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Humility: a virtue critical to both successful COVID-19 research and patient care

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> "If you are humble, nothing will touch you, neither praise nor disgrace…." - Mother Teresa

Healthcare professionals and researchers spend years acquiring expertise in their fields. We learn to pride ourselves on competence and knowing what to do or what questions in a given situation. However, having the humility to recognize to recognize how much we do not know has long been recognized as an asset for even expert physicians.[1]

In December 2019, an outbreak of atypical pneumonia was reported in Wuhan, China. This disease, now known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is called coronavirus disease 2019 (COVID-19).[2] While recent experiences with outbreaks of Zika virus and Middle Eastern Respiratory Syndrome have increased our awareness of the potential for new viral pathogens, no one has years of experience treating or studying this disease – no one is truly an expert in COVID-19. Yet the impact of this tiny single stranded RNA-enveloped virus on human activity has been truly been humbling.

As economic activity throughout the world ground to a halt, the academic medical community rapidly responded to the challenge of a new disease turning out a plethora of medical literature at a very rapid pace. A simple search using the term "COVID-19" on PubMed conducted on June 11, 2020 returned 21,542 publications. Medical societies rapidly issued guidelines for management of patients which emphasized supportive care.[3] While much of the literature is low quality evidence (anecdotes, case reports/case series, and hypothesis generating studies), it has played a critical role by not only giving clinicians guidance in how to manage these patients, but also by raising many additional questions that urgently need to be answered with rigorous research.

By the time we saw our first case in Delaware, we had learned from analysis of cohorts in China that over 80% of symptomatic patients have relatively mild symptoms, around 14% have more severe symptoms and only about 5% become critically ill.[2] This immediately raises the yet to be answered questions: why do some people become critically ill while others are only mildly ill or even asymptomatic? Is the differential response to this infection related to genetic or environment factors or both? If we understand this, will it lead us to interventions that might move more patients from the critically or severely ill categories into the mild category?

As time progressed, the medical community began to develop more theories about the pathogenesis of COVID-19. It was proposed that the disease occurred in 3 stages.[4] Stage 1 is early infection. Symptoms at this stage are mild and some patients may not progress beyond this stage. Stage 2 is the pulmonary phase where hypoxemia may develop, and also where the host inflammatory response starts to become more of a problem than the virus itself. A small proportion of patients will transition to stage 3 where hyperinflammation from the host response is the main problem and may become fatal. It was also noted that seemed to be thrombosis was more common in patients with COVID-19 than in other critically ill patients.[5,6] Again, this

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knowledge raises additional questions about why some patients progress and others do not, and what interventions might improve outcomes.

Our evolving understanding of the pathophysiology of COVID-19 has allowed us to make educated guesses about interventions that may be helpful. For example, early in the disease process antiviral therapies such as Hydroxychloroquine and Remdesivir have been proposed as treatment options. As the disease progresses to the hyperinflammatory stages, steroids and immunomodulatory drugs such as Tocilizumab have been proposed as potential treatments.[7] Additionally, some experts have proposed more aggressive prophylaxis against venous thromboembolism than is normally used in hospitalized patients. All of these interventions (with the possible exception of steroids) are currently being evaluated in randomized controlled trials. These trials will not only provide important information on the effectiveness of these interventions, but will also provide critical information on the adverse effects associated with use of these drugs in the COVID-19 patient population. Unfortunately, the history of medicine is full of biologically plausible interventions that ultimately proved to have more harm than benefit (e.g., hormone replacement therapy for the purpose of reducing cardiovascular risk and activated protein C for the treatment of sepsis).

Physicians act responsibly by considering if they have equipoise about treatments before enrolling patients in clinical trials. For example, if a physician feels there is sufficient reason to believe that steroids either cause harm or have benefit in COVID-19 then he or she would not have equipoise to allow his or her patient to participate in a trial where the steroids were assigned to be given, or not based on randomization.

It is critical that we take a disciplined rigorous approach to studying this disease and some physician-scientists have suggested that these potential interventions should only be used in the setting of clinical trials. However, faced with the urgent need to “do something” – particularly for the 5% of patients who develop life threatening critical illness – and limited clinical research infrastructures, many physicians have decided that limiting these interventions to only patients enrolled in trials is not appropriate. Instead, clinicians are making their best guesses based on incomplete knowledge and trying to do their best for their patients. Therefore, at the same time as we attempt to study these interventions, they are also all being used by clinicians to treat patients. This seems to be true both at large academic centers where clinical trials are being conducted and in the community.

As we treat patients, it is tempting for physicians to become convinced that certain treatments are effective or ineffective based on physiology, pathology, personal experience, and low-quality evidence. This failure to be humble can be particularly tempting for clinicians used to being “the expert” on their disease. Clinically, this can result in significant variation from institution to institution in terms of clinical practice based on the different thought leaders at individual centers. From a research perspective, it can cause loss of equipoise resulting in a chilling effect on recruitment for randomized trials needed to determine which treatments, if any, will ultimately prove effective. In the worst-case scenario, it can result in policy making based on anecdote. It remains critically important to remember that we do not have all the answers yet, and in fact, probably do not even know all the right questions.

The challenge of simultaneously “doing something” and figuring out the right thing to do is not unique to the COVID-19 pandemic, but it is amplified under the current circumstances. This challenge can only be met with healthy dose of humility. It is inevitable that some of our best

guesses will be wrong. However, being clear about what we do not know will allow us to ask intelligent questions and do the rigorous studies required to find the answers. Ultimately, if we do that, our patients will be the winners.

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