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Updated guidance on the management of COVID-19: from an American Thoracic Society/European Respiratory Society coordinated International Task Force (29 July 2020)

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For patients with acute COVID-19 pneumonia who require oxygen support, the International Task Force made suggestions for remdesivir and dexamethasone, but against hydroxychloroquine. Post-discharge management of COVID-19 survivors is a research priority. https://bit.ly/32B96uI

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome-coronavirus-2. Consensus suggestions can standardise care, thereby improving outcomes and facilitating future research.

Methods: An International Task Force was composed and agreement regarding courses of action was measured using the Convergence of Opinion on Recommendations and Evidence (CORE) process. 70% agreement was necessary to make a consensus suggestion.

Results: The Task Force made consensus suggestions to treat patients with acute COVID-19 pneumonia with remdesivir and dexamethasone but suggested against hydroxychloroquine except in the context of a clinical trial; these are revisions of prior suggestions resulting from the interim publication of several randomised trials. It also suggested that COVID-19 patients with a venous thromboembolic event be treated with therapeutic anticoagulant therapy for 3 months. The Task Force was unable to reach sufficient agreement to yield consensus suggestions for the post-hospital care of COVID-19 survivors. The Task Force fell one vote shy of suggesting routine screening for depression, anxiety and post-traumatic stress disorder.

Conclusions: The Task Force addressed questions related to pharmacotherapy in patients with COVID-19 and the post-hospital care of survivors, yielding several consensus suggestions. Management options for which there is insufficient agreement to formulate a suggestion represent research priorities.

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Introduction

Coronavirus Disease 2019 (COVID-19) is a multi-system disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). More than 19 million cases of COVID-19 have been confirmed, more than 720 000 persons have died, and new cases continue to emerge at an alarming rate [1]. During the earliest stages of the pandemic, an International Task Force was convened by the American Thoracic Society (ATS) and European Respiratory Society (ERS) to address important clinical questions using the scarce direct evidence that was available at the time, as well as indirect evidence. The goal of consensus guidance is to identify opportunities to standardise care, thereby improving process-related and clinical outcomes, and facilitating research. Management decisions for which there is insufficient agreement to formulate consensus guidance identify topics for which there is adequate equipoise to support clinical trials.

New knowledge continues to be published, providing an increasing evidentiary basis for sound clinical care. In this iteration of COVID-19 guidance, the Task Force updates its prior guidance on the

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pharmacological management of acute COVID-19 [2], including remdesivir, hydroxychloroquine (HCQ) and dexamethasone. The changes to these consensus suggestions reflect the publication of several randomised trials since the prior guidance was issued. In addition, since the number of COVID-19 survivors is increasing, little is known about the natural history of survivors [3], and no standardised approach to caring for such individuals has been developed, the Task Force addresses questions about the long-term follow-up of COVID-19 survivors.

The Task Force's suggestions fall into two categories: a suggestion for the intervention (the intervention should be used) or a suggestion against the intervention (the intervention should not be used except in the context of a clinical trial) (table 1 and figure S1). The Task Force made seven consensus suggestions (table 2). In the absence of sufficient agreement to make a consensus suggestion, the Task Force made no suggestion for or against a course of action (there is clinical equipoise), thereby identifying research priorities. The Task Force identified nine research priorities (table 3).The clinical and research suggestions in this document do not constitute official positions of the ATS, ERS or institutions of the Task Force members. The clinical suggestions should never be considered mandates as no suggestion can incorporate all potential clinical circumstances. They are not intended to supplant physician judgment as it pertains to individual patients. The suggestions are interim guidance that should be re-evaluated as new evidence accumulates.

Methods

An International Task Force was composed with the support of the ATS and ERS. Invitations were initially sent to ATS members who are clinically active in medical centres involved in COVID-19 patient care. The invitees were asked to suggest additional participants from around the world who were on the frontline of COVID-19 patient care, with an emphasis on pulmonologists, critical care physicians, and infectious disease experts. Finally, the ERS identified additional experts.

Questions of clinical importance were identified by a subcommittee that consisted of clinicians who were establishing clinics to follow COVID-19 survivors long-term at their home institutions. The questions were constructed using a modified PICO (Patient, Intervention, Comparator, Outcomes) format and then modified using an iterative process of teleconferences and email dialogue. Finally, the questions were reviewed for clarity by a separate, larger subcommittee.

Agreement was measured using the Convergence of Opinion on Recommendations and Evidence (CORE) process, a Delphi-like process (figure 1). The CORE process is a consensus-based approach to making clinical suggestions. It yields suggestions that are highly concordant with suggestions developed using Institute of Medicine adherent methodology for clinical practice guidelines [4, 5]. Briefly, SurveyMonkey software was used to create a multiple-choice survey. Each survey question consisted of three parts: 1) presentation of the modified PICO question; 2) multiple choices including a strong or weak suggestion for or against a course of action, or no suggestion; 3) and a free-text box for comments (figure S2). For questions related to pharmacotherapy (*i.e.* remdesivir, systemic corticosteroids and HCQ) randomised trials and large controlled observational studies were summarised in a non-systematic fashion and provided as part of the relevant survey question. The survey was initially administered from 16–21 July 2020. A second survey was then constructed that was identical to the first, except results from the first round were added including: 1) the proportion of participants who selected each multiple-choice option; 2) comments from the participants (table S1); and 3) references provided by the participants. The survey was re-administered from 24–29 July 2020.

