Empiric Therapies for COVID-19: Destined to Fail by Ignoring the Lessons of History

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Manifestations of disease, as perceived by physicians, can shape conceptual views and favor specific therapeutic actions. Historically, these factors appear to have an outsized influence on medical thinking in general. Disease concepts derived from empirical observations during pandemics impose a trade-off. We obtain unparalleled insight into medical thought and practice, but risk incurring the cost of unfortunate mistakes. The psychologist and Nobel Prize winner in economics Daniel Kahneman describes two mental systems that shape our judgments and decision-making in his book, *Thinking, Fast and Slow*: System One is intuitive, emotional, and fast, whereas System Two is deliberative and logical and has slower onset.[1] If we extrapolate these observations to clinical medicine, we often rely on either System One or System Two depending on particular situations. Errors can emerge when we default to fast and emotional responses in situations that instead require more deliberate and logical assessments. These include instances in which the desire to help—our humanitarian role as physicians, associated with an "adrenaline rush"—results from attempts to relieve human suffering. As mercenaries of misfortune, it is inevitable we engage medical interventions based on an incomplete understanding of the pathophysiology—in other words, without understanding the full risks and benefits.

During the ongoing COVID-19 pandemic, members of the medical community continue to provide care with the utmost nobility, empathy, and desire for action amid uncertainty. However, as the number of cases continues to increase worldwide, we urge caution in evaluating the current state of scientific understanding, our approaches to treatment, and the safety of empiric medical interventions targeting COVID-19. We are concerned that the extensive history of unintended adverse consequences of therapies for emerging infectious diseases in the past is being ignored in the development of approaches to COVID-19 treatment. It is likely harms will emerge from current empiric therapies for COVID-19 given what can be learned from history.

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HISTORICAL EXAMPLES OF UNINTENDED ADVERSE CONSEQUENCES

Whereas influenza can be treated with neuraminidase inhibitors,[2] there are currently no established effective antiviral therapies for COVID-19, which is similar to two other coronavirus diseases from the 21st century, SARS (Severe Acute Respiratory Syndrome) in 2003 and MERS (Middle-Eastern Respiratory Syndrome) in 2012.[3] Even in times of global pandemic, we need to consider potential harms and adverse consequences of novel treatments and show justifiable ratio of risk versus benefit. With the absence of proven COVID-19 therapy and the desire to fulfill our oath of *primum non nocere* (first, do no harm) in mind, we review selected unintended adverse events of developing therapies for infectious diseases.

Two types of error in our decision-making strategies are errors of omission and errors of commission.[4] Errors of omission, defined as instances in which a medical intervention was not carried out when there was a clear indication to do so, are less conspicuous in the history of infectious disease therapeutics. Errors of commission, in contrast, have become a more concerning component of our approach to COVID-19 therapy, perhaps prompted by our desire to act. Errors of commission are defined as instances in which a specific medical intervention that should have been avoided was instead performed. We will discuss historical examples of errors of commission to highlight parallels with the current pandemic (Appendix Figure).

During influenza epidemics in the 18th century, some physicians advocated the use of therapeutic lancet phlebotomies, while others recommended indiscriminate use of opium, which led to high rates of addiction.[5] Neither intervention was supported by a reassuring body of evidence. Many recommended mercury-based preparations during major outbreaks of syphilis in medieval protestant Europe. Because of accumulated mercurial toxicity, many persons suffered long-term sequelae including chronic kidney injury and peripheral neuropathy.[6] After the discovery of the tuberculous bacillus, Robert Koch attempted the inoculation of tuberculin as a curative intervention for tuberculosis.[7] Under pressure from the king of Prussia to present his findings at the International Medical Meeting in Berlin, Germany, in 1890, Koch conducted a poorly executed clinical trial. Rudolf Virchow then demonstrated endobronchial spread of the infection with resultant clinical worsening in

those who received Koch's tuberculin. In 1905, Harold Wolfersan Thomas at the Liverpool School of Tropical Medicine treated cases of African trypanosomiasis with the arsenical drug Atoxyl (arsanilic acid), which demonstrated some efficacy but also caused optic nerve atrophy leading to blindness.[8]

There have also been errors of commission in the development of vaccines. One such event, known as the Cutter incident, followed from an incompletely inactivated batch of polio vaccine that caused 40,000 cases of abortive poliomyelitis and many cases of paralysis and death.[9] In the early phases of the development of the yellow fever vaccine, Hideyo Noguchi tried to develop a vaccine based on the erroneous assumption that yellow fever was caused by *Leptospira icteroides*.[10] In 1976, an error of commission occurred in response to an outbreak of a few dozen cases of Influenza A/H_1N_1 in Fort Dix, New Jersey: The accelerated implementation of a swine influenza–vaccination program led to many cases of Guillian-Barré Syndrome among recipients.[11] Immunization experts defended this decision to vaccinate by arguing that "when lives are at risk, it's better to err on the side of overreaction over underreaction."[11] However, this is a risk-perception versus risk-management concept that drives potential errors of commission.

