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

Gregory S Canfield, MD1, Jonathan S Schultz, MD1, Sam Windham, MD1, Sias Scherger, MD1, Andrés F Henao-Martinez, MD1, Leland Shapiro, MD1,2, Carlos Franco-Paredes, MD1,3*, Daniel B Chastain, PharmD4, Taylor Wand, BSc1, Martin Krsak, MD1

1Department of Medicine, Division of Infectious Diseases, University of Colorado, Anschutz Medical Center, Aurora, Colorado; 2Department of Medicine, Division of Infectious Diseases, Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, Colorado; 3Instituto Nacional de Salud, Hospital Infantil de México, Federico Gomez, México City, Mexico; 4Department of Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Albany, Georgia.

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To err is human, but to understand that we have erred and to be willing to change our ways is perhaps the most important lesson of medicine.

—Rudolf Virchow, in his book, Die Krankheitsvorgänge in den Organen (1856)

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.

**HISTORICAL EXAMPLES OF UNINTENDED ADVERSE CONSEQUENCES**

Whereas influenza can be treated with neuraminidase inhibitors, 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. 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. 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. 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. After the discovery of the tuberculous bacillus, Robert Koch attempted the inoculation of tuberculin as a curative intervention for tuberculosis. 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 Wolfers-
san Thomas at the Liverpool School of Tropical Medicine treat-
ed 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 develop-
ment of vaccines. One such event, known as the Cutter inci-
dent, 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/H1N1 in Fort Dix, New Jersey:
The accelerated implementation of a swine influenza–vaccina-
program led to many cases of Guillain-Barré Syndrome
among recipients.11 Immunization experts defended this de-
cision to vaccinate by arguing that “when lives are at risk, it’s
to err on the side of overreaction over underreaction.”12
However, this is a risk-perception versus risk-management con-
cept that drives potential errors of commission.
A more recent error of commission involved the use of dro-
tregoin alfa (activated protein C) in the treatment of sepsis.
This drug became the first and only Food and Drug Admin-
istration–approved drug for sepsis treatment. The approval
process of this medication relied on one clinical trial, which
was terminated early because of perceived overwhelming evi-
dence 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 re-
purposing 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 hydroxy-
chloroquine by the FDA based on limited and poor-quality evi-
dence,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 rais-
es 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 com-
unity to administer IL-6 receptor antagonists as a COVID-19
treatment. The rationale for this approach includes observa-
tions in case series in which IL-6 levels correlated with adverse
clinical outcomes.13 IL-6 antagonists have a proven track re-
cord of improving the outcome in autoimmune diseases. How-
ever, 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. More-
over, 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 immedi-
cate concern of administering IL-6 receptor antagonists in this
patient population is the potential reactivation of latent tu-
berculosis infection and hepatitis B, colonic perforation, and
increased rate of infections in general.
The greatest hope at this early stage of the COVID-19 pan-
demic 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 bene-
fit.18 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 remde-
sivir group. In response to these reports, the FDA has now is-
sued emergency use authorization of remdesivir for treating
COVID-19. Given the precedence of conflicting study data in
therapeutic development for infectious diseases, we urge cau-
tion 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 empha-
sized among decision makers.

CONCLUSION
Errors of commission present particular concerns for risk in
treating COVID-19 patients and suggest that sometimes inac-
tion is preferable to action. With many pandemics, there is a
history of repeating mistakes, and we believe this can be cur-
tailed 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 lega-
cies of the COVID-19 pandemic.

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