Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

Do No Harm

Reaffirming the Value of Evidence and Equipoise While Minimizing Cognitive Bias in the Coronavirus Disease 2019 Era

Venktesh R. Ramnath, MD
La Jolla, CA
David G. McSharry, MD
Dublin, Ireland
Atul Malhotra, MD
La Jolla, CA

KEY WORDS: critical care; decision-making; health-care utilization

The coronavirus disease 2019 (COVID-19) pandemic has tested the mettle of critical care practitioners worldwide by raising anxieties about how best to battle the disease. Notably, the pandemic has exposed the fragility of belief in longstanding medical evidence, equipoise with novel therapies, and objective rationales in medical decision-making, all of which underpin the principle of primum no nocere ("do no harm").

The extent to which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) illness parallels that of other virulent respiratory viruses may not be widely recognized. Although the data are still evolving, SARS-CoV-2 causes ARDS with lower severity of illness on presentation[1] and case mortality projections that slightly exceed those of influenza. SARS-CoV-2 matches the transmissibility through droplets of the influenza A virus (H1N1) and seasonal influenza, human metapneumovirus, adenovirus, and other respiratory viruses causing their own yearly fatalities. Protective measures, including social distancing, mask-wearing, and hand hygiene, effectively reduce infection rates from all respiratory viruses. In fact, the recent drop in influenza attack rates in Japan was directly attributed to mitigation measures adopted for control of SARS-CoV-2. Finally, although some initially suggested that a new phenotype of ARDS due to SARS-CoV-2 (COVID-19 ARDS) required attention,[2] consensus now converges on COVID-19-related ARDS instead lying within the spectrum of known inflammatory lung disease and existing definitions of ARDS (eg, Berlin criteria[3]), which are best managed by using decades-long understanding and experience. In other words, COVID-19 pneumonia seems to be a more sinister version of diseases that most clinicians already understand well.

On the front lines of COVID-19, however, unproven therapies have been used under an "off-label" rubric. Examples include the use of hydroxychloroquine, lopinavir/ritonavir, tocilizumab, early use of steroids, convalescent plasma, and others. With some exceptions (eg, remdesivir[4]), most therapies lack significant benefit to date and are associated with potential or actual harm.[5,6] As such, the use of these therapies cautions us to reflect on a possible role of cognitive biases in medical decision-making[7] (Table 1). For example, the high acuity and slow course of severe COVID-19 cases make us vulnerable to both information bias (the tendency to make associations based on incomplete or inaccurately measured data) and action bias (the feeling that "doing something" is inherently better than "doing nothing"). Fragmented information available through social media and mainstream media outlets can cause anchoring and framing effects based on how data are presented and received that can further complicate objective evaluation. Representativeness bias may label all patients with acute respiratory failure as having COVID-19, and premature closure can deprioritize other diagnoses (eg, potential coexistent pulmonary embolism), while overconfidence and confirmation bias may unconsciously reinforce the decisions we make.

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

AFFILIATIONS: From the Division of Pulmonary, Critical Care, and Sleep Medicine (Drs Ramnath and Malhotra), UC San Diego Health; and the Mater Misericordiae University Hospital and University College Dublin (Dr McSharry).

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Venktesh R. Ramnath, MD, 9300 Campus Point Dr, La Jolla, CA 92093; e-mail: vramnath@health.ucsd.edu

DOI: https://doi.org/10.1016/j.chest.2020.05.548

TABLE 1] Various Cognitive Biases Frequently Encountered in Critical Care Management of COVID-19 Patients

