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COVID-19: Interim Guidance on Management Pending Empirical Evidence. From an American Thoracic Society-led International Task Force

Announcer:
Welcome to CME on ReachMD. This activity entitled “COVID-19: Interim Guidance on Management Pending Empirical Evidence” is provided by the American Thoracic Society. Prior to beginning the activity, please review the faculty information and learning objectives.

Dr. Wilson:
My name is Kevin Wilson. I’m Professor of Medicine at Boston University School of Medicine, as well as the American Thoracic Society Chief of Guidelines and Documents. The American Thoracic Society convened an international task force to develop interim guidance on management pending empirical guidance for the disease COVID-19.

COVID-19 is a disease that is caused by the coronavirus SARS-CoVirus-2. It’s a global pandemic right now with cases that are increasing rapidly worldwide. Management approaches to COVID-19 vary, and this reflects a scarcity of evidence that exists to guide clinicians. Management ranges from supportive care alone to off-label or compassionate use of investigational drugs. The goal of our project was to provide interim guidance while awaiting better empirical evidence. The interim guidance was based on a combination of the scarce direct evidence that exists, indirect evidence, and clinical observation. It was our feeling that by standardizing care and by providing consensus guidance, we can improve the quality of care and facilitate research.

We convened an international task forces composed of clinicians from institutions that are in the front line of COVID care. Task force consisted of 80 individuals from multiple countries, and I was particularly pleased to be joined by my coauthors, Sanjay Chotirmall, Chunxue Bai, and Jordi Rello. The task force consisted mostly of infectious disease doctors, as well as intensive care doctors and a select few others. We employed an electronic consensus building tool to measure agreement amongst the task force. When agreement exceeded 70 percent, this exceeded our threshold to make a formal consensus suggestion.

First issue addressed by the task force was the importance of generating evidence. The task force recognized that evidence is desperately needed, and little exists at this time. The task force also agreed that randomized trials are the optimal way of generating evidence. However, the task force recognized that, realistically, investigational interventions are being used all the time at the bedside, and they represent an important opportunity to learn while treating and while awaiting those randomized trial results. Therefore, the task force made a strong recommendation that data be collected in a way that controls confounding and enables causal inferences for any patient who is undergoing an investigational therapy. Patients who receive an intervention should then be compared with those who have not received the intervention, and then management should be adjusted accordingly.

The second question that was addressed by the task force had to do with the prescription of hydroxychloroquine or chloroquine. In this presentation, I am going to refer to hydroxychloroquine exclusively, and everything I say applies to chloroquine as well. The task force did not reach a sufficient agreement to make a suggestion either for or against the use of hydroxychloroquine in outpatients with COVID-19 or in inpatients with COVID-19 but without pneumonia. In contrast, the task force reached 73 percent agreement, or was able to make a consensus suggestion, to use hydroxychloroquine for inpatients who had evidence of pneumonia.

What we found is that the task force was divided into two camps, and this is common whenever you're asking a question that is only informed by very low-quality evidence. One camp – we should wait for randomized trials, or you might treat patients with an ineffective and potentially harmful therapy, thereby depleting supplies. The other group said, 'Well, wait a minute. COVID-19's potentially lethal, so if there's a therapy that might be helpful and it's unlikely to be harmful, it should be tried.' As the acuity and the severity of the illness increased, more clinicians moved from the former camp to the latter camp. In other words, more clinicians who were initially willing to wait for clinical trial evidence before deciding whether to treat were willing to treat based on scarce data as the disease became more acute or more severe.

In order to reach a full consensus, though to suggest hydroxychloroquine, certain conditions had to be met as agreed upon by the task force.

First, shared decision-making should be necessary. What that means is that the clinician should inform the patient of the potential benefits as well as the potential harm and let them know that this is investigational.

Second, data should be collected for observational study.

Third, the condition should be sufficiently severe to warrant the investigational therapy.

Fourth, the drug should not be in short supply, and finally, the clinician should monitor their patients closely for adverse side effects and maintain a low threshold to discontinue the medication should the side effects appear.

The second agent that was addressed by the task force was the agent remdesivir. The task force was not asked about the use of remdesivir in outpatients or in inpatients without pneumonia. Instead, the task force focused on whether or not remdesivir should be used in inpatients with evidence of pneumonia. The task force agreed 68 percent that remdesivir should be prescribed, but this fell just short of the 70 percent threshold that was necessary to make a formal consensus suggestion. Therefore, the task force made no suggestion either for or against remdesivir.

Most of the participants on the task force felt similarly about remdesivir as they did about hydroxychloroquine. However, the hydroxychloroquine had achieved a slightly greater amount of agreement because participants were more familiar with the drug. The drug had been in existence for multiple decades, its side effect profile was well known, and the participants were comfortable with it. In contrast, remdesivir is a new investigational drugs with not as well-known of a side effect profile.

