Annals of Internal Medicine

Misinterpretation of Clinical Research Findings and COVID-19 Mortality

Arturo Casadevall, MD, PhD; and Liise-anne Pirofski, MD

The first 3 years of the COVID-19 pandemic witnessed an unprecedented pace of research that delivered vaccines, antiviral agents, and anti-inflammatory therapies that dramatically lessened the morbidity and mortality of COVID-19. However, some research findings led to clinical practice recommendations that were later associated with excess mortality.

Early in the pandemic, when no proven therapies were available, there were reports that the antimalarial drug hydroxychloroquine had antiviral effects. This prompted a flurry of research to determine whether it could be repurposed for COVID-19 and led to the U.S. Food and Drug Administration (FDA) authorizing its use (1). These studies had many flaws, including not providing sufficient information to evaluate efficacy. One was later retracted (1). Nonetheless, hydroxychloroquine continued to be used despite many well-done studies showing that it was not only ineffective but associated with increased mortality (2) and despite its authorization being revoked by the FDA.

Although corticosteroids reduced mortality in critically ill patients with COVID-19 in a large randomized controlled trial (RCT) (3), rather than being broadly beneficial, their effect was limited to patients who required oxygen. Importantly, this limitation was biologically plausible because corticosteroids reduce inflammation and severe COVID-19 is caused by immune-mediated damage. However, the drug was then used in many hospitalized patients who were in an earlier phase of the disease, in whom a benefit had not been established. This led to massive overuse and worse outcomes, including increased mortality in patients who were not critically ill (4). Such use in non–critically ill patients was associated with a detrimental outcome in a meta-analysis (5) and ran counter to recommendations.

Failure to incorporate known principles of antibody therapy into the design of COVID-19 therapy trials also had a detrimental effect (6). The FDA authorized COVID-19 convalescent plasma (CCP) for hospitalized patients with COVID-19 in August 2020, based on both biological plausibility and evidence from a large observational study (7). By the fall of 2020, an estimated 30% to 40% of all hospitalized patients in the United States had received CCP. An epidemiologic analysis found that CCP use and mortality were inversely correlated and estimated that CCP may have saved about 100 000 lives (7). However, in early 2021, RCTs from the United Kingdom, Italy, and Canada that mainly evaluated CCP in severely ill hypoxic patients who were hospitalized reported that CCP did not reduce mortality (6). Despite FDA authorization for certain patients, this prompted guideline committees to recommend against CCP, and its use decreased. A temporal trend analysis found that reduced CCP use in the winter of 2020–2021 was associated with 30 000 excess deaths (7). Two years later, an analysis of aggregated RCT evidence from more than 3 dozen trials suggested that CCP significantly reduced mortality in hospitalized patients who were treated with high-titer plasma early in the disease course (8).

Today, hydroxychloroquine is no longer used, corticosteroids are primarily used in critically ill patients, and CCP has found a niche for treatment of immunocompromised patients (9). Although different factors resulted in the misuse of each agent for COVID-19, reconciling biological plausibility with the results of clinical studies might have prevented errors that led to detrimental outcomes. For hydroxychloroquine, the assumption that an antimalarial drug could be an effective antiviral was initially based on its antiviral activity in vitro. However, observational and randomized trials in patients with COVID-19 did not demonstrate efficacy (1), highlighting that in vitro biological plausibility must be validated in vivo. For corticosteroids, their efficacy in critically ill patients in a study that also included non–critically ill patients in whom they were not effective led to widespread use despite the knowledge that immunosuppressive therapy impairs antiviral immunity. The immunosuppressive effect of corticosteroids is a basic tenet of their mechanism of action.

For CCP, recommendations against its use were based on negative results from trials that, like studies of corticosteroids, were largely conducted in hospitalized patients in whom it was unlikely to be effective, such as those who required oxygen supplementation. This is consistent with prior use of antibody therapies that were generally only effective soon after disease onset—a premise that was validated in a meta-analysis of outpatient COVID-19 RCTs (10). With regard to biological plausibility, CCP efficacy in early COVID-19 is consistent with its antiviral activity, and its inefficacy in the later inflammatory phase is consistent with the likelihood that specific antibody cannot reverse established pulmonary inflammation. Discarding CCP despite its established antiviral properties, a century of successful use of antibody therapies for viral diseases, and incontrovertible evidence from vaccine trials that specific antibody prevents disease progression resulted in the failure to take advantage of the window during which it may have been life-saving.