Cognitive Bias	Definition	Example in COVID-19	Recommendation
Ambiguity (risk) aversion	Tendency to make choices that minimize feelings of uncertainty and risk	Inclination to adopt off-label therapies when other strategies (eg, prone positioning) do not result in rapid, observable improvements in clinical condition	Consider that medicine is an inductive science that never provides 100% probabilities
Action (commission) bias	The tendency to choose action over inaction	Decision to use an unproven medication (eg, hydroxychloroquine) as part of treatment plan because "doing something is better than doing nothing"	Remember the value of "watchful waiting" in many non-COVID-19 ARDS scenarios Engage in restraint to give the lung sufficient time to heal Enroll patients into clinical trials
Premature closure	Failure to consider concomitant or alternative diagnoses after an initial diagnosis is made	Not evaluating for possible pulmonary embolus in a patient with symptoms of pneumonia when COVID-19 test returns positive, despite profound hypoxemia out of proportion to lung involvement on chest imaging	Consider alternative diagnoses, especially those with high prevalence in critical care (eg, [postviral] sepsis, VTE, ventilator-associated complications)
Availability bias	Easily recalled information incorrectly guides decision-making because it was recently received and/or readily available	Prescribing tocilizumab in a patient with COVID-19 illness after hearing about cytokine release syndrome from a colleague	Consider that diverse data are part of clinical diagnosis-making process Ask yourself: any particular information given more or less weight due to recent and/or memorable experiences?
Overconfidence	Inflated confidence in clinical judgment does not match actual accuracy	Decision to administer high PEEP on ventilator for all COVID-19 positive patients without considering assessments of recruitability and hemodynamics Avoiding engaging in sedation interruptions and ABCDEF bundle because "COVID-19 patients universally need longer time on the ventilator"	Trust evidence-based strategies and adopt analytical strategies to all available data Realize that physicians can often be wrong, despite best intentions
Representativeness bias	Tendency toward stereotyping and forming associations between truly unrelated facts	Ordering therapeutic (systemic) anticoagulation when D-dimer returns as positive in a COVID-19 patient Expecting high mortality in all obese, COVID-19 patients of advanced age with hypertension	Remember that COVID-19 base rates and true prevalence of disease are still evolving
Confirmation bias	Seeking and noticing information that confirms our initial diagnostic expectation	Inclination to order fourth test of COVID-19 after results of prior 3 tests return negative in a patient with radiographic evidence of pneumonia and *Escherichia coli* bacteremia	Consider possibility and implications of false-positive test result Avoid delays in treating non-COVID-19 causes of radiographic findings

(Continued)

TABLE 1] *(Continued)*

Cognitive Bias	Definition	Example in COVID-19	Recommendation
Framing effect	Phenomenon of differing reactions to the same information depending on how it is presented	Medication A with 90% cure rate for COVID-19 is incorrectly viewed as superior to Medication B with a 5% failure rate	Slow down and consider each piece of information independently
Anchoring bias	Tendency to adhere to information presented earlier rather than later in time course	Initial triage report of "shortness of breath, cough" leads to COVID-19 evaluation only, despite later evaluation revealing hemoptysis, palpitations, leg swelling, ultimately missing a pulmonary thromboembolism	Consider all available information before making a differential diagnosis
Information bias	Belief that the higher quantities of information are superior for making diagnoses ("more is better")	Many anecdotal, observational, retrospective trials for steroids in COVID-19 ARDS are cited when favoring use of steroids rather than considering fewer but higher-quality studies showing benefits of remdesivir[4] in COVID-19	Consider quality in addition to the quantity of evidence

ABCDEF bundle = Assess, prevent, and manage pain (A), Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT) (B), Choice of analgesia and sedation (C), Delirium: assess, prevent, and manage (D), Early mobility and exercise (E), and Family engagement and empowerment (F); COVID-19 = coronavirus disease 2019; PEEP = positive end-expiratory pressure.

As a result, complications can occur. First, use of medications with lower thresholds of scrutiny can actually hurt patients. Hydroxychloroquine use is now restricted due to concerns of life-threatening cardiotoxicities in COVID-19 patients.[8] Steroids are associated with variable mortality, although increased mortality was seen in influenza pneumonia.[9] Although one retrospective study among patients with COVID-19 ARDS suggested that treatment with methylprednisolone decreased risk of death,[10] prospective studies are necessary to make definitive conclusions. Calls to avoid angiotensin-converting enzyme inhibitors have complicated attempts to control hypertension and cardiac disease that can cause immediate detrimental effects.[11] Second, "compassionate use" of unproven therapies can be ethically challenging for patients, families, and practitioners. Risks include exacerbating inequities inherent to gaining access to such medications and experiencing disappointment when putative benefits become impossible to confirm and may even prolong suffering.[12] Third, unregulated use of unproven therapies, most notably hydroxychloroquine, has reduced supplies and hampered access to treatments with proven benefit for rheumatologic and malarial diseases affecting millions of people.[13] Furthermore, attention placed on untested medications can detract from belief in other therapies such as the ABCDEF bundle (Assess, prevent, and manage pain [A], Both spontaneous awakening trials [SAT] and spontaneous breathing trials [SBT] [B], Choice of analgesia and sedation [C], Delirium: assess, prevent, and manage [D], Early mobility and exercise [E], and Family engagement and empowerment [F])[14] that show outcome improvements from years of careful study in patients who are ventilated. Finally, anecdotal use of off-label medications hinders equipoise to perform proper clinical trials that *could make true* scientific advancements. By adopting reflection and humility in how we use available therapies, physicians can bolster efforts against antivaccine, anti-brain death, and other challenges to medical wisdom that already suggest an ebbing of public trust in medical science in the United States.