Agreement among the Task Force on directionality was tabulated for each multiple-choice question. For example, if 5, 20, 50, 13 and 12 individuals selected a strong suggestion for, weak suggestion for, no suggestion, weak suggestion against, and strong suggestion against, respectively, the results were reported as 25% for the intervention, 50% neither for nor against the intervention, and 25% against the

TABLE 1 Task Force suggestions and interpretations

Task Force	Interpretation
Suggests	The Task Force believes that the benefits exceed the harms and the intervention should be used
Makes no suggestion for or against	The Task Force believes that the benefit–risk ratio is uncertain, more evidence is needed and, for now, clinical equipoise exists
Suggests against/not	The Task Force believes that the harms may exceed the benefits and, therefore, the intervention should not be used except in the context of a clinical trial

TABLE 2 Summary of Task Force suggestions[#]

The Task Force made the following consensus suggestions
For hospitalised patients with COVID-19 pneumonia who require supplemental oxygen but are not mechanically ventilated, the Task Force **suggests remdesivir**: 86% suggest remdesivir, 11% make no suggestion for or against remdesivir, and 3% suggest not using remdesivir
For hospitalised patients with COVID-19 pneumonia who are mechanically ventilated, the Task Force **suggests remdesivir**: 77% suggest remdesivir, 16% make no suggestion for or against remdesivir, and 7% suggest not using remdesivir
For hospitalised patients with COVID-19 pneumonia who require supplemental oxygen but are not mechanically ventilated, the Task Force **suggests dexamethasone**: 84% suggest dexamethasone, 13% make no suggestion for or against dexamethasone, and 3% suggest not using dexamethasone
For hospitalised patients with COVID-19 pneumonia who are mechanically ventilated, the Task Force **suggests dexamethasone**: 96% suggest dexamethasone, 1% make no suggestion for or against dexamethasone, and 3% suggest not using dexamethasone
For adults who were hospitalised with COVID-19 pneumonia and had confirmed venous thromboembolism, the Task Force **suggests therapeutic anticoagulant therapy for 3 months** to reduce the risk of recurrent venous thromboembolism: 95% favour therapeutic anticoagulant therapy for 3 months, 1% favour therapeutic anticoagulant therapy for >3 months, and 4% make no suggestion for either approach
For hospitalised patients with COVID-19 pneumonia who require supplemental oxygen but are not mechanically ventilated, the Task Force **suggests not using HCQ except within a clinical trial**: 3% suggest HCQ, 9% make no suggestion for or against HCQ, and 88% suggest not using HCQ
For hospitalised patients with COVID-19 pneumonia who are mechanically ventilated, the Task Force **suggests not using HCQ except within a clinical trial**: 0% suggest HCQ, 9% make no suggestion for or against HCQ, and 91% suggest not using HCQ

COVID-19: coronavirus disease 2019; HCQ: hydroxychloroquine. [#]: >70% agreement among Task Force members.

intervention. At least 70% agreement was necessary to make a consensus suggestion for or against an intervention. This threshold optimises the concordance of CORE-derived consensus suggestions with

TABLE 3 Summary of research priorities

The Task Force identified the following research needs for previously hospitalised patients with COVID-19 pneumonia who were discharged in the past 30–60 days
Routine testing to establish a new baseline? Pulmonary function testing 6-min walk test Computed tomography of the chest Transthoracic echocardiography Cardiopulmonary exercise testing
Continue prophylactic anticoagulant therapy as outpatients until the D-dimer normalises?
Serological testing to assess immune response to the infection?
Attending medical visits without screening for active infection if serological tests positive?
Serological testing of household contacts to determine if mild or asymptomatic infection?
Referral to a multidisciplinary clinic for post-intensive care syndrome?
Referral to pulmonary rehabilitation regardless of lung function?
Routine screening for: Cognitive impairment Depression Anxiety Post-traumatic stress disorder
Routine referral for mental health counselling?

COVID-19: coronavirus disease 2019.