A more recent error of commission involved the use of drotrecogin alfa (activated protein C) in the treatment of sepsis. This drug became the first and only Food and Drug Administration–approved drug for sepsis treatment. The approval process of this medication relied on one clinical trial, which was terminated early because of perceived overwhelming evidence of efficacy. Despite the initial high medical and financial expectations, Eli Lilly (Indianapolis) withdrew the drug when a larger, international clinical trial (PROWESS-SHOCK) did not show a similar benefit.[12]

THE COVID-19 ERA

The gravity of the COVID-19 pandemic has motivated the repurposing of previously available therapies. This explains the use of medications like hydroxychloroquine, interleukin-6 (IL-6) receptor antagonists, and remdesivir.[13-15]

Despite early authorization of emergency use for hydroxychloroquine by the FDA based on limited and poor-quality evidence,[16] this drug has yet to demonstrate treatment efficacy for COVID-19. On the contrary, other, controlled, retrospective studies have shown that hydroxychloroquine might actually increase mortality, possibly through prolongation of the QT-interval.[16,17] Also, diversion of this drug to treat COVID-19 raises the concern of hydroxychloroquine shortages for treatment of patients with autoimmune disease, in whom the drug has proven benefit. We question the hasty FDA authorization for emergency use of hydroxychloroquine for COVID-19.

There is also great enthusiasm among the medical community to administer IL-6 receptor antagonists as a COVID-19 treatment. The rationale for this approach includes observations in case series in which IL-6 levels correlated with adverse clinical outcomes.[13] IL-6 antagonists have a proven track record of improving the outcome in autoimmune diseases. However, we must avoid the logical trap of *post hoc, ergo propter hoc* (after this, therefore because of this) dictum from which one would assume that, based on those observations of high IL-6 levels and adverse outcomes, lowering IL-6 levels will necessarily improve outcomes in COVID-19. The supposed role of IL-6 in causing COVID-19 is based on scant preliminary observations and on the yet unproven assumption that IL-6 association with disease severity is a cause-effect relationship and not an association separate from pathogenesis. Moreover, there is sufficient scientific evidence that, in the case of severe influenza infections, IL-6 limits inflammation and protects against severe and potentially life-threatening lung injury. The road ahead for IL-6 inhibition to treat COVID-19 is perilous and should be entered cautiously. One immediate concern of administering IL-6 receptor antagonists in this patient population is the potential reactivation of latent tuberculosis infection and hepatitis B, colonic perforation, and increased rate of infections in general.

The greatest hope at this early stage of the COVID-19 pandemic may be remdesivir, which is a direct-acting antiviral. Here again, initial case series in prestigious medical journals signaled the possibility of a morbidity and mortality benefit.[14] Despite these encouraging signs, a recent clinical trial from China that was limited by incomplete patient enrollment demonstrated a lack of efficacy of remdesivir in accelerating clinical improvement or limiting mortality.[18] In spite of these negative results, preliminary data from the Adaptive COVID-19 Treatment Trial (ACTT) has revealed a nonsignificant signal of reduced mortality and shorter time to recovery in the remdesivir group. In response to these reports, the FDA has now issued emergency use authorization of remdesivir for treating COVID-19. Given the precedence of conflicting study data in therapeutic development for infectious diseases, we urge caution in drawing interpretations of benefit based on these early reports. Early termination of clinical studies is often associated with a 30% overestimation of clinical benefit.[19] Furthermore, the availability of remdesivir is limited, which raises substantial ethical concerns on the preferential allocation of the drug to selected populations in high-income countries. At the time of this report, uncertainty regarding the risk-benefit balance of remdesivir and other COVID-19 treatments should be emphasized among decision makers.

CONCLUSION

Errors of commission present particular concerns for risk in treating COVID-19 patients and suggest that sometimes inaction is preferable to action. With many pandemics, there is a history of repeating mistakes, and we believe this can be curtailed by heeding the lessons of history. In the end, we may learn that avoiding therapeutic interventions that are poorly supported may prove to be one of the most important legacies of the COVID-19 pandemic.

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