



Perspective

Covid-19 — A Reminder to Reason

Ivry Zagury-Orly, B.Sc., and Richard M. Schwartzstein, M.D.

How long will this pandemic last? When will we find a treatment or vaccine? Which drug should we give our patients? Will we run out of personal protective equipment (PPE)? When

will everyone return to work? We find ourselves in a time of great economic, social, and medical uncertainty. Faced with a crisis, Lee Iacocca, the late automobile company executive, once said, “So what do we do? Anything. Something. . . . If we screw it up, start over. Try something else. If we wait until we’ve satisfied all the uncertainties, it may be too late.” Similarly, in the heat of the Great Depression, Franklin Roosevelt commented, “Take a method and try it. If it fails, admit it frankly and try another. But by all means, try something.” Though a trial-and-error approach may be appropriate in business and politics, should it be applied to medical decision making during a pandemic?

Even as we acknowledge that the world now feels strange and

that doctors are susceptible to human anxieties, we should remember to accept uncertainty rationally and beware of potential undesirable consequences of our instinctive desire to see patterns in what may be random happenstance. Our mission as healers, in a situation such as the Covid-19 pandemic, makes us feel compelled to *do* something. As doctors trained in the scientific method, however, we are committed to practicing evidence-based medicine, which is premised on the ability to interpret scientific reports on supposed diagnostic and therapeutic advances. We need to retain a healthy skepticism and remember the principle of clinical equipoise, particularly when considering interventions that could cause harm.¹ Otherwise, in our effort to “do

good” for our patients, we may fall prey to cognitive biases and therapeutic errors.²

Under conditions of information overload and uncertainty-related anxiety, we have an increased tendency to inappropriately favor recently acquired information because of its ease of recall — a heuristic known as availability bias.³ We might think, “I spoke to a colleague in Italy yesterday who told me she had a patient whose oxygenation problem was due to clots in the lung,” leading us to decide, “I’m going to give thrombolytics now.”

Similarly, our sense of urgency about *doing* something may increase our likelihood of anchoring³ — closing our decision-making process prematurely, before exploring reasonable alternatives: “The patient has had three negative tests for coronavirus, but I don’t care — I’m sure that’s what she has.”

And confirmation bias causes us to focus on information that re-

inforces our preconceived notions at the expense of contradictory information. We see a patient with hypotension and a reduced ejection fraction on echocardiography and presume he has Covid-19–related cardiomyopathy, despite his focal ECG abnormalities and history of coronary disease.

In a time when the rational–emotional scale is tipping to the emotional side, we begin relying more heavily on anecdotes, particularly personal experiences that may carry inordinate weight in our minds. Journalists use the power of stories to connect with readers and tug at their emotions. Physicians, trained as scientists, are expected to follow a hypothesis-driven, rational, evidence-based approach to clinical decision making, but we, too, can be swayed by stories under the pressures of a crisis.

Throughout the world, therapeutic management for SARS-CoV-2 has largely been supportive, and to date, no specific therapy has been scientifically proven to reduce mortality. Physicians are treating patients, with unsparing generosity, using medications such as chloroquine, hydroxychloroquine, azithromycin, lopinavir-ritonavir, and interleukin-6 inhibitors outside their indicated, approved uses and without study protocols, with little scientific evidence supporting their administration beyond extrapolation from *in vitro* studies revealing their antiviral and antiinflammatory properties.⁴ Aside from the potential side effects of drugs such as hydroxychloroquine and interleukin-6 inhibitors, which include fatal cardiac arrhythmias and possible worsening of infection, respectively,⁴ prescribing medications on the basis of case reports

does little to help advance science or our ability to combat future recurrences of coronavirus.