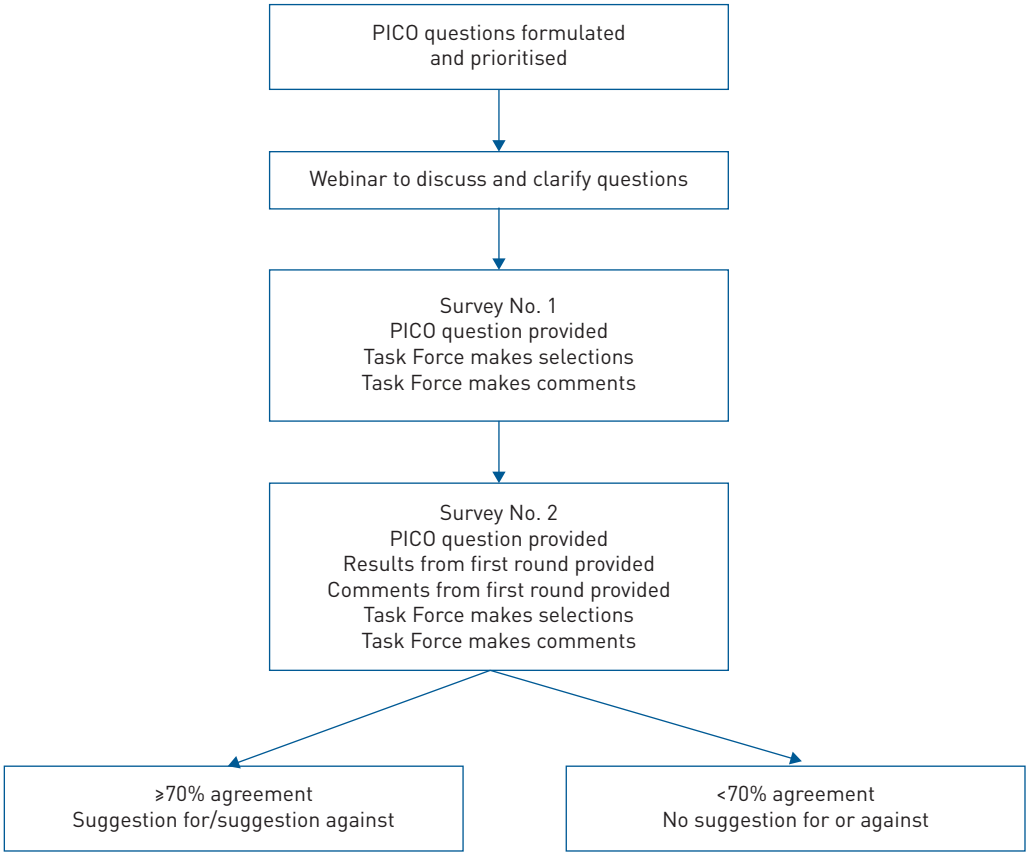


FIGURE 1 The Convergence of Opinion on Suggestions and Evidence process. PICO: Patient, Intervention, Comparator, Outcomes.

Institute of Medicine adherent guideline suggestions [4]. Following the tabulation of results, the manuscript was written and finalised after further iterative input from the Task Force.

Results

Invitations were sent to 112 clinicians. 99 (88%) clinicians representing 22 countries agreed to participate in the Task Force. The lone reason for declining was being too busy with clinical care responsibilities. Two individuals dropped out prior to this version of the guidance. Among the 97 remaining Task Force members, 77% were male, 38% were from the USA, 33% were from Europe, 18% were from Asia, 73% were respiratory physicians, 59% were critical care physicians, and 10% were infectious disease physicians. 71 (73%) out of the 97 remaining Task Force members completed the surveys.

Pharmacotherapy of acute COVID-19

1) **For hospitalised patients with COVID-19 pneumonia who require supplemental oxygen but are not mechanically ventilated or receiving extracorporeal membrane oxygenation (ECMO), the Task Force suggests remdesivir:** 86% suggest remdesivir, 11% make no suggestion for or against remdesivir, and 3% suggest not using remdesivir.
2) **For hospitalised patients with COVID-19 pneumonia who are mechanically ventilated or receiving ECMO, the Task Force suggests remdesivir:** 77% suggest remdesivir, 16% make no suggestion for or against remdesivir, and 7% suggest not using remdesivir.

The Task Force defined COVID-19 pneumonia as radiographic opacities or, if a chest radiograph has not been performed, an oxygen saturation measured by pulse oximetry ⩽94% accompanied by symptoms and signs of infection. Two randomised trials informed the Task Force.

The first was the Adaptive COVID-19 Treatment Trial (ACTT), a multi-centre, double-blind, placebo-controlled randomised trial of 1063 COVID-19 patients that released its results early after an interim analysis [6]. Those who received remdesivir had a shorter median (95% CI) time to recovery (11 (95% CI 9–12) days *versus* 15 (95% CI 13–19) days), a higher recovery rate ratio (1.32 (95% CI 1.12–1.55)), and a

trend toward lower mortality (8% *versus* 11.6%, HR 0.70 (95% CI 0.47–1.04), p=0.059) compared to placebo. There were potentially important subgroup differences. Among those requiring conventional supplemental oxygen, there was improvement in recovery (rate ratio 1.47 (95% CI 1.17–1.84)) and mortality (HR 0.22 (95% CI 0.08–0.58)). However, among those requiring high-flow supplemental oxygen or noninvasive ventilation, there were too few events to either confirm or exclude an effect on recovery (rate ratio 1.20 (95% CI 0.79–1.81)) or mortality (HR 1.12 (95% CI 0.53–2.38)). Similarly, among those requiring invasive mechanical ventilation or ECMO, there were too few events to either confirm or exclude an effect on recovery (rate ratio 0.95 (95% CI 0.64–1.42)) or mortality (HR 1.06 (95% CI 0.59–1.92)).

