against the use of hydroxychloroquine with or without azithromycin for treatment of COVID-19, regardless of availability or cost for LMICs.

Recommendation for LMICs. We recommend against using hydroxychloroquine ± azithromycin in treating COVID-19 (strong recommendation, high quality of evidence).

3. For hospitalized COVID-19 patients in LMICs, should lopinavir–ritonavir be given? *Rationale.* Numerous antimicrobial drugs are being evaluated for management of COVID-19 patients, including lopinavir–ritonavir.

Recommendations from other guidelines. WHO COVID-19 Guidelines[6]: We recommend that antivirals including lopinavir/ritonavir not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials.

NIH COVID-19 Treatment Guidelines[2]: The COVID-19 Treatment Guidelines Panel recommends against using lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII) for the treatment of COVID-19, except in a clinical trial.

Surviving Sepsis COVID Guidelines[3]: In critically ill adults with COVID-19, we suggest against the routine use of lopinavir/ritonavir (weak suggestion).

Search strategy and MeSH terms. PubMed was searched for following terms or its equivalents through November 12, 2020: "lopinavir-ritonavir AND COVID-19," "lopinavir-ritonavir AND COVID-19 AND LMICs." This search yielded 420 results; 16 were clinical trials and/or randomized clinical trials; 24 were meta-analyses, reviews, and/or systematic reviews; 148 were from LMICs.

Evidence. Multiple agents have been identified with in vitro activity against SARS-CoV-2, although evidence is limited in the clinical efficacy of these repurposed agents, particularly in the critically ill population.[17] Lopinavir–ritonavir was shown to be ineffective in a moderate-sized randomized controlled trial.[40] A small 2:1 open-label randomized controlled study of triple therapy (lopinavir–ritonavir, interferon-beta, and ribavirin) compared with lopinavir–ritonavir alone demonstrated decreased viral shedding in the triple therapy arm.[41] Furthermore, the WHO SOLIDARITY trial did not show any mortality benefit to using lopinavir/ritonavir in hospitalized patients with COVID-19.[14] The RECOVERY trial, an adaptive multicenter randomized controlled trial evaluating multiple potential treatments for COVID-19 discussed earlier, suspended the

lopinavir–ritonavir arm of the study because of a lack of efficacy. They reported no difference in mortality, risk of progression to mechanical ventilation, or duration of hospitalization among 1,596 patients on lopinavir–ritonavir versus 3,376 patients on usual care alone.[42] In some cases, significant bradycardia with atrioventricular block has been reported in older critically ill COVID-19 patients treated with lopinavir/ritonavir.[43] Therefore, routine use of lopinavir–ritonavir in the treatment of COVID-19 is not recommended.

Availability, feasibility, affordability, and safety. We do not recommend lopinavir–ritonavir, regardless of availability or cost for LMICs.

Recommendation for LMICs. We recommend against using lopinavir–ritonavir in treating COVID-19 (strong recommendation, high quality of evidence).

4. For hospitalized COVID-19 patients in LMICs, should broad-spectrum antimicrobial therapy be given empirically for potential coinfections? *Rationale.* Among patients with COVID-19 infection, coinfections due to bacterial, viral, fungal, or parasitic pathogens may necessitate appropriate antimicrobial treatments for potential coinfection.

Recommendations from other guidelines. NIH COVID-19 Treatment Guidelines[2]: In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication (BIII). If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy (AIII).

Surviving Sepsis COVID-19 Guidelines[3]: In mechanically ventilated patients with COVID-19 and respiratory failure, we suggest using empiric antimicrobials/antibacterial agents, over no antimicrobials (weak suggestion). If the treating team initiates empiric antimicrobials, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology results and the patient's clinical status (weak suggestion).

WHO COVID-19 Guidelines[6]: We recommend for patients with suspected or confirmed severe COVID-19 the use of empiric antimicrobials to treat all likely pathogens, based on clinical judgment, patient host factors, and local epidemiology, and this should be done as soon as possible (within 1 hour of initial assessment if possible), ideally with blood cultures obtained first. Antimicrobial therapy should be assessed daily for de-escalation.