Furthermore, the intense desire to try new, unproven remedies may distract health care providers from offering patients the best-quality supportive care possible. Evidence on palliative care in oncology, which in some advanced cancers is associated with longer life than intensive therapies, clarifies the value of focused supportive care. Recent survival rates among U.S. patients with respiratory failure due to Covid-19 appear better than those in early reports, possibly because we are paying greater attention to the basics of care for acute respiratory distress syndrome. Only recently have randomized, controlled trials of therapeutic interventions for Covid-19 been launched.⁴ The “what do you have to lose?” approach, a common plea of desperate families, must be balanced by the dictum of the Hippocratic Oath: first, do no harm.

Causing harm in our efforts to *do* something is not unprecedented. According to a systematic review of treatment effects in the last coronavirus (SARS-CoV) outbreak in 2003, four studies identified ribavirin as causing possible harm to infected patients.⁵ More than one third of patients treated with ribavirin developed hemolytic anemia, but the absence of a control group precluded ruling out the possibility that the infection itself caused this complication. Even more alarming, of the 29 studies of steroid use, 25 were inconclusive: in many cases, because of inconsistent reporting or lack of a control group, the study provided no conclusions regarding treatment efficacy, and 4 studies suggested possible harm.⁵ The

thirst for a treatment in an uncertain time led to flawed studies that may have contributed to negative physical, social, and economic consequences.

Despite the temptation to provide hope by using untested remedies, we should instead push for studies designed to meet the standards necessary to reach reasonable conclusions about efficacy⁵ — an admittedly difficult task during a crisis. We are now engaged, for example, in a blinded, randomized, controlled trial of remdesivir, a new antiviral, as well as a drug that inhibits the action of interleukin-6, but we have been resisting pleas to communicate anecdotes of success; we push back because that is not how science is done.

Anxiety and fear of contagion despite evidence that PPE use is effective may also alter care. Though clinicians have become infected with SARS-CoV-2, it's often unclear whether the infection was attributable to a work exposure or a contact outside the hospital; up to this point rates of infection among health care workers do not appear to differ between those who work on units with Covid-positive patients and those who don't. Yet some clinical consultations are being conducted without the consultant speaking to or examining the patient. Procedures are being delayed or deferred on the basis of extrapolation from anecdotes about possible exposure.

One of us (R.M.S.) began his career at the beginning of the AIDS epidemic. Nobody knew exactly how the disease was transmitted, and it was universally fatal; anxiety among doctors and nurses was high. Nevertheless, with precautions, we had to per-

form surgeries, bronchoscopies, and other invasive procedures. Emotional reactions are understandable, but we need to call on reason if we are to do our jobs effectively.

Thus far in the Covid-19 pandemic, we've observed that therapeutic management has often been initiated and altered on the basis of individual case reports and physician opinion, rather than of randomized trials. In these uncertain times, physicians fall prey to cognitive error and unconsciously rely on limited experiences, whether their own or others', instead of scientific inquiry. We believe that physicians should be acting in concert with clinical equipoise. We should be skeptical of any purported therapeutic strat-

egy until enough statistical evidence is gathered that would convince any "open-minded clinician informed of the results" that one treatment is superior to another.¹

We are living through an unprecedented biopsychosocial crisis; physicians must be the voice of reason and lead by example. We must reason critically and reflect on the biases that may influence our thinking processes, critically appraise evidence in deciding how to treat patients, and use anecdotal observations only to generate hypotheses for trials that can be conducted with clinical equipoise. We must act swiftly but carefully, with caution and reason.

Disclosure forms provided by the authors are available at NEJM.org.

From Harvard Medical School (I.Z.-O., R.M.S.) and the Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center (R.M.S.) — both in Boston.

This article was published on April 28, 2020, at NEJM.org.

1. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-5.
2. Simpkin AL, Schwartzstein RM. Tolerating uncertainty — the next medical revolution? *N Engl J Med* 2016;375:1713-5.
3. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. *Science* 1974;185:1124-31.
4. Kalil AC. Treating COVID-19 — off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA* 2020 March 24 (Epub ahead of print).
5. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006;3(9):e343.

DOI: 10.1056/NEJMp2009405

Copyright © 2020 Massachusetts Medical Society.