The second was a randomised, double-blind, placebo-controlled multi-centre trial of 236 COVID-19 patients from Wuhan, China [7]. Among all patients, there was no difference in mortality (14% *versus* 13%), time to clinical recovery (HR 1.23 (95% CI 0.87–1.75)), or adverse effects (66% *versus* 64%). However, in the subgroup of patients with <10 days of symptoms, there was a trend toward a shorter time to clinical recovery (HR 1.52 (95% CI 0.95–2.43)). The trial was stopped early due to difficulties in recruitment of new patients because the outbreak was controlled in Wuhan. Although remdesivir was generally well tolerated, a higher proportion of remdesivir recipients than placebo recipients had dosing prematurely stopped by the investigators due to adverse events (12% *versus* 5%) including respiratory failure and acute respiratory distress syndrome (ARDS).

The Task Force prioritised the larger ACTT trial and concluded that the benefits of remdesivir likely exceed its harms, burdens and cost in patients hospitalised with COVID-19 pneumonia, the population enrolled in the trial. Task Force members who considered the trial's subgroups in their decision making were troubled by the lack of benefit among the subgroup of patients who received high-flow supplemental oxygen or noninvasive ventilation, as well as the subgroup of patients who received invasive mechanical ventilation or ECMO, and therefore chose to make no suggestion for or against remdesivir in the more severely ill patients. This is the reason there was lower agreement in favour of remdesivir therapy among the more severely ill patients.

3) **For hospitalised patients with COVID-19 pneumonia who require supplemental oxygen but are not mechanically ventilated or receiving ECMO, the Task Force suggests not using HCQ except within a clinical trial:** 3% suggest HCQ, 9% make no suggestion for or against HCQ, and 88% suggest not using HCQ.
4) **For hospitalised patients with COVID-19 pneumonia who are mechanically ventilated or receiving ECMO, the Task Force suggests not using HCQ except within a clinical trial:** 0% suggest HCQ, 9% make no suggestion for or against HCQ, and 91% suggest not using HCQ.

In a prior version of the guidance, the Task Force noted that HCQ use was already widespread, so it made a weak suggestion in favour of the use of HCQ with appropriate patient consent, data collection, data analysis, and modification of clinical practice if indicated by the results of ongoing clinical studies [1]. The updated suggestions were informed by the results of large observational studies and the preliminary release of information from multiple randomised controlled trials.

Two large retrospective cohort studies from the New York City area (NY, USA), each with approximately 1500 patients, found no benefit on in-hospital mortality from HCQ [8, 9]. A large retrospective cohort study from Detroit (MI, USA) subsequently found a mortality benefit associated with HCQ use [10], although there is speculation that this finding may be a result of significant confounding because patients who received HCQ were more than twice as likely to be treated with corticosteroids than those who did not receive HCQ [11].

Multi-centre, randomised, placebo-controlled trials on HCQ are beginning to be completed. The ORCHID (Outcomes Related to COVID-19 treated with HCQ among In-patients with symptomatic Disease) trial was stopped early because interim data indicated that HCQ provided no additional benefit compared to placebo control for the treatment of COVID-19 in hospitalised patients [12], and the HCQ arm of the World Health Organization SOLIDARITY trial was stopped early due to a lack of benefit on mortality of hospitalised patients compared to standard care [13]. According to a pre-peer-review manuscript, the RECOVERY trial compared 1561 patients randomised to HCQ to 3155 patients randomised to standard care [14]. HCQ did not impact mortality (rate ratio 1.09 (95% CI 0.96–1.23), p=0.18) and showed no benefits in any other outcomes. There was no benefit in the subsets of patients requiring mechanical ventilation (rate ratio 1.03 (95% CI 0.81−1.30)) or supplemental oxygen (rate ratio 1.08 (95% CI 0.92−1.26)) at randomisation. The HCQ arm was therefore removed from the trial. Lack of efficacy has also been reported from a Brazilian trial of mild-to-moderate COVID-19 [15].

In light of the new evidence, the Task Force agreed that HCQ should not be used for patients with COVID-19 pneumonia unless in the context of clinical trials.

5) **For hospitalised patients with COVID-19 pneumonia who require supplemental oxygen but are not mechanically ventilated or receiving ECMO, the Task Force suggests dexamethasone:** 84% suggest dexamethasone, 13% make no suggestion for or against dexamethasone, and 3% suggest not using dexamethasone.
6) **For hospitalised patients with COVID-19 pneumonia who are mechanically ventilated or receiving ECMO, the Task Force suggests dexamethasone:** 96% suggest dexamethasone, 1% make no suggestion for or against dexamethasone, and 3% suggest not using dexamethasone.

The Task Force was informed primarily by the RECOVERY trial [16]. The RECOVERY trial was a multi-centre, open-label, randomised trial that randomly assigned hospitalised patients with COVID-19 to dexamethasone 6 mg daily for 10 days (n=2104) or standard care (n=4321). Patients who received dexamethasone had decreased 28-day mortality (22.9 *versus* 25.7%, HR 0.83 (95% CI 0.75–0.93)). Subgroup analyses showed that the mortality benefit was greatest among patients on mechanical ventilation or ECMO (29.3 *versus* 41.4%, rate ratio 0.64 (95% CI 0.51 to 0.81)), smaller among patients on supplemental oxygen (23.3 *versus* 26.2%, rate ratio 0.82 (95% CI 0.72 to 0.94)), and absent among patients not on supplemental oxygen (17.8 *versus* 14.0%, rate ratio 1.19 (95% CI 0.91 to 1.55)). Patients on high-flow supplemental oxygen or noninvasive ventilation were not analysed as a separate subgroup. A subsequent observational study reported that methylprednisolone was associated with more ventilator-free days and a higher probability of extubation in COVID-19 patients, but it did not find a mortality difference [17].