The task force addressed other pharmaceutical therapies as well. The first was lopinavir and ritonavir in combination. The task force was unable to achieve sufficient agreement to make a suggestion either for or against lopinavir. The task force uncertainty was largely based upon a recent randomized trial of lopinavir-ritonavir in COVID-19, which found effects that would have been meaningful if real, but the study was too small. In other words, the confidence intervals were too wide to either confirm or exclude the effects. The task force felt strongly, though, that additional research was warranted.

The next agent that was addressed by the task force was tocilizumab. The reason for looking at this is that patients with COVID-19 have increased IL-6 levels, and tocilizumab is known to be effective in other IL-6-mediated diseases. In this case, however, there is insufficient agreement to make a suggestion either for or against the agent. The task force's uncertainty was largely based upon its conclusion that because the agent is effective in some IL-6-mediated diseases does not necessarily mean it should be extrapolated to COVID-19 just because it is also an IL-6-mediated disease, but the task force agreed again that additional research was warranted.

The task force addressed the use of systemic steroids for the specific treatment of COVID-19. This was not meant to address whether or not systemic steroids should be used in comorbid conditions amongst patients with COVID-19. The reason for the investigation was because COVID-19 patients have known increased proinflammatory cytokines and biomarkers, which would seem to favor steroids, but there have been steroids in other viral infections to suggest that steroids may increase viral replication and shedding, which would argue against it. Sixty-eight percent of the task force agreed that systemic steroids should not be used for the specific treatment of COVID-19. This was just short of the enough agreement to make a consensus suggestion against systemic steroids. Therefore, there is no suggestion for or against systemic steroids. The task force did want to emphasize, however, that this was specifically intended to be about use of systemic steroids in the treatment of COVID-19 and not for comorbid conditions, including ARDS.

The task force then moved away from pharmaceutical agents and looked at various techniques that may be used in critically ill patients. The first one that was addressed was prone ventilation. They asked about whether prone ventilation should be used for patients with COVID-19 who have refractory hypoxemia due to progressive pneumonia or ARDS. Other clinical practice guidelines have looked at prone ventilation for ARDS due to other causes other than COVID-19 and recommended it. The task force almost unanimously agreed that prone ventilation should be used. There was 90 percent agreement, which was sufficient for a consensus suggestion to try prone ventilation in patients with refractory hypoxemia due to progressive COVID-19 pneumonia. The suggestion was based on an

assumption that ARDS from other causes is similar to ARDS in COVID-19. Since that time, there has been data coming out that suggests that ARDS may be different in COVID-19 compared to other causes of ARDS. Nonetheless, the task force thought it was worth trying because there does seem to be at least moderate benefits even in such patients. It is also low risk and is low cost.

The final intervention that the task force looked at was ECMO, extracorporeal membrane oxygenation, again for patients with refractory hypoxemia due to progressive COVID-19 pneumonia and specifically those who tried and failed prone ventilation. The task force agreed 75 percent, which was good enough for a consensus suggestion, to try ECMO, and it should be tried in patients with refractory hypoxemia due to progressive COVID-19 pneumonia. The task force emphasized, however, that it recognized that it may not be feasible in a pandemic because ECMO is resource-intensive. It also poses particular challenges in terms of infection control, and a lot of blood products can be needed at a time when blood product supply is quite scarce.

There were several limitations to the task force's work. One, there may have been selection bias amongst the participants. Specifically, most of the participants had some sort of relationship, either direct or indirect, with the American Thoracic Society. Among the participants in the task force, there was variable experience. Some were on the front lines taking care of one patient at a time day-in/day-out. Others were thought leaders in the area of a pandemic and viral infection. The task force did not address one of the most important questions right now, which is the combination of hydroxychloroquine or azithromycin, but the task force hopes to address that in the future iteration of its work. Finally, the data was not collected in a way that allowed us to compare the answers amongst participants. For example, we could not compare whether or not the responses were different from North Americans compared to Europeans. We also could not assess whether or not the responses were different from senior people compared to junior participants, and so on.

So, in conclusion, the task force reached consensus suggestion to recommend hydroxychloroquine in patients with COVID-19 pneumonia who are hospitalized, with the condition that the shared decision-making should take place, that data should be collected for research, that the condition should be sufficiently severe to warrant investigational therapy, that the drug is not in short supply, and that the patient be monitored for adverse effects. In addition, the task force made consensus suggestions to try prone ventilation in patients with refractory hypoxemia due to progressive COVID pneumonia or ARDS as well as to consider ECMO on a case-by-case basis for patients with refractory hypoxemia and progressive COVID pneumonia due to ARDS who fail prone ventilation. So, the task force is hopeful to address additional questions with future iterations of this interim guidance in the near future.

We welcome additional questions that healthcare public may have so that we ensure that we're addressing questions that are important to potential readers. In addition, the task force plans to continue to review the suggestions within this document, and we'll revisit them or update them as necessary as new evidence becomes available. This document will remain open access on the American Thoracic Society website and is thus considered a living document because we will be updating it as we go along. Thank you for your time.

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