Search strategy and MeSH terms. PubMed was searched for the following terms through November 12, 2020: "antimicrobials or antibiotics in COVID 19." This search yielded 3,474 results; 65 were clinical trials and/or randomized clinical trials; 103 were meta-analyses, reviews, and/or systematic reviews; 858 were from LMICs.

Evidence. Although bacterial and fungal coinfection rates with SARS-CoV-2 appear to be low, empiric antibiotics are routinely used in hospitalized and critically ill patients.[44] A retrospective review of more than 88,000 blood cultures obtained during the height of the pandemic in New York in March 2020 demonstrated bacteremia to be rare in confirmed SARS-CoV-2 cases, with 1.6% having pathogenic bloodstream infections when commensal skin flora was excluded.[45] Because similar evidence is not available for LMICs, the following recommendation is based on expert consensus only. In addition to specific therapy for COVID-19, coverage for local endemic pathogens that may present in a manner similar to COVID-19 should be considered, particularly while confirmation of SARS-CoV-2 infection is pending. If the diagnosis is unclear, where feasible, urine, blood, and sputum cultures should be collected for patients presenting with sepsis or septic shock, followed by empiric treatment with broad-spectrum antimicrobials while awaiting SARS-CoV-2 or other microbiological testing results. For patients in shock suspected to be due to a bacterial infection, empiric antimicrobials should be started as early as possible because delays in antibiotic administration may increase mortality.[3] Empiric antimicrobials should be discontinued or de-escalated following confirmation of SARS-CoV-2 infection, given the low level of coinfection. In areas with limited microbiologic laboratory capacity, management should be guided by clinical suspicion and pretest probability of coinfections. The type of coinfections will vary depending on local epidemiology, but considerations should include bacterial, Rickettsial, fungal (coccidioidomycosis and histoplasmosis), viral (dengue, HIV, and influenza), or parasitic (malaria) infections.

Availability, feasibility, affordability, and safety. For COVID-19 patients in LMICs, whether or not empiric broad-spectrum antimicrobial treatment is indicated depends on the prevalence of coinfections, which likely varies from region to region, as well as the availability and cost of empiric antimicrobial treatment. Given that COVID-19 patients may present with severe illness, including shock, it is reasonable to start empiric antimicrobial treatment for common endemic illnesses that could present in a similar manner while waiting for microbiologic results or clinical course indicates an alternative infectious etiology. In the absence of a confirmed microbiologic diagnosis, a defined course of antibiotics based on clinical response is reasonable to complete. De-escalation of empiric antimicrobials is critical to limit antibiotic selection pressure that drives the development of multidrug–resistant organisms in LMICs. Antibiotic stewardship in the midst of the pandemic is paramount.

Recommendation for LMICs. We suggest close monitoring without additional empiric antimicrobials if there are no clinical or laboratory signs of other infections (weak recommendation, very low quality of evidence). We suggest empiric antimicrobial treatment for likely coinfecting pathogens if an alternative infectious cause is likely (weak recommendation, very low quality of evidence).

5. For hospitalized COVID-19 patients in LMICs, should corticosteroids be given? *Rationale.* Corticosteroids have been proposed as a treatment for acute respiratory distress syndrome (ARDS) because of their anti-inflammatory and antifibrotic properties, but clinical trials have yielded inconsistent results. In addition, there is a concern that corticosteroids may increase viral shedding in viral pneumonitis. The use of corticosteroids is also variable in the context of septic shock, and practice varies because their effect on mortality is debated, although studies consistently demonstrate a reduction in the duration of shock. Corticosteroids are therefore an important consideration for COVID-19 patients with shock.

Recommendations from other guidelines. WHO COVID-19 Guidelines[1]: Strong recommendation in favor of corticosteroids; weak recommendation against corticosteroids in non-severe disease.

NIH COVID-19 Treatment Guidelines[2]: See remdesivir section.

Surviving Sepsis COVID-19 Guidelines[3]: For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy ("shock-reversal"), over no corticosteroid (weak suggestion).

Search strategy and MeSH terms. Electronic searches were carried out in PubMed using the following MeSH terms through November 12, 2020: (steroids OR corticosteroids OR dexamethasone OR hydrocortisone) AND (COVID-19 OR COVID 19 OR SARS-CoV-2 OR SARS-CoV-2 OR coronavirus disease 2019) AND LMICs. PubMed search of these terms yielded 1,504 studies; 18 were clinical trials and/or randomized clinical trials; 53 were meta-analyses, reviews, and/or systematic reviews; 295 were from LMICs.

