Critical Care Explorations

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Fact Versus Science Fiction: Fighting Coronavirus Disease 2019 Requires the Wisdom to Know the Difference

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Since December 2019, countries have quickly shifted from spectators to victims of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak. The coronavirus disease 2019 (COVID-19) pandemic has overwhelmed healthcare systems and crippled economies around the world, including the United States. Unlike China, many countries had time to prepare for their epidemics and, as of March 25, remain in the early stages. Time has allowed the scientific community to bear arms and mount expedited research efforts in unforeseen fashion. The collaboration between academic institutions and government agencies is unprecedented and inspiring. Countless hours and sleepless nights from academics around the world have resulted in a united front to mitigate morbidity and mortality from COVID-19. Despite these concerted efforts, another pandemic, in its own right, threatens to destroy the meticulously built scientific juggernaut surrounding COVID-19. Those are alternative facts. This commentary uses a recent study of hydroxychloroquine to demonstrate the dire need for randomized clinical trials, but more importantly, to explore the potential consequences of misinformation, how fear fuels its impact, and offer guidance to maintain scientific integrity without relinquishing hope.

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Chloroquine, and its less toxic metabolite hydroxychloroquine, are chemotherapeutic agents used to treat malaria (1). Chloroquine/hydroxychloroquine also inhibits certain inflammatory pathways resulting in the treatment of multiple rheumatological disorders (1). The SARS-CoV outbreak in 2003 led to yet another therapeutic potential when chloroquine was found to inhibit SARS-CoV attachment by altering the binding protein and receptor required for entry (2). Despite other in vitro studies identifying a potential role in killing infected cells (3, 4), in vivo trials have yet to confirm these findings (5). In fact, preclinical trials of chloroquine in other viruses, dengue fever, and chikungunya, demonstrated enough promise to warrant further clinical trials; however, the preclinical effects did not translate to humans (6, 7). As of March 25, there remains no randomized control trial in humans with evidence that chloroquine or hydroxychloroquine is beneficial in SARS-CoV or SARS-CoV-2. To date, the only randomized control trial with published data found no benefit (viral clearance) between the 15 patients treated with chloroquine compared with 15 patients treated with a placebo (C. Jun, unpublished observations, 2020). Although an abstract published online February 19, 2020 touts efficacy with chloroquine in 100 patients, there remains no publication of these data (8). However, a recent nonrandomized, observational study by Gautret et al (9) found decreased viral load in patients treated with hydroxychloroquine compared with a control group chosen from another hospital. These findings are noteworthy for many reasons, specifically for reasons not commonly noted.

The lack of randomization and adjustment in the study by Gautret et al (9) introduces selection and confounding bias, respectively. This alone should temper any interpretation, but the more subtle discretion regarding the six excluded patients from the treatment (hydroxychloroquine) group, warrants an equivalent amount of skepticism. Of these patients, one died, three clinically deteriorated requiring intensive care admission, one withdrew secondary to a drug-related complication, and another was lost to follow-up. Excluding these patients drastically biases the results toward a benefit. In fact, if included, the number needed to harm with hydroxychloroquine is six (hydroxychloroquine 19.2% vs control 0% harm), which is arguably of greater clinical significance compared with decreasing unadjusted viral load. Furthermore, the

mechanistic primary outcome with an implausible sample size calculation (a presumed 50% efficacy) creates enough methodological concerns to prevent anything beyond the hypothesis-generating conclusions from this study. The limitations stated above are not groundbreaking and were likely appreciated by the regular and seasoned academic readership. Unfortunately, the "readership" of not only this article but all academic literature has broadened immensely over the past 3 months. The world is, understandably, grasping for a discovery; while the scientific community operates under a worldwide microscope in desperate need of a critical appraisal filter. Despite its methodological limitations and lack of clinical relevance, the article by Gautret et al (9) continues to trend on social media days after its publication. This article and its repercussions reinforce the adage that "a lie can travel halfway around the world while the truth is still putting on its shoes."

Since its publication, prescriptions for chloroquine and hydroxychloroquine have dramatically increased, standard operating procedures have incorporated hydroxychloroquine as a standard of care, lethal overdoses have occurred, and there are rising concerns that shortages may affect availability for U.S. Food and Drug Administration-approved uses of these medications. Premature acceptance of efficacy is not new (swine flu vaccination [10] or recombinant human activated protein C [11]), but it is these prior experiences that influence current standards to require high quality and often multiple randomized control trials to change practice. This high bar contributes to the estimated 17 years it can take for best practices to be translated into medical practice (12). This glacial, yet safe and meticulous, pace is unacceptable in our current crisis. Lowering the bar and maintaining scientific rigor is possible when the scientific community harmoniously pivots toward a single target. Remarkably, we have succeeded in this movement by coming together as an international community. Unfortunately, unless we maintain the narrative from our scientific surge, the "bar" we have meticulously repositioned may fall quickly to the floor.