Given the importance of the mortality outcome and the widespread availability, cost-effectiveness, and clinical familiarity with dexamethasone, the Task Force overwhelmingly agreed that dexamethasone should be prescribed in the populations that showed decreased mortality in the RECOVERY trial. However, the Task Force also urged caution, particularly when administering to patients who require only a small amount of supplemental oxygen (may not benefit as much as those who are more severely ill), are aged >70 years and mechanically ventilated (few such patients were included in the RECOVERY trial), or are diabetic (poor glycaemic control is associated with increased mortality in diabetics with COVID-19 [18]).

Alternative glucocorticoids are a reasonable choice (40 mg of solumedrol daily is equivalent) if dexamethasone is not available. Use of early dexamethasone in patients with COVID-19 pneumonia to avoid progression to ARDS and mechanical ventilation needs to be demonstrated, and delayed resolution of viral shedding needs further study.

Follow-up of COVID-19 survivors: post-hospital testing

For adults who were hospitalised with COVID-19 pneumonia, the Task Force:

7) **Makes no suggestion for or against routine post-hospital pulmonary function testing (PFT) within 30–60 days to establish a new baseline:** 60% favour routine post-hospital PFT within 30–60 days, 34% make no suggestion for or against routine PFT, and 6% favour no routine PFT.
8) **Makes no suggestion for or against routine chest computed tomography (CT) within 30–60 days to establish a new baseline:** 38% favour routine chest CT within 30–60 days, 38% make no suggestion for or against routine chest CT, and 24% favour no routine chest CT.
9) **Makes no suggestion for or against routine transthoracic echocardiography (TTE) within 30–60 days to establish a new baseline:** 11% favour routine TTE within 30–60 days, 66% make no suggestion for or against routine TTE, and 24% favour no routine TTE.
10) **Makes no suggestion for or against routine cardiopulmonary exercise testing (CPET) within 30–60 days to establish a new baseline:** 7% favour routine CPET within 30–60 days, 66% make no suggestion for or against routine CPET, and 27% favour no routine CPET.

Early evidence suggests that some survivors of COVID-19 develop long-term respiratory sequelae. Abnormal lung function (*i.e.* reduced diffusion capacity, restrictive abnormalities, and small airways obstruction) has been identified within 2 weeks of discharge [19] and such abnormalities appear to be more common among patients whose acute COVID-19 was severe or who had high levels of inflammatory markers or abnormal coagulation, as reflected by D-dimer elevation [20]. Such lung function abnormalities are often accompanied by pulmonary fibrosis [20–23], which has been detected as early as 3 weeks after onset of symptoms regardless of whether the acute illness was mild, moderate or severe [24, 25]. Emerging data also suggests that cardiovascular complications (*i.e.* arrhythmia, acute cardiac injury and cardiomyopathy) are common among patients with COVID-19 [26–29] and some survivors develop

long-term cardiac sequelae; for example, structural and inflammatory changes in the heart have been found more than 2 months after recovery [30].

There was agreement among the Task Force that it would be useful to have pulmonary (PFTs and chest CT scans) and cardiac (TTE and CPET) measurements within 30–60 days after discharge to assess the severity of impairment and to establish a baseline from which to follow recovery over time. However, there was also concern about the practicality of obtaining these tests during the ongoing COVID-19 pandemic. Many institutions are struggling to overcome backlogs that developed when elective in-person clinical services were closed and several of the tests require extra precautions because they are aerosol generating (*i.e.* PFTs and CPET), which complicates the feasibility of testing (time, cost, staff, equipment, use of personal protective equipment) [31]. Recognition of this balance is reflected in the amount of agreement among the Task Force, as the number who favoured testing declined as the test became more expensive or burdensome. Ultimately, the Task Force concluded that in the absence of empirical evidence that routine testing improves outcomes equipoise should be maintained, and no suggestions were made for or against routine baseline testing. It is essential to note that the Task Force's decisions were strictly for routine baseline testing within 30–60 days. The results should not be extrapolated to testing patients with indications for such testing, such as new symptoms, worsening symptoms or persistent symptoms. For such patients, the need for testing should be determined on a case-by-case basis.

Follow-up of COVID-19 survivors: post-hospital anticoagulant management

11) **For adults who were hospitalised with COVID-19 pneumonia, the Task Force makes no suggestion for or against continuing prophylactic-dose anticoagulant therapy as outpatients until their D-dimer normalises to reduce the risk of venous thromboembolism:** 41% favour continuing prophylactic anticoagulant therapy until the D-dimer normalises, 49% make no suggestion for either approach, and 10% favour discontinuing prophylactic anticoagulant therapy on discharge.
12) **For adults who were hospitalised with COVID-19 pneumonia and had confirmed venous thromboembolism, the Task Force suggests therapeutic-dose anticoagulant therapy for 3 months to reduce the risk of recurrent venous thromboembolism:** 95% favour therapeutic anticoagulant therapy for 3 months, 4% make no suggestion for either approach, and 1% favour therapeutic anticoagulant therapy for >3 months.

