Treatment of COVID-19 – Evidence-Based or Personalized Medicine?

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The speed and ferocity of the COVID-19 pandemic seem to have thrown the principles of sober 21st century scientific medicine out the window. Guidelines are recommending drug treatments on the basis of little more than anecdotal evidence, clinicians are treating patients on the basis of non-peer-reviewed preprints, and prestigious journals are accused of rushing underpowered and even uncontrolled observational studies into print. As editors, we are keenly aware of the difficult balance between the need for rapid communication and the desire for robust data. Cooler heads caution that evidence-based medicine must not be abandoned, and unproven therapies should not be used outside of proper randomized controlled trials (1, 2). However, this advice is widely unheeded, as clinicians understandably are making the calculation that their patient is deteriorating and may not live long enough for the results of carefully performed and analyzed studies to be available-- and so they decide to take a chance. Neither side is necessarily wrong.

Although COVID-19 is as amenable to scientific study as any other infection, its enormous variability in clinical course and severity pose unique challenges for evidence-based medicine. SARS-CoV-2 initially evades interferon-dependent antiviral responses, allowing the virus to gain a foothold in the host (3). Most individuals eventually mount a protective immune response and recover uneventfully. However, others, particularly older patients and those with comorbid conditions such as hypertension, obesity and diabetes, experience more serious complications (4). Patients with progressive COVID-19 develop lower respiratory tract involvement, which may cause hypoxia with few or no respiratory symptoms (5), a dangerous situation that can be initially overlooked. Worsening COVID-19 is typically accompanied by a dysregulated inflammatory response (6), which is triggered by the SARS-CoV-2 virus and associated with marked elevations of IL-6 and several other cytokines, and may continue and escalate even as the viral burden diminishes (7). Acute respiratory distress is a frequent complication, but in particularly severe cases, a hypercoagulable state and

endothelial injury combine to create microthrombi in the lungs and other organs (8), often with lethal consequences.

This dynamic sequence of overlapping events with considerable heterogeneity among patients creates an enormous challenge for clinicians and clinical researchers alike. In the initial stages of infection, administration of interferon might be helpful to boost respiratory antiviral responses (9), but most patients require no specific intervention. Those with more significant infections require careful monitoring to ensure that they are not developing severe hypoxemia requiring supplemental oxygen (10). Antiviral agents are most likely to be useful early in the course of infection when viral loads are highest and before irreversible damage has occurred (11), but it is not a simple matter to predict the likelihood of clinical progression during the earliest stages of illness. A constellation of laboratory abnormalities are useful as biomarkers to monitor clinical progression: worsening lymphopenia and elevations of the neutrophil-lymphocyte ratio, CRP, LDH, ferritin, and IL-6 are predictive of further deterioration (12–14). Elevations of D-dimer may be particularly ominous as an indicator of intensifying coagulopathy and potentially lethal macro- or micro-vascular thrombotic events (15). Elevations of troponin T or creatinine signal secondary cardiac or kidney injury (16, 17). The clinician attempting to help a patient to navigate safely through the Scylla and Charybdis of virus and host response must ascertain the patient's clinical trajectory and how best to intervene, usually without a robust body of evidence for guidance. For a clinical investigator, the challenge is to define the subsets of patients who are most likely to benefit from a specific intervention, whether an antiviral, an immunomodulator, an anticoagulant, a non-pharmacological intervention, or some combination of the above. The failure to precisely define the target population and the timing of an intervention may make effective therapies appear ineffective (18), and similarly the failure to properly control for patient heterogeneity and the natural history of COVID-19 may cause ineffective therapies to appear effective (19).

This issue of *Clinical Infectious Diseases* contains several articles that illustrate different aspects of the challenges facing clinicians caring for patients with COVID-19. Larson et al. limited treatment to evidence-based interventions in 135 patients with COVID-19 (20), and none of their patients required mechanical ventilatory support or died, even though the cohort included patients with comorbidities associated with an increased risk of illness severity. This is a reminder that most COVID-19 infections are self-limiting with a benign clinical course, which makes it imperative to develop rigorous criteria to identify those patients who might benefit from specific interventions. Garcia-Vidal et al. adopted a more personalized approach to hospitalized patients with COVID-19 in Barcelona, dividing them into groups according to whether they exhibited physiology consistent with hyperinflammation, bacterial coinfection or hypercoagulability (21). Lower rates of progression and mortality were observed in the patients receiving treatment interventions that targeted their specific physiological pattern, in comparison to control patients who received standard care. Along similar lines, Hall et al. argue in a Viewpoints article that the variable immune responses exhibited by different patients with SARS-CoV-2 infections require a personalized approach with regard to the use of immunomodulatory therapy that is based on the specific immunophenotype of the patient (22).

Evidence-based medicine has revolutionized and brought greater rationality to medical practice (23). However, evidence-based studies require patients who are sufficiently alike because of a shared condition, so that their responses to a clinical intervention will be generalizable. This seems to place evidence-based medicine at odds with personalized medicine, which emphasizes the aspects of each patient that make them a unique individual (24). Patients with COVID-19 are not only not all alike, they can be profoundly different from one another, with regard to both severity and pathophysiology. The heterogeneity of COVID-19 requires us to apply the principles of both evidence-based and personalized approaches to make rational treatment decisions, but also to

ensure that we are not being misled by compelling anecdotes. For now, clinicians must carefully assess the physiological status of an individual patient and their clinical course, while weighing the potential benefits and adverse effects of a treatment intervention, often on the basis of an inadequate evidence base. Clinical investigators who wish to improve this evidence base must be similarly aware of the complex dynamics of COVID-19 and take care to focus on patient populations who are most likely to benefit from a specific intervention, as well as to be wary of confounding by COVID-19's myriad effects. Evidence-based and personalized approaches each have much to offer the practice of medicine, and we are going to need both to combat COVID-19.

Potential conflicts of interest:

Dr. Fang reports personal fees and non-financial support from BioFire, personal fees and non-financial support from Cepheid, personal fees from IDSA, outside the submitted work. Dr. Schooley reports grants from Gilead Sciences, personal fees from SEMPRA Energy, personal fees from Abbvie, personal fees from CytoDyn, outside the submitted work; In addition, Dr. Schooley has a patent planned in the area of long acting anti-coronavirus compound discovery. pending.

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