Additional search term used was ARDS AND corticosteroids. PubMed search of this term yielded 2,565 studies; 164 were clinical trials and/or randomized clinical trials; 64 were meta-analyses or systematic reviews; 249 were from LMICs.

Evidence. The RECOVERY trial is an ongoing adaptive, multicenter, randomized controlled trial evaluating multiple potential treatments for COVID-19. The dexamethasone arm of the study compared dexamethasone 6 mg daily for up to 10 days (n = 2,104) versus placebo (n = 4,321) in hospitalized patients with COVID-19. The preliminary report describes a substantial reduction in mortality with dexamethasone (rate ratio: 0.83; 95% CI: 0.75–0.93, $P < 0.001$).[46] Prespecified subgroup analysis showed a particular mortality benefit for patients receiving mechanical ventilation (rate ratio: 0.64; 95% CI: 0.51–0.81) and patients receiving conventional supplemental therapy (rate ratio: 0.82; 95% CI: 0.72–0.94) but not those without supplemental oxygen (rate ratio: 1.19; 95% CI: 0.91–1.55) with an overall number needed to treat of 32 (95% CI: 19–112) and fragility index of 11.[19] This follows an randomized controlled trial (RCT) in patients with ARDS without COVID-19 published in 2020 comparing dexamethasone to placebo (n = 277), which demonstrated a reduction in ventilator-free days (4–8 days; 95% CI: 2.57–7.03, $P < 0.0001$) and reduced 60-day mortality (between-group difference –15.3% [–25.9 to –4.9]; $P = 0.0047$), although the trial was stopped early because of low enrollment.[47] A recent meta-analysis of eight RCTs (n = 1,091) comparing glucocorticoid therapy with placebo in patients with ARDS demonstrated a reduction in in-hospital mortality (RR: 0.79; 95% CI: 0.64–0.98; $P = 0.03$) and intensive care unit mortality (RR: 0.64; 95% CI: 0.42–0.97; $P = 0.04$).[48]

Corticosteroids have been shown to slow viral RNA clearance in SARS and other viral pathogens, but viral shedding in SARS-CoV-2 occurs relatively early. This may explain why it is helpful to delay corticosteroid therapy to a time when viral replication is expected to have diminished and restricting it to those with evidence of significant inflammation, evidenced by a requirement for supplemental oxygen or mechanical ventilation.

The WHO REACT Working Group performed a prospective meta-analysis of randomized studies evaluating the role of corticosteroids among critically ill COVID-19 patients which included the trials that were terminated early because of the findings of the RECOVERY trial (Randomized Embedded Multifactorial Adaptive Platform [REMAP], COVID-19-associated ARDS treated with DEXamethasone [CoDEX], Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease [CAPE COVID]).[49–52] The meta-analysis found a significant reduction in 28-day mortality with corticosteroids (OR: 0.66; 95% CI: 0.53–0.82; $P < 0.001$). The ratio of ORs between hydrocortisone and dexamethasone was 1.06 (95% CI: 0.37–2.99) using meta-regression, although the optimal dose of hydrocortisone could not be recommended. In the event that dexamethasone is not available in COVID-19, we believe it is reasonable to use equivalent doses of alternate corticosteroid (e.g., hydrocortisone 50 mg IV q6h, prednisolone IV/PO 40 mg Q24H, or methylprednisolone 30 mg IV Q24H).

The role of corticosteroids for COVID-19 patients in refractory shock is more fully discussed in a companion article in this series.[53] In brief, although the data come mostly from HICs, corticosteroids are generally recommended for patients in refractory shock. Systematic reviews of randomized controlled trials suggest mortality reduction and faster time to shock reversal.[54,55] Although none of these trials were specifically conducted among COVID-19 patients, we believe it is reasonable to extend these findings to COVID-19 patients. Also, although no studies have specifically studied hydrocortisone or other steroids in COVID-19, it is reasonable to believe that if a patient is getting hydrocortisone or other equivalent steroid for refractory shock, then adding dexamethasone to the regimen is not needed.