COVID-19 patients frequently have abnormal markers of coagulation including elevated D-dimers, increased prothrombin time, and a low platelet count [32–37]. Observational studies demonstrate that increased D-dimer levels are associated with higher risk of intensive care unit (ICU) admission or death in COVID-19 patients [34, 35, 38, 39] and uncontrolled studies indicate poor outcomes among patients with severe coagulopathy [35, 38, 40]. As examples, a Chinese study of 191 patients found that an elevated D-dimer (>1.0 $\mu g \cdot mL^{-1}$) on admission was associated with increased mortality (OR 18.4 (95% CI 2.6–128.5)) [38] and a case–control study of 183 COVID-19 patients demonstrated that those who died had higher D-dimers, increased fibrin degradation products, longer prothrombin time, and longer activated partial thromboplastin time on admission compared to survivors [39]. In addition to abnormal markers of coagulation, post-mortem studies and lung biopsies from COVID-19 patients with ARDS demonstrate extensive pulmonary microvascular thrombi [41–43] and observational studies report a high prevalence of thromboembolic complications (*e.g.* pulmonary embolism) [32]. Thrombotic findings are the basis for anticoagulant therapy in COVID-19.

Prophylactic dose anticoagulant therapy

In hospitalised patients without COVID-19, extending thromboprophylaxis post-discharge reduces outpatient venous thromboembolism at a cost of more frequent severe bleeding [44, 45]. However, it is uncertain if these effects can be extrapolated to patients with COVID-19. In an uncontrolled study of 184 COVID-19 patients, all of whom received pharmacological thromboprophylaxis, the cumulative incidence of a composite outcome (symptomatic pulmonary embolism, deep-vein thrombosis, ischaemic stroke, myocardial infarction or systemic arterial embolism) was nearly 50%, with the majority (87%) of events being pulmonary embolism [46]. In a retrospective cohort study of 449 patients with severe COVID-19, there was no difference in 28-day mortality when heparin- and non-heparin-treated patients were compared [34]. Mortality was lower among heparin users in the subgroups of patients with a sepsis-induced coagulopathy score over four and patients with a D-dimer level more than six-times the upper limit of normal. Thus, to date, there is no definitive evidence that prophylactic-dose anticoagulant therapy benefits patients with COVID-19. A substantial number of clinical trials are in progress (ClinicalTrials.gov) and should provide definitive answers in the coming months.

Given the paucity of evidence in COVID-19 patients, nearly half of the Task Force was unwilling to make a recommendation for or against extended prophylactic-dose anticoagulation in patients with COVID-19,

highlighting the uncertainty about this issue and the need for empirical research. It is noteworthy that a sizeable minority (41%) of the Task Force was willing to use prophylactic-dose anticoagulation post-discharge until D-dimers normalised, indicating concern about the effectiveness of routine thromboprophylaxis and the importance of COVID-19-related thrombosis on long-term outcomes.

Therapeutic dose anticoagulant therapy

There is no empirical evidence regarding the optimal duration of treatment of venous thromboembolism in patients with COVID-19. Therefore, the Task Force's decision was informed by indirect evidence from patients without COVID-19, as summarised in clinical practice guidelines [47]. The Task Force concluded that COVID-19 should be considered a provoking factor and, therefore, COVID-19 patients with confirmed venous thromboembolism should be treated with therapeutic-dose anticoagulation for 3 months.

Follow-up of COVID-19 survivors: post-hospital infection control

13) For adults who were hospitalised with COVID-19 pneumonia, the Task Force makes no suggestion for or against routine post-hospital serological testing to assess their immune response to the infection: 31% favour routine serological testing, 57% make no suggestion for or against either approach, and 12% favour no routine serological testing.

14) For adults who were hospitalised with COVID-19 pneumonia, the Task Force makes no suggestion for or against allowing patients whose serological tests demonstrate antibodies against SARS-CoV-2 to attend in-person medical appointments without screening for active infection: 23% favour allowing the patient to attend without screening, 39% make no suggestion for or against either approach, and 38% favour requiring the usual screening for active infection.

15) For the household contacts of adults who were hospitalised with COVID-19 pneumonia, the Task Force makes no suggestion for or against routine serological testing to determine if they had mild or asymptomatic infection: 33% favour routine serological testing, 49% make no suggestion for or against routine serological testing, and 18% favour no routine serological testing.

The antibody response to SARS-CoV-2 in hospitalised patients with PCR-confirmed COVID-19 has not been fully characterised. Patients can develop antibodies to any of the following four major structural viral proteins: spike (S), nucleocapsid (N), matrix (M), and envelope (E). Antibodies to the S protein are considered neutralising antibodies since they can block the fusion of SARS-CoV-2 to the ACE-2 receptor on epithelial cells.