Clinicians can reset the balance in a number of ways. First, an awareness of our innate tendencies to exhibit cognitive biases is essential. Although a purely objective approach is difficult, we must apply ourselves to self-critique and open, active discussions with colleagues about the strengths and limitations of available data prior to using putative therapies. Actions that diminish

equipoise should be viewed as exceptions rather than norms. Second, we must restrict unproven therapies to clinical trials to protect equipoise. Despite our best intentions, every off-label use of an unproven therapy may dent the research-based edifice upon which medical science rests. Instead, we can channel this energy to develop collaborative relationships with academic and industry partners to enroll more patients into clinical trials. Third, clinicians must remember that medicine is an inductive (not deductive) science and therefore cannot delivery 100% diagnostic certainty even under "perfect" conditions.

Medicine often delivers reliable and positive results when therapies based on rigorous scientific evidence such as randomized controlled trials are adopted as standards of care. Indeed, because COVID-19 patients often require prolonged ventilator management, we must ensure that ARDS is accurately diagnosed and treated appropriately.[15] Finally, clinicians should practice cautious optimism, vigilance, and a strong sense of humility, knowing that COVID-19 is just the latest—not the last—medical crisis for mankind. Such approaches will positively affect our efforts to combat COVID-19 and other global medical threats, such as the escalating prevalence of antibiotic-resistant bacteria. By following these strategies, critical care clinicians will not only better steer patients away from harm but also reinvigorate and sustain the scientific progress.

References

1. Tang X, Du R, Wang R, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1 [published online ahead of print March 26, 2020]. *Chest*. https://doi.org/10.1016/j.chest.2020.03.032.
2. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA*. 2020;323(22):2329-2330.
3. Sjoding MW, Hofer TP, Co I, Courey A, Cooke CR, Iwashyna TJ. Interobserver reliability of the Berlin ARDS definition and strategies to improve the reliability of ARDS diagnosis. *Chest*. 2018;153(2):361-367.
4. NIH: National Institute of Allergy and Infectious Diseases. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19. Accessed April 29, 2020.
5. Rice TW, Janz DR. In defense of evidence-based medicine for the treatment of COVID-19 ARDS [published online ahead of print April 22, 2020]. *Ann Am Thorac Soc*. https://doi.org/10.1513/AnnalsATS.202004-325IP.
6. Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome: a cautionary case report [published online ahead of print April 25, 2020]. *Chest*. https://doi.org/10.1016/j.chest.2020.04.024.
7. Saposnik G, Redelmeier D, Ruff CC, Tobler PN. Cognitive biases associated with medical decisions: a systematic review. *BMC Med Inform Decis Mak*. 2016;16(1):138.
8. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Accessed April 28, 2020.
9. Moreno G, Rodríguez A, Reyes LF, et al. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med*. 2018;44(9):1470-1482.
10. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention [published online ahead of print February 24, 2020]. *JAMA*. https://doi.org/10.1001/jama.2020.2648.
11. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med*. 2020;382(17):1653-1659.
12. Raus K. An analysis of common ethical justifications for compassionate use programs for experimental drugs. *BMC Med Ethics*. 2016;17(1):60.
13. Why hoarding of hydroxychloroquine needs to stop. https://www.npr.org/sections/health-shots/2020/03/23/820228658/why-hoarding-of-hydroxychloroquine-needs-to-stop. Accessed April 28, 2020.
14. Pun BT, Balas MC, Barnes-Daly MA, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. *Crit Care Med*. 2019;47(1):3-14.
15. Weiss CH, Baker DW, Tulas K, et al. A critical care clinician survey comparing attitudes and perceived barriers to low tidal volume ventilation with actual practice. *Ann Am Thorac Soc*. 2017;14(11):1682-1689.