Availability, feasibility, affordability, and safety. Corticosteroids are widely available, and dexamethasone, hydrocortisone, and prednisolone are all on the WHO Essential Medication List.[56] A 5-mg dose of dexamethasone costs approximately $0.30 in India, which makes it far more affordable than remdesivir.[57] Furthermore, dexamethasone may offer a survival benefit in contrast to remdesivir. For treatment of refractory shock, the median cost of injectable hydrocortisone is also relatively inexpensive (U.S. dollar $0.47 per vial) compared with other intensive care therapies.[58] Corticosteroids used in the context of septic shock are not associated with a significant risk of serious adverse outcomes.[54]

Recommendation for LMICs. We recommend the use of oral or intravenous low-dose dexamethasone in adults with COVID-19 disease who require oxygen or mechanical ventilation (strong recommendation, high quality of evidence). We recommend the use of alternate equivalent doses of steroids in the event that dexamethasone is unavailable (strong recommendation, low quality of evidence).

We recommend against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (strong recommendation, high quality of evidence). We recommend the use of low-dose corticosteroids in patients with refractory shock requiring vasopressor support (strong recommendation, moderate quality of evidence).

6. For hospitalized COVID-19 patients in LMICs, should convalescent plasma be transfused? *Rationale.* Convalescent plasma may have neutralizing antibodies that could aid in more rapid clearance of SARS-CoV-2. The use of convalescent plasma during SARS-CoV-1, Middle East Respiratory Syndrome (MERS)-CoV, and H1N1 outbreaks appeared safe and reduced viral load with consequent decreases in cytokines.[59–61]

Recommendations from other guidelines. WHO COVID-19 Guidelines[6]: We recommend that convalescent plasma not be

administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials.

NIH COVID-19 Treatment Guidelines[2]: There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19 (AIII).

Surviving Sepsis COVID-19 Guidelines[3]: In critically ill adults with COVID-19, we suggest against the routine use of convalescent plasma (weak suggestion).

Search strategy and MeSH terms. Electronic searches were carried out in PubMed. The following MeSH terms and their free-text equivalents were used: Convalescent Plasma AND COVID-19 AND LMICs.

This search as of November 12, 2020, yielded 530 studies; 10 were randomized clinical trials; 23 were meta-analyses, reviews, and/or systematic reviews; six were from LMICs.

Evidence. Convalescent plasma from those who have recovered from COVID-19 infection has emerged as a potential adjuvant treatment in those with severe infection, based on prior work during outbreaks of other emergent respiratory viral infections including SARS, MERS, and H1N1.[59,60,62] Proposed mechanisms evaluated during those other epidemics include accelerated viral clearance and blunting of a pro-inflammatory profile with decreases in IL-6, IL-10, and tumor necrosis factor-α.[61] Timing of administration appears to influence patient outcome because those who received convalescent plasma with detectable SARS virus by PCR and seronegativity were discharged at a higher rate than those who received it in the setting of both PCR and seropositivity. Multiple case series have described the use of convalescent plasma in COVID-19 patients, but these reports are significantly limited by small sample sizes and confounded by concomitant use of other investigational treatments.[63–67] An observational study of hospitalized COVID-19 patients from Iran found no significant difference in mortality between 115 patients who were given convalescent plasma and 74 control patients (14.8% versus 24.3%, respectively, $P = 0.09$).[68] A small open-label randomized trial from China did not detect a mortality benefit of convalescent plasma in the severe and non-severe disease, although it may have been underpowered because of low enrollment.[69] The PLACID trial randomized 464 hospitalized patients with mild COVID-19 from India to convalescent plasma plus standard care versus standard care alone.[70] Mild disease was defined as a P_aO_2/F_iO_2 ratio between 200 and 300 mmHg or respiratory rate > 24 with oxygen saturation ≤ 93% on room air, and the primary outcome was the composite of progression to severe disease (P_aO_2/F_iO_2 ratio ≤ 100 mmHg) or death at 28 days. The study found no significant difference in the primary outcome (risk ratio: 1.04; 95% CI: 0.71–1.54). Therefore, current evidence does not support the use of convalescent plasma for COVID-19 patients.