Data from a limited number of cohort studies of hospitalised patients with COVID-19 suggest that almost 100% of hospitalised patients will develop immunoglobulin (Ig)M and IgG antibodies by the tenth day of hospitalisation [48–53]. Several correlations have been observed: more severe disease is associated with higher antibody levels; more severe disease is associated with higher titres of neutralising antibodies and higher total antibody levels are associated with higher levels of neutralising antibodies. IgM seroconversion occurs earlier than IgG in most patients but, occasionally, it may occur at the same time or after IgG.

Further studies are necessary to define the duration of antibody responses, presence and duration of neutralising antibodies, tissue distribution of antibodies, and possible cross-reactivity with any of the four endemic human coronaviruses. Due to the current knowledge gaps, the Task Force concluded that current data on antibody testing is insufficient to guide clinical decision making, although the Task Force recognised that antibody testing may help in public health surveillance to define disease burden and in the identification of convalescent plasma donors.

Follow-up of COVID-19 survivors: post-hospital physical and mental rehabilitation

For adults who were hospitalised with COVID-19 pneumonia, the Task Force:

16) Makes no suggestion for or against routine referral to a dedicated multidisciplinary clinic specialising in post-intensive care syndrome (PICS): 44% favour routine referral, 49% make no suggestion for or against either approach, and 7% favour follow-up with primary care with as-needed specialty referral.

17) Makes no suggestion for or against routine referral to a dedicated pulmonary rehabilitation programme regardless of the presence or severity of lung function abnormalities: 17% favour routine referral regardless of lung function, 49% make no suggestion for or against either approach, and 34% favour referral based on lung function abnormalities.

18) Makes no suggestion for or against routine post-hospital screening for cognitive impairment within 30–60 days: 29% favour routine screening, 55% make no suggestion for or against routine screening, and 16% favour no routine screening.

19) Makes no suggestion for or against routine post-hospital screening for depression, anxiety, and post-traumatic stress disorder (PTSD) within 30–60 days: 69% favour routine screening, 24% make no suggestion for or against routine screening, and 7% favour no routine screening.

20) Makes no suggestion for or against routine post-hospital referral for mental health counselling within 30–60 days: 9% favour routine referral, 71% make no suggestion for or against routine referral, and 20% favour no routine referral.

Most evidence related to the recovery of hospitalised patients is derived from cohorts of ICU survivors. Physical, cognitive and mental health abnormalities are common among survivors and such deficits are collectively termed PICS [54–58]. Roughly 80% of COVID-19 survivors experience physical, cognitive or mental health impairments consistent with PICS after discharge [59–61]. PICS clinics have become part of post-ICU care in some parts of the world [62–64] but there is little empirical evidence about the outcomes of such clinics. Half of the Task Force declined to suggest for or against routine referral to a PICS clinic because, in the absence of empirical evidence of a benefit, they did not want to reduce equipoise that may be necessary across settings with variable resources. It is noteworthy, however, than among Task Force members who indicated a preference, routine referral to a PICS clinic was chosen six-times more often than follow-up with a primary care clinician with as-needed consultation of specialists.

Physical outcomes

Half of COVID-19 survivors report fatigue and >40% have persistent dyspnoea at 3 months [65]. Pulmonary rehabilitation provides exercise training and education to improve the physical and psychological condition of individuals with chronic respiratory diseases [66, 67]. While the strongest data exist for patients with COPD [68], pulmonary rehabilitation is also beneficial in other chronic respiratory conditions [69], including survivors of critical illness due to viral pneumonias [70–72]. Early experience with pulmonary rehabilitation in COVID-19 survivors from China indicates that a 6-week pulmonary rehabilitation programme can improve pulmonary function, quality of life measures and anxiety [73], although additional research is needed [73–76].

Half of the Task Force declined to suggest for or against referral of all COVID-19 survivors to pulmonary rehabilitation because, in the absence of empirical evidence of a benefit, they did not want to reduce the equipoise that may be necessary across settings with variable resources. Among the remaining half of the Task Force who suggested pulmonary rehabilitation, two-thirds thought that referral should be based upon lung function abnormalities and one-third thought that referral should occur regardless of the presence or severity of lung function abnormalities.

Cognitive outcomes

No studies have reported the prevalence of cognitive impairment among survivors of COVID-19, so extrapolation from other severe illnesses is necessary. Cognitive impairment comparable to mild Alzheimer's dementia has been estimated to occur in 25% of survivors of critical illness [77] and may be associated with prolonged delirium [78, 79], severe hypoxaemia [78–81], early neurological manifestations [82], and duration of sedative-analgesia administration [80, 83]. COVID-19 patients have risk factors for cognitive deficits [84], but there is no empirical evidence that cognitive deficits are as frequent among COVID-19 survivors or that interventions can improve cognitive outcomes [85, 86]. Therefore, the Task Force was unwilling to suggest for or against routine screening for cognitive deficits 30–60 days after discharge.

