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EDITORIAL COMMENTARY

# Making Sense of Contradictory Evidence in Coronavirus Disease 2019 Trials

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> "The test of a first-rate intelligence is the ability to hold two opposed ideas in the mind at the same time, and still retain the ability to function."
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> — F. Scott Fitzgerald, "The Crack-Up," February 1936

The coronavirus disease 2019 (COVID-19) pandemic is the defining event of our professional lives. Our standards of medical evidence have come into question, as clinicians have grasped at anything to help us make decisions regarding the care of the patients in front of us right now. Although the quality of our data has improved since those first desperate months, we continue to struggle with the interpretation of the growing mass of research.

In the United States, 3 major panels have released treatment guidelines for COVID-19. The first, the Surviving Sepsis Campaign, released its interim guidance in March 2020, focusing on core critical care interventions such as ventilatory support and hemodynamics [1]. The National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) have produced guidelines that differ in some areas of emphasis but are in agreement in most areas of overlap, such as recommending glucocorticoids and remdesivir for the treatment of severe disease [2, 3]. The World Health Organization (WHO) has produced its own living guideline document, which differs from the IDSA and NIH recommendations in some key areas [4]. Significant among these is a recommendation against the use of remdesivir.

The NIH-sponsored Adaptive COVID-19 Treatment Trial (ACTT) is an ongoing, multicenter, international trial of COVID-19 therapeutics. The first iteration of ACTT, known as ACTT-1, randomized hospitalized patients with COVID-19 to receive remdesivir vs placebo for up to 10 days, with time to recovery as the primary endpoint [5]. After monitoring 1063 participants for 28 days after enrollment, ACTT-1 reported a reduction in the time to recovery with the use of remdesivir, from 15 days with placebo to 10 days with remdesivir. Mortality was lower with remdesivir in ACTT-1 but did not meet statistical significance. This benefit of remdesivir was most marked in patients with hypoxemia requiring only low-flow supplemental oxygen (<15 L/minute), whereas patients requiring mechanical ventilation did not show any meaningful improvement.

The results of ACTT-1 led to the incorporation of remdesivir into the IDSA and NIH guidelines. More recently, however, the WHO-sponsored Solidarity trial appeared to refute these results. Solidarity was an open-label, pragmatic trial of 11 300 adults hospitalized with COVID-19 in 405 hospitals and in 30 countries, without double-blinding or placebo controls [6]. Participants were randomized to receive remdesivir, hydroxychloroquine, interferon-β1a, co-formulated lopinavir-ritonavir, interferon in combination with lopinavir-ritonavir, or the local standard of care as a control. The primary endpoint was in-hospital mortality, with initiation of mechanical ventilation and duration of hospitalization as secondary endpoints. At the conclusion of the study, death occurred in 301 of 2743 (12.5%) patients receiving remdesivir and in 303 of 2708 (12.7%) control patients. Contrary to the results of ACTT-1, patients receiving remdesivir were more likely to still be in the hospital on day 7 (69%) than control patients (59%).

There is controversy about the interpretation of ACTT-1 vs Solidarity, and concurrently as to the accuracy of the IDSA and NIH guidelines vs the WHO guidelines. I suggest that we should consider not whether one trial or one guideline is "false" but rather how they all may be true. The answer lies in the different information obtained from homogeneous vs heterogeneous settings, as well

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as what we may learn from blinded randomized controlled trials (RCTs) vs large pragmatic trials.

We should not be surprised by divergent results in trials performed in different locations. Studies of interventions in critical illness have overwhelmingly been negative when mortality is used as a primary endpoint; a 2015 meta-analysis by Landoni and colleagues identified only 7 specific therapies proven to decrease mortality in the intensive care unit [7]. Similarly, widely accepted treatments in industrialized countries, such as fluid bolus administration in septic shock, may be harmful when studied in resource-limited settings [8, 9]. In this light, it is not surprising that the results of ACTT-1 (conducted in wealthy countries with well-resourced hospitals) differ from those of Solidarity, where low- and middle-income countries predominated.

The Solidarity investigators should be commended for conducting a large trial under difficult circumstances, but limitations with trial design are not overcome by the brute force of sample size. For example, Solidarity is an open-label trial. Blinding might have little impact on mortality as a hard endpoint, but its impact on hospitalization is greater. Patients in Solidarity randomized to remdesivir often stayed in the hospital to receive a full 10 days of therapy, whereas patients in ACTT-1 were typically discharged as soon as able. In addition to obscuring the beneficial effect of remdesivir reported in ACTT-1, these extended hospitalizations of patients in Solidarity may have exposed them to increased risks of infection, thrombosis, and other complications. Unfortunately, the limited initial data hamper our ability to understand these differences.

Resource availability plays a large role in outcomes. Given the wide variations in routine care across Solidarity's participating sites, and the limited accompanying data about those standards, it is difficult to assess the importance of a single drug like remdesivir. ACTT-1, on the other hand, occurred in relatively homogeneous clinical settings, with a consistent standard of care across most sites.

Over the course of 2020, the trend in the care of patients with COVID-19 has been to reinforce the value of core principles in intensive care and hospital medicine. Hospital mortality for serious infections has improved significantly over the past 20 years in the United States [10]. This improvement is not the result of one large intervention but rather due to dozens of incremental improvements. Early in the pandemic, there was an argument that the respiratory failure seen in COVID-19 was not "true" acute respiratory distress syndrome but rather a different entity requiring different ventilator strategies [11]; similarly, the high incidence of thrombosis in COVID-19 led to suggestions that full anticoagulation should be considered in all patients with respiratory failure [12]. Although unanswered questions remain, COVID-19 guidelines now recommend standard low tidal volume ventilation and conventional thromboprophylaxis in most patients. If we are unsure about the provision of routine care in Solidarity, it is difficult to state that remdesivir has no effect.

The double-blinded, placebo-controlled RCT remains the gold standard of clinical research for a reason. The Solidarity trial does not meet this standard, but it does answer another important question: Is remdesivir is the best tool for the job across diverse settings? In well-resourced centers like those of ACTT-1, patients and health systems can benefit from a shortened recovery time, where surging COVID-19 cases are leading to bed and staff shortages. Conversely, the opportunity cost of remdesivir simply may not be worth it in a resource-limited setting, where core therapies such as ventilators, thromboprophylaxis, and nursing care at optimum patient ratios may be in short supply. In these settings, the many superb clinicians caring for patients with COVID-19 may decide that finite resources are better spent on other proven treatments and not used for a single expensive drug.

Science is not a football game with a winner and a loser. Solidarity and ACTT-1 are both significant contributions to our understanding of COVID-19, conducted by reputable and ethical investigators. We do our patients no favors when we choose sides over their results. If we can understand the reasons for these differences, though, then they can inform the next study to further advance our care. Only together can we overcome the challenge and the tragedy of COVID-19.

## Notes

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