Inaccurate facts stem from two levels. The ability to identify and suppress both misinformation and disinformation is crucial to maintaining the scientific process. Misinformation is incorrect or misleading information (13), whereas its more devious counterpart, disinformation is false information deliberately and often covertly spread to obscure the truth (14). The example above represents misinformation. We can safely assume the differing interpretations occurred unintentionally, and we hope to provide guidance for future situations while we await results from randomized clinical trials.

Misinformation occurs to a greater degree during disasters (15). A natural human tendency during a crisis is to find resolution, even when it does not exist (16). Fear fuels these efforts to dissipate this uncertainty. The limitations of the study by Gautret et al (9) are not lost on seasoned academic researchers. However, despite warnings from healthcare leaders and public health agencies, there continues to be a premature adoption of hydroxychloroquine as treatment based on limited preclinical data and misinformed interpretation of a nonrandomized study. Importantly, compassionate and well-intentioned healthcare workers are not immune to these tendencies. Arguably, healthcare workers are more vulnerable to misinformation in our current climate, as the careful and curious lens, previously used to critically appraise the literature, is now blurred by their intrinsic passion to "do something." Intentions aside, misinformation is a current public health emergency! If left unchecked, preventable patient morbidity and mortality will occur while simultaneously dismantling the remarkable ongoing efforts to defeat COVID-19. There may be a risk to the integrity of not only hydroxychloroquine trials but also other investigational drug trials currently ongoing. Widespread use and misconception of hydroxychloroquine being a cure may result in reduced enrollment in hydroxychloroquine trials or hesitation to enroll in other drug trials that are not hydroxychloroquine. These potential ripple effects from misinformation pose the greatest threat to our ongoing fight against COVID-19.

Merchant and Asch (17) layout countermeasures to combat misinformation. First, it is essential to leverage our position in social media and advocate for transparency (**Table 1**). Accomplishing this will undoubtedly require a unified effort by the medical community given the majority of social media influence resides outside of healthcare. Fortunately, we can turn to science to provide some insight. A recent article in *Scientific Reports* analyzed the social media mechanisms associated with social bursts during significant worldly events. Although the motivation to propagate ("liking" or "retweeting") a topic is commonly influenced by the user's fondness for the topic, during significant events the influence is shifted and amplified based on their degree of trust in the source of information (18). We live in a world where an entertainer, politician, or idol's endorsement is echoed to millions. In contrast, a world-renown scientist or medical provider reaches people on the magnitude of thousands. This creates

TABLE 1. Sources of Misinformation and Actions Items for the Medical Community

Misinformation Source	Actions to Control the Narrative
Social media	A call to arms of healthcare provider presence on social media
	Provide insight into new articles (mini-peer review)
	Offer a meaning of significance (#needRCT)
	(Consider) Social media companies pairing with journals to vet dissemination of misinformation
	(Consider) Establishing uniform social media guidelines for appraising evidence
News	Physician/research experts must be doing interviews
	Write newspaper articles > high impact journal commentary when appropriate
Journals	Expedited reviews when possible
	Solicit commentaries for controversial coronavirus disease 2019 articles to be published together
	Joint author and journal social media post
Hospitals	Oversight when implementing protocols to guide evidence-based decision-making

RCT = randomized control trial.

a vacuum of credible medical information. As the world looks to the medical community, they do so through underutilized mechanisms where our voice is barely a whisper. We currently have an ethical responsibility as leaders in our field to be prominent, speak out against misinformation, and deliver the facts. Just as we are condensing the timeline for research, we must streamline our professional opinions, in realtime, through social media engagement. Similarly, it is imperative that journals expedite responses to misinformation, solicit commentary for controversial topics, and deliver a unified message in collaboration with the authors. Resultantly, the scientific community controls the narrative while preserving its veracity. This is crucial because if left unchecked, the narrative appears increasingly malleable as the virus and fear spread. The spotlight is currently on the academic community more than ever. We owe it to the research coordinators, investigational drug service pharmacists, the couriers, the project managers, the statisticians, the trainees performing chart reviews, our mentors, and our mentees, to ensure their unrelenting and ongoing efforts are not in vain. Equally as important, we owe it to our family, friends, and community to be the beacon of hope while preserving scientific integrity.

A T.S. Eliot quote (19) was recently reframed to reflect our duty as a scientific community,

> we aim to arrive where we have started—at the bedside of the critically ill and injured patient—caring in ways that were yesterday unimagined, today unknown, and will become tomorrow standard. (20)

Dr. Tignanelli is a principal investigator for two randomized control trials investigating angiotensin-receptor blockers in the treatment of coronavirus disease 2019 among inpatient and outpatients. Co-investigators include Dr. Ingraham. Dr. Ingraham received funding from National Institutes of Health and National Heart, Lung, and Blood Institute (T32HL07741).

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