Data on the safety or adverse events associated with convalescent plasma are limited, but there is concern for anaphylactic shock and possible antibody-dependent enhancement where non-neutralizing antibodies facilitate viral entry and replication, leading to more severe and rapid infection.[71] A study of the U.S. FDA Expanded Access Program for COVID-19 plasma registry identified 36 immediate adverse events in 5,000 patients who received convalescent plasma for COVID-19, suggesting a reasonable safety profile in the United States.[72] Multiple additional prospective randomized controlled trials are underway to evaluate the safety and efficacy of convalescent plasma for COVID-19 infection.

Availability, feasibility, affordability, and safety. Convalescent plasma is not a widely available option in most LMICs. Safety concerns appear to be minimal for immediate transfusion-related adverse events based on the U.S. FDA registry for convalescent plasma in COVID-19 patients. The cost of screening for other transmissible diseases, such as HIV and hepatitis C virus, may be cost-prohibitive.

Recommendation for LMICs. We recommend against the use of convalescent plasma in LMICs, except in the context of a clinical trial with adequate screening for other transmissible pathogens (strong recommendation, low-quality evidence).

7. For COVID-19 patients in LMICs, should IL-6 inhibitors (e.g., tocilizumab) be given? *Rationale.* For patients with COVID-19, there is concern that severe illness may be in part due to increased inflammation and associated cytokine release, including IL-6. Therefore, it has been hypothesized that IL-6 inhibitors, such as tocilizumab, may be useful in the treatment of COVID-19 patients with severe illness.

Recommendations from other guidelines. WHO COVID-19 Guidelines[6]: We recommend that tocilizumab, interferon-β1a, and other immunomodulators not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials.

NIH COVID-19 Treatment Guidelines[2]: There are insufficient data to recommend either for or against the use of IL-6 inhibitors (e.g., sarilumab, siltuximab, and tocilizumab) for the treatment of COVID-19.

Search strategy and MeSH terms. PubMed was searched for tocilizumab, SARS-CoV-2, novel coronavirus, COVID-19, resource limited setting, resource limited, low- and middle-income country searched through November 15, 2020.

This search resulted in 637 articles; four were clinical trials or randomized clinical trials; 20 were systematic reviews or meta-analysis; 96 were from LMICs.

Evidence. Tocilizumab is a recombinant anti-human IL-6 inhibitor that has been previously approved by the FDA to treat rheumatoid arthritis and cytokine release syndrome after chimeric antigen receptor T cell therapy.[73] Because of elevated levels of IL-6 and other cytokines found in COVID-19 patients, it has been hypothesized that it may be useful in the treatment of the cytokine release storm observed in SARS-CoV-2 infections.[74]

A single-center, retrospective study from China reported improved defervescence, oxygen saturations, and CT scan abnormalities among 21 patients with severe and critical COVID-19 pneumonia.[75] Another observational study of five solid organ transplant patients infected with SARS-CoV-2–related ARDS showed a decrease in inflammatory markers and vasopressor use as well as improved oxygenation. However, four of the patients

developed subsequent bacteremia after receiving tocilizumab.[76] A multicenter, retrospective cohort study from Italy looked at standard of care therapy versus standard of care plus tocilizumab given nonrandomly to intensive care unit patients with COVID-19 pneumonia. There was a suggestion that tocilizumab may reduce the composite primary endpoint of the need for mechanical ventilation or death.[77] Beyond these initial observational studies, as of November 15, 2020, there were 37 studies listed on clincaltrials.gov that were enrolling, actively recruiting, or had completed their enrollment for studying tocilizumab for the treatment of COVID-19. Therefore, whether tocilizumab will have a role in treatment of COVID-19 remains to be seen. The only published RCT at the time of this writing compared tocilizumab with placebo among 243 hospitalized patients with mild COVID-19 who had two or more of the following features: fever, pulmonary infiltrates, or need for supplemental oxygen but less than 10 L/minute. The trial found no difference in the primary outcome of risk of mechanical ventilation or death (HR: 0.83; CI: 0.38–1.81; $P = 0.64$). However, it should be noted that clinically meaningful benefit was not been excluded by this trial, given the wide CI around the hazard ratio.[78] The COVACTA trial is a multicenter, randomized controlled trial comparing tocilizumab with placebo among hospitalized COVID-19 patients with severe pneumonia.[79] A preliminary press release reported no difference in primary outcome of clinical improvement or secondary outcomes of 30-day mortality, time to discharge, or ventilator-free days. An early press release of another study, the REMAP-CAP trial, suggests favorable results of tocilizumab among 303 mechanical ventilated patients. However, the details of the latter two studies are not known fully at this time, and the findings have yet to undergo peer review.[80] Therefore, this appears to be an evolving topic, and the use of tocilizumab cannot be recommended at this time beyond the context of clinical trials.