One common thread in the foibles associated with the use of hydroxychloroquine, corticosteroids, and CCP was the failure to consider biological plausibility in clinical decision making. Although it could be argued that the pathogenesis of COVID-19 was not fully understood in the first year of the pandemic, it was known that a related virus, SARS-CoV-1, rapidly transitioned from a viral to an inflammatory phase of disease and that most

This article was published at Annals.org on 16 May 2023.

patients died due to the latter. For hydroxychloroquine, biological plausibility was clung to because of in vitro data, although efficacy was disproved in vivo; for corticosteroids, biological plausibility was not sufficiently considered based on their known mechanism of action and their use in non–critically ill patients, in whom trial data showed they were not effective; and for CCP, biological plausibility was not considered in the design of RCTs of hospitalized patients based on its known mechanism of antiviral action—namely, antiviral activity and historical evidence of clinical efficacy.

Clinical research amid the pandemic underscores the need for clinicians conducting trials to consider biological plausibility in study design and interpretation. Even during a pandemic, physicians should consider the complex interplay between the scientific underpinnings of the relevant disease and clinical outcomes. This could refine clinical practice and avoid missteps in the future, which would be a positive legacy from the COVID-19 pandemic.

From Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, Baltimore, Maryland (A.C.); and Division of Infectious Diseases, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York (L.P.).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M23-0737.

Corresponding Author: Arturo Casadevall, MD, PhD, Johns Hopkins School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205; e-mail, acasade1@jhu.edu.

Author contributions are available at Annals.org.

Ann Intern Med. doi:10.7326/M23-0737

References

1. **Manivannan E, Karthikeyan C, Moorthy NSHN, et al.** The rise and fall of chloroquine/hydroxychloroquine as compassionate therapy of COVID-19. Front Pharmacol. 2021;12:584940. [PMID: 34025393] doi:10.3389/fphar.2021.584940

2. **Axfors C, Schmitt AM, Janiaud P, et al.** Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nat Commun. 2021;12:2349. [PMID: 33859192] doi:10.1038/s41467-021-22446-z

3. **Horby P, Lim WS, Emberson JR, et al.; RECOVERY Collaborative Group.** Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693-704. [PMID: 32678530] doi:10.1056/NEJMoa2021436

4. **Sahu AK, Mathew R, Bhat R, et al.** Steroids use in non-oxygen requiring COVID-19 patients: a systematic review and meta-analysis. QJM. 2021;114:455-463. [PMID: 34347106] doi:10.1093/qjmed/hcab212

5. **Patel C, Parmar K, Patel D, et al.** Effect of corticosteroid therapy on mortality in COVID-19 patients—a systematic review and meta-analysis. Rev Med Virol. 2022;32:e2386. [PMID: 35971278] doi:10.1002/rmv.2386

6. **Focosi D, Franchini M, Pirofski LA, et al.** COVID-19 convalescent plasma and clinical trials: understanding conflicting outcomes. Clin Microbiol Rev. 2022;35:e0020021. [PMID: 35262370] doi:10.1128/cmr.00200-21

7. **Casadevall A, Dragotakes Q, Johnson PW, et al.** Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. Elife. 2021;10. [PMID: 34085928] doi:10.7554/eLife.69866

8. **Senefeld JW, Gorman EK, Johnson PW, et al.** Mortality rates among hospitalized patients with COVID-19 treated with convalescent plasma: a systematic review and meta-analysis. medRxiv. Preprint posted online 12 January 2023. doi:10.1101/2023.01.11.23284347

9. **Bloch EM, Focosi D, Shoham S, et al.** Guidance on the use of convalescent plasma to treat immunocompromised patients with COVID-19. Clin Infect Dis. 2023. [PMID: 36740590] doi:10.1093/cid/ciad066

10. **Levine AC, Fukuta Y, Huaman MA, et al.** COVID-19 convalescent plasma outpatient therapy to prevent outpatient hospitalization: a meta-analysis of individual participant data from five randomized trials. Clin Infect Dis. 2023. [PMID: 36809473] doi:10.1093/cid/ciad088

Author Contributions: Conception and design: A. Casadevall, L. Pirofski.
Analysis and interpretation of the data: L. Pirofski.
Drafting of the article: A. Casadevall, L. Pirofski.
Critical revision for important intellectual content: A. Casadevall, L. Pirofski.
Final approval of the article: A. Casadevall, L. Pirofski.
Administrative, technical, or logistic support: A. Casadevall.