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EDITORIAL

Selecting Treatments During an Infectious Disease Pandemic: Chasing the Evidence

How do clinicians assess and incorporate information on treating a potentially fatal new disease? The COVID-19 pandemic brought this question into focus as rapidly emerging evidence informed decisions on implementing and deimplementing treatments. Traditionally, peer-reviewed, published, randomized clinical trials define the standard of care for treatment. In the setting of COVID-19, a more rapid response evolved: Available drugs were repurposed for treatment on the basis of in vitro data, anecdotal reports, case series, and retrospective observational studies because of desperation to "do something." This was fueled by colleagues, patients and their families, the popular press, and social media and led to a cacophony of treatment approaches.

An extreme example occurred early in the pandemic (1): The results of a small uncontrolled study of hydroxychloroquine plus azithromycin were initially disseminated on YouTube on 17 March 2020 and then electronically published in the *International Journal of Antimicrobial Agents* on 20 March 2020 (2). On 21 March 2020, a U.S. political leader tweeted that this drug combination has "a real chance to be one of the biggest game changers in the history of medicine." On 3 April 2020, the journal posted a statement of concern about the study's methodology, noting that although "it is important to help the scientific community by publishing new data fast, this cannot be at the cost of reducing scientific scrutiny and best practices" (3). Ultimately, published randomized clinical trials failed to demonstrate benefit. Of note, several subsequent studies that received considerable attention—published in peer-reviewed journals (4, 5) or as non–peer-reviewed preprints, the latter advocated by some funding agencies and journals for more rapid data dissemination—were retracted because of concerns about data quality or integrity, in a trend that continues (6).

To help bring order to this chaos, within a few months of the first confirmed U.S. case of COVID-19 the National Institutes of Health (7, 8) and some professional societies expeditiously developed online guidelines that could be rapidly updated on the basis of emerging evidence. Over time, the quality of data behind many recommendations changed from "expert opinion" to observational, retrospective data and ultimately to randomized controlled clinical trials.

How have clinicians treated COVID-19 in this rapidly changing landscape? Mehta and colleagues (9) address this by describing temporal trends in the use of 3 drugs for the treatment of COVID-19 in U.S. patients hospitalized over a 13-month period beginning in February 2020. They studied 137 870 adults in the National COVID Cohort Collaborative (N3C), a retrospective cohort constructed from electronic health record data at 43 health centers. They focused on 3 drugs: hydroxychloroquine, remdesivir, and dexamethasone. Hydroxychloroquine was available because it had approval from the U.S. Food and Drug Administration (FDA) for other indications. It demonstrated in vitro activity against SARS-CoV-2, prompting emergency use authorization (EUA) status by the FDA, but it was ultimately found to be ineffective and the emergency use authorization was revoked. Remdesivir, an antiviral agent, improved time to recovery but not survival in randomized clinical trials of hospitalized patients with COVID-19, supporting FDA approval, and these data led to conflicting guideline recommendations. Dexamethasone demonstrated a mortality benefit in hospitalized patients with COVID-19 who required oxygen, particularly those receiving mechanical ventilation. The authors found a rapid increase in hydroxychloroquine use with a reassuringly rapid decline over weeks as evidence emerged of its lack of efficacy. Use of remdesivir and subsequently dexamethasone increased in association with emerging efficacy data and guideline recommendations from the National Institutes of Health. Of note, the authors found considerable variation in use of the 3 drugs across health centers; variation was greatest with remdesivir, and dexamethasone use differed significantly, especially among patients receiving mechanical ventilation.

The authors emphasize their key finding that approximately one fifth of mechanically ventilated patients did not receive corticosteroids despite release of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial results in June 2020 that showed a survival benefit in this subgroup. Their data, however, show a remarkably rapid uptake of corticosteroid therapy within a month of the press release from the RECOVERY trial (16 June 2020) and the strong recommendation for use in the COVID-19 treatment guidelines from the National Institutes of Health (25 June 20). The reasons for the plateau in dexamethasone use at approximately 80% of ventilated patients and the variability across centers are unknown. The adoption of corticosteroid use may have been complicated by lack of definitive efficacy data in related infections (such as SARS and Middle East respiratory syndrome); data from other viral respiratory illnesses showing harm; initial guidelines advising against their use; and concerns about the potential for increased viral replication, immunosuppression, and adverse effects (including hyperglycemia). Furthermore, the generalizability of RECOVERY was questioned given a higher mortality rate in the control group than in the United States overall. Of note, the combination of remdesivir and dexamethasone was used commonly with scant available clinical data and only an "expert opinion" recommendation in guidelines.

Strengths of Mehta and colleagues' study include the large sample size, the diverse patient population, and the geographic diversity of the centers that contributed data. These features enabled the authors to characterize interhospital variation in use of the drugs and to superimpose trends in use on the timeline of emerging data. They had few exclusions (<4%) due to data quality issues.

The authors acknowledge several important limitations of their study, such as the inclusion of predominantly

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academic medical centers. They do not provide specific information on the types of hospitals included but note that their findings may not generalize to community-based hospitals, at which most care in the United States is provided. Although exploration of potential causes of variability across hospitals would be of interest, they did not analyze hospital-level factors and presumably could not address patient-level factors. In this regard, they also acknowledge their lack of patient- level data, such as oxygen use (aside from mechanical ventilation), which limited their analysis of the appropriateness of corticosteroid use to the subset of patients who were ventilated.

Mehta and colleagues clearly showed how rapidly clinicians can navigate a cacophony of data and incorporate important and meaningful results of clinical research into practice during an infectious disease pandemic. Clinicians adopted a drug with a mortality benefit (dexamethasone), abandoned a drug with no benefit and the potential for harm (hydroxychloroquine), and recognized the nuances of a third drug (remdesivir) that had FDA approval based on decreased clinical progression but lacked a demonstrated mortality benefit. There have been and will continue to be refinements in the clinical care of COVID-19 based on new evidence that emerges from other carefully conducted trials, including global platform trials. Real-time updates of online treatment guidelines and recent innovations, such as living systematic reviews (10), will help clinicians keep pace with emerging data and continue to improve clinical outcomes. Lessons learned from COVID-19 will improve how we assess and disseminate emerging data, leading to efficient implementation (or deimplementation) of evidence-based treatments.

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