Availability, feasibility, affordability, and safety. Tocilizumab is not widely available outside of HICs. In addition, the safety concern of secondary infection and gastrointestinal perforation outweighs the benefit of its use in LMICs outside of the close monitoring of clinical trials.[81]

Recommendations for LMICs. We recommend against the use of IL-6 inhibitors, such as tocilizumab, for the treatment of COVID-19 in LMICs outside of clinical trials (strong recommendation, low quality of evidence).

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Authors' addresses: Varun U. Shetty, University of Pittsburgh Medical Center, Pittsburgh, PA, E-mail: shettyvu@upmc.edu. Brian Jason Brotherton, Kijabe Medical Center, Kijabe, Kenya, and University of Pittsburgh, Pittsburgh, PA, E-mail: jb042107@gmail.com. Andrew Achilleos, Casey Park, and Shaurya Taran, University of Toronto, Ontario, Canada, E-mails: andrew.achilleos@nhs.net, casey.park@medportal.ca, and shaurya.taran@mail.utoronto.ca. Kevan M. Akrami, Universidade Federal da Bahia, Salvador, Brazil, and University of California San Diego, San Diego, CA, E-mail: kevan.akrami@gmail.com. Lia M. Barros and Natalie Cobb, University of Washington, Seattle, WA, E-mails: lbarros@uw.edu and ncobb@uw.edu. William Checkley, Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MD, E-mail: wcheckl1@jhmi.edu. Stephanie Maximous, University of Pittsburgh, Pittsburgh, PA, E-mail: maximousi@upmc.edu. David Misango, Aga Khan University, Nairobi, Kenya, E-mail: david.misango@aku.edu. Burton W. Lee, University of Pittsburgh, Pittsburgh, PA, and National Institutes of Health, Bethesda, MD, E-mail: leebw@nih.gov.

GROUP MEMBERS OF THE "COVID-LMIC TASK FORCE"

Heads: Alfred Papali (Atrium Health, Charlotte, NC) and Marcus Schultz (Mahidol University, Bangkok, Thailand; University of Oxford, Oxford, United Kingdom; Amsterdam University Medical Centers, location "AMC", Amsterdam, The Netherlands).

Advisors: Neill K. J. Adhikari (Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada); Emilie J. Calvello Hynes (University of Colorado School of Medicine, Department of Emergency Medicine, Denver, CO); Martin Dünser (Kepler University Hospital and Johannes Kepler University Linz, Linz, Austria) and Mervyn Mer (University of the Witwatersrand, Johannesburg, South Africa).