Mental health outcomes

Mental health experts have warned that PTSD could become the "second tsunami of the SARS-CoV-2 pandemic" [87] affecting the survivors of acute illness and their families, as well as the population at large living under prolonged conditions of heightened anxiety and isolation [88]. There is little data on the epidemiology of mood disorders in COVID-19 patients, but small single-centre studies report symptoms of depression and anxiety in over one-third of COVID-19 patients [89], consistent with findings in survivors of other serious illnesses [89, 90].

Despite limited empirical evidence, the Task Force fell just one vote shy of making a consensus suggestion for routine screening for depression, anxiety and PTSD, reflecting the long-established acceptability of screening for mental health conditions as established by the US Preventative Services Task Force [91]. Any mental health screening programme is most beneficial when directly linked to systems for follow-up and

treatment of patients who screen positive [91]. The Task Force did not agree with routine referral for mental health counselling, reflecting the Task Force's preference to focus mental health counselling resources on those who screen positive, unless empirical evidence of a benefit from routine referral is established.

Conclusions

The International Task Force used a Delphi-like process called the CORE process to address clinical questions related to pharmacotherapy of acute COVID-19 pneumonia and the outpatient follow-up of COVID-19 survivors. The former was informed by accumulating empirical evidence, whereas the latter was informed by clinical rationale because no empirical evidence exists. There are two main goals of consensus suggestions. The first is to standardise care, thereby improving outcomes by eliminating dangerous outlying practices and facilitating research by defining usual care (table 2). The second is to identify key areas where equipoise (uncertainty) exists and research is needed (table 3).

A suggestion for an intervention conveys the Task Force's belief that the benefits exceed the harms and, therefore, the intervention should be used. The Task Force made consensus suggestions for remdesivir and dexamethasone in patients with acute COVID-19 pneumonia who require any type of oxygen support: *i.e.* conventional supplemental oxygen, high flow supplemental oxygen, noninvasive ventilation, invasive mechanical ventilation, or ECMO. It is noteworthy that there was more agreement for remdesivir in less severely ill patients (*i.e.* conventional supplemental oxygen) than more severely ill patients (*i.e.* invasive mechanical ventilation or ECMO) and, conversely, there was more agreement for dexamethasone in more severely ill patients than less severely ill patients, reflecting the trends in beneficial outcomes across subgroups in the clinical trials and some Task Force members' willingness to incorporate the subgroup analyses into their clinical decisions. The Task Force also suggested therapeutic anticoagulant therapy for 3 months in COVID-19 patients with venous thromboembolism, rather than a longer duration.

In contrast, a suggestion against an intervention indicates that the intervention should not be used unless in the context of a clinical trial. The Task Force suggested against HCQ on the basis of accumulating empirical evidence that HCQ confers no benefit in the populations considered by the Task Force. For all other questions there was insufficient agreement to make a consensus suggestion, reflecting scarcity of empirical evidence and the Task Force's view that in the absence of empirical evidence of benefit, equipoise should be maintained.

The primary strength of the guidance is the derivation of suggestions using a process that has been shown to create suggestions that are usually concordant with guideline suggestions created using Institute of Medicine adherent methodology [4, 5]. In addition, the large, multi-disciplinary International Task Force was composed of clinicians from countries with a high prevalence of COVID-19, providing a volume of non-systematic clinical observations greater than most uncontrolled studies. This is particularly important because, in the absence of empirical evidence, judgments must be informed by non-systematic observations. Finally, the time from finalising the questions to completing the suggestions was <14 days; therefore, the suggestions are relatively up to date despite the rapid emergence of new evidence during the pandemic.

The primary weakness of the guidance is that evidence is being generated and published so quickly that guidance can become outdated in the short duration between completion and publication. Another limitation is the lack of a formal evidence synthesis to inform the Task Force's suggestions, although it is unlikely that the Task Force was unaware of major relevant randomised trials or large controlled observational studies because the body of evidence is still quite small given the short duration since the onset of the COVID-19 pandemic. Finally, the CORE process is a relatively new process that has been validated by a single group of investigators using ATS clinical practice guidelines; thus, its generalisability to other groups and non-respiratory topics is uncertain.

It is noteworthy that the International Task Force made no suggestion for or against routine referral for pulmonary rehabilitation, pulmonary function testing, or mental health testing within 30–60 days after discharge despite an ERS/ATS Task Force on pulmonary rehabilitation making suggestions in favour of these actions within 6–8 weeks in a recently published report that used similar methods [92]. In studies that validated the CORE process, the rare discordant recommendations were typically attributable to different panels with varying interpretations of scarce or low quality evidence [4, 5]. This is probably the reason for the different suggestions from our International Task Force and the ERS/ATS Task Force on pulmonary rehabilitation. Specifically, the ERS/ATS Task Force on pulmonary rehabilitation was composed of pulmonary rehabilitation experts who were probably more confident that these actions confer beneficial effects and, therefore, more willing to suggest the actions despite minimal evidence. In contrast, our International Task Force was more circumspect, conveying a preference to make no recommendation for or against the actions and to maintain equipoise until empirical evidence is published given the resources necessary to implement the suggestions. Importantly, the two groups do not recommend opposite or

different courses of action; rather, one group was willing to suggest a course of action now, whereas the other group decided to withhold its endorsement pending more evidence. These differences highlight the need to reconsider all suggestions as new evidence accumulates.

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