Subgroup members, in alphabetical order: Andrew Achilleos (Sunnybrook Health Sciences Centre, Toronto, Canada); Hanan Y. Ahmed (Department of Internal Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia); Kevan M. Akrami (Universidade Federal da Bahia, Salvador, BA, Brazil and University of California San Diego, San Diego, CA); Lia M. Barros (University of Washington, Seattle, WA); B. Jason Brotherton (Kijabe Medical Center, Kijabe, Kenya); Sopheakmoniroth Chea (Calmette Hospital, Phnom Penh, Cambodia); William Checkley (Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MD); Elif Cizmeci (Interdepartmental Division of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada); Natalie Cobb (University of Washington, Seattle, WA); Finot Debebe (Department of Emergency Medicine and Critical Care, Addis Ababa University School of Medicine, Addis Ababa, Ethiopia); Juliana C. Ferreira (University of São Paulo, São Paulo, Brasil); Gabriela Galli (University of Pittsburgh School of Medicine, Pittsburgh, PA); Tewodros Haile (Department of Internal Medicine, College of Health Sciences, Addis Ababa University); Bhakti Hansoti (Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Rebecca Inglis (Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit [LOMWRU], Mahosot Hospital, Vientiane, Lao People's Democratic Republic and Department of Intensive Care, Oxford University Hospital Trust, Oxford, United Kingdom); Burton W. Lee (University of Pittsburgh, Pittsburgh, PA; NIH, Bethesda, MD.); Faith Lelei (AIC Kijabe Hospital, Kijabe, Kenya); Ganbold Lundeg (Mongolian National University of Medical Sciences, Ulan Bator, Mongolia); David Misango (The Aga Khan University, Nairobi, Kenya); Ary Serpa Neto (Department of Critical Care Medicine and Institute of Education and Research, Hospital Israelita Albert Einstein, São Paulo, Brazil; Department of Intensive Care, Amsterdam University Medical Centers, location "AMC," University of Amsterdam, Amsterdam, The Netherlands); Jennifer L. Pigoga (Division of Emergency Medicine, University of South Africa, Cape Town, South Africa); Alfred Papali (Atrium Health, Charlotte, NC); Casey Park (Interdepartmental Division of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada); Rajyabardhan Pattnaik (Ispat General Hospital, Rourkela, India); Luigi Pisani (Department of Anesthesia and Intensive Care, Miulli Regional Hospital, Acquaviva delle Fonti, Italy; Doctors with Africa–CUAMM, Padova, Italy; Mahidol–Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand); Elisabeth D. Riviello (Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA); Kristina E. Rudd (University of Pittsburgh School of Medicine, Pittsburgh, PA); Marcus Schultz (Mahidol University, Bangkok, Thailand; University of Oxford, Oxford, United Kingdom; Amsterdam University Medical Centers, location "AMC", Amsterdam, The

Netherlands); Varun U. Shetty (University of Pittsburgh Medical Center, Pittsburgh, PA); Gentle S. Shrestha (Tribhuvan University Teaching Hospital, Kathmandu, Nepal); Chaisith Sivakorn (Mahidol University, Salaya, Thailand); Shaurya Taran (Interdepartmental Division of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada); T. Eoin West (University of Washington, Seattle, WA).

Group members of the subgroup "Therapeutics": Varun U. Shetty (University of Pittsburgh Medical Center, Pittsburgh, PA); B. Jason Brotherton (Kijabe Medical Center, Kijabe, Kenya and University of Pittsburgh, Pittsburgh, PA); Andrew Achilleos (University of Toronto, Toronto, Ontario, Canada); Kevan M. Akrami (Universidade Federal da Bahia, Salvador, BA, Brazil and University of California San Diego, San Diego, CA); Lia Barros (University of Washington, Seattle, WA); William Checkley (Division of Pulmonary and Critical Care, School of Medicine, Johns Hopkins University, Baltimore, MD); Natalie Cobb (University of Washington, Seattle, WA); Stephanie Maximous (University of Pittsburgh, Pittsburgh, PA); David Misango (Aga Khan University, Nairobi, Kenya); Casey Park (University of Toronto, Toronto, Ontario, Canada); Shaurya Taran (University of Toronto, Toronto, Ontario, Canada); and Burton W. Lee (University of Pittsburgh, Pittsburgh, PA and NIH, Bethesda, MD).

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APPENDIX

Development of recommendations and suggestions. *Selection of task force members.* The selection of the group members was based on interest in specific aspects of COVID-19 and direct experience in low- and middle-income countries (LMICs). Alfred Papali and Marcus Schultz contacted potential team members through email and in person early in the pandemic of COVID-19 and created subgroups assigned to separate areas in COVID-19 management, that is, "triage," "safety," "organization," "microbiology and laboratory tests, imaging tools, and diagnostic and prognostic modeling," "acute respiratory failure," "acute kidney injury," "coagulopathy," "prevention and therapy," "shock," and "support after initial care."**

Selection of subgroup members. Varun U. Shetty, B. Jason Brotherton, Andrew Achilleos, Kevan M. Akrami, Lia M. Barros, William Checkley, Natalie Cobb, Stephanie Maximous, David Misango, Casey Park, Shaurya Taran, and Burton W. Lee were assigned to this subgroup based on their specific expertise and interest in the topic.

Discussions. The subgroup worked via electronic-based communications to establish the procedures for the literature review and drafting of tables for evidence analysis. Discussions occurred both within the subgroup and with members of other subgroups. First, a set of clearly defined questions regarding therapeutics for COVID-19 patients were formulated. These were reviewed for content and clarity by the subgroup members and heads from the other subgroups. After approval by the subgroup members and heads from the other subgroups, the subgroup members split up, each seeking evidence for recommendations regarding the specific questions posed, seeking help from the subgroup members in identifying relevant publications, where necessary. During this process, questions could be combined, so the subgroup was finally left with seven major questions. The subgroup summarized the evidence in a report and formulated a set of recommendations and suggestions after several online discussions. After approval within the subgroup, the report was sent for approval by all members of the task force.

TABLE A1
Quality of evidence

A	Randomized clinical trials	High
B	Downgraded randomized clinical trial(s) or upgraded observational studies	Moderate
C	Observational studies	Low
D	Downgraded observational studies or expert opinions	Very low

Factors that may decrease strength of evidence include high likelihood of bias; inconsistency of results, including problems with subgroup analyses; indirectness of evidence (other population, intervention, control, outcomes, and comparison); imprecision of findings; and likelihood of reporting bias. Factors that may increase strength of evidence: large magnitude of effect (direct evidence, relative risk > 2 with no plausible confounders), very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels), and dose–response gradient. Adapted from Dondorp Ref. 1.

Search techniques. The literature search followed the same techniques as previously described.[1] Searches were conducted in PubMed, EmBase and the Cochrane Library. Furthermore, the subgroup members identified investigations from LMICs and also searched for unpublished study results.

Grading of recommendations. The subgroup members classified quality of evidence as high or low recommendations as strong or weak. The factors influencing this classification are presented in Appendix Table 1.

The subgroup members paid extensive attention to availability, feasibility, and safety matters in LMICs. A strong recommendation was worded as "we recommend" and a weak recommendation as "we suggest." A number of recommendations could remain "ungraded", when, in the opinion of the subgroup members, such recommendations were not conducive for the process described earlier (Appendix Table 2).

Reporting. The report was edited for style and form by Alfred Papali or Marcus Schultz, with final approval by the subgroup and then by the entire "COVID–LMIC Task Force." A final document was submitted to the *American Journal of Tropical Medicine and Hygiene* for potential publication and made open access.

Disclaimer. No members of the "organization" subgroup represented industry, and there was no industry input into guidelines development. No member of the "organization" subgroup received honoraria for any role in the guideline development process. No members of the "Shock" subgroup represented industry, and there was no industry input into guidelines development. No members of the "Shock" subgroup received honoraria for any role in the guideline development process. None reported conflict of interest. Open access fees for this manuscript, and all 9 others in the series, were supported by the Wellcome Trust of Great Britain.

** In total, there were 38 Task Force members representing five medical specialties or disciplines (emergency medicine, intensive care, infectious disease, internal medicine, and critical care nursing) from five out of six World Health Organization (WHO) geographic regions. The Task Force consisted of 16 full-time LMIC members, 16 full-time HIC members - all with direct LMIC experience - and 6 members with joint LMIC/HIC appointments.

TABLE A2
Strong vs. weak recommendations*

What is considered	How it affects the recommendation
High evidence	The higher the quality of evidence, the more likely is a strong recommendation
Certainty about the balance of benefits vs. harms and burdens	The larger/smaller the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely is a strong/weak recommendation
Certainty in or similar values	The more certainty or similarity in values and preferences, the more likely is a strong recommendation
Resource implications	The lower/higher the cost of an intervention than the alternative, the more likely is a strong/weak recommendation
Availability and feasibility in LMICs	The less available, the more likely is a weak recommendation
Affordability for LMICs	The less affordable, the more likely is a weak recommendation
Safety of the intervention in LMICs	The less safe in an LMIC, the more likely is a weak recommendation

Adapted from Ref. 1.
*In case of a strong recommendation, we use "we recommend. . ."; in case of a weak recommendation, we use "we suggest. . ."

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