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Reflections on a Year of SARS-CoV-2

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As we are writing this editorial 12 months following the publication of "The 2019 Novel Coronavirus: A Crown Jewel of Pandemics?", there are 96 million cases with over 2 million total deaths, a public health tragedy of staggering proportions [1]. The early stages of the pandemic were characterized by scientific uncertainty, with many authors postulating hypotheses about the transmission of SARS-CoV-2, the appropriate medical treatment, and the most effective public health measures. In retrospect, many of the early takes on coronavirus ended up being incorrect. Since January 2020, science has advanced at a breathtaking pace and the disease caused by SARS-CoV-2 has taken on dimensions few of us anticipated. In this piece, we aim to reflect on the last year, discussing aspects of the pandemic that the scientific community correctly anticipated, and highlighting where we went wrong.

For the SARS-CoV-2 pandemic to have taken on its current dimensions, two conditions must have been met: first, a viral transmission pattern that was unusually infectious, and second, an ineffective public health response. Last January, we anticipated SARS-CoV-2 to spread similarly to MERS-CoV and SARS-CoV, mainly after infected patients started presenting respiratory tract symptoms. We were just beginning to appreciate the potential for human-to-human transmission. However, one of the most surprising and alarming discoveries was the fact that SARS-CoV-2 could spread asymptomatically [2]. In the early stages of the pandemic, with the number of cases small, our ability to identify asymptomatic transmission was impaired leading to a drastic underestimation of the viral transmission potential of the virus [3]. Furthermore, the high reproductive number (R_0), combined with the relatively mild disease severity, led to efficient spread. Unlike SARS-CoV and MERS-CoV, where the disease severity and viral dynamics contained the outbreaks and decreased their likelihood of becoming pandemics, the SARS-CoV-2 outbreak hit the Goldilocks zone of infectivity and severity [4].

The fact that asymptomatic transmission has been a major vector in the propagation of the disease shifted the main transmission locus from a healthcare setting to a community setting [5]. This shift made an effective public health response crucial, and our failings in that arena magnified the effect of the pandemic. Our first major failing was the delayed recognition and reporting of the severity of the disease. Our second failing was the reticence of governments around the world to implement lockdowns and social distancing measures, which lead to the virus accelerating its spread in the community and overwhelming the capacity of healthcare systems. Third, mixed public health messaging undermined public confidence and led to skepticism in adopting social distancing measures when they were implemented. The asymptomatic spread combined with an ineffective public health response made our January 2020 prediction—that SARS-CoV-2 could be easily contained by identifying and quarantining symptomatic patients—nearly impossible to come to fruition.

Our understanding of COVID-19 symptomatology has evolved, and we now begin to appreciate the breadth of presenting symptoms, the unique disease course, and the long-lasting sequelae of the disease. In addition to the upper respiratory and viral pneumonia symptoms that were initially reported, we have seen patients initially presenting with anosmia, abdominal pain, headaches, diarrhea, or skin rashes [6]. Similar to the range of symptoms that patients have reported is the vast gamut of disease courses. While up to 20% of patients are completely asymptomatic, others have experienced everything from mild malaise and myalgias to illness severe enough to warrant intensive care [7].

Of course, the intensive care clinician was more likely to encounter the severe forms of the disease. Last January, we recognized ARDS as a major complication of severe COVID-19 courses, contributing to much of the critical care need in the months ahead. In the coming months, we began to observe COVID-19 co-

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agulopathies, potential myocardial injuries, as well as a wide range of other pathologies associated with prolonged ICU stays [8, 9]. One of the challenges we faced was discerning signal from noise—with the majority of scientific attention devoted to this disease, many spurious associations of COVID-19 and various diseases have been postulated—yet very few have been definitively proven. This challenge, however, was nowhere as difficult as in determining the optimal COVID-19 treatment.

The treatment for COVID-19 has been mired by controversy, but the key takeaway of the last 12 months is that there is no silver bullet. Several therapies have been suggested: hydroxychloroquine, azithromycin, remdesevir, dexamethasone, bamlanivimab, casirivimab plus imedvimab, with few holding up to strict scientific scrutiny. Based on our current understanding of the disease, two main processes are driving the pathogenesis of COVID-19. In the early stages of the infection, the disease is mediated by the replication of SARS-CoV-2; later stages of the disease are driven by an over-exaggerated immune response to the virus, leading to tissue damage and a viral sepsis phenotype [10]. This creates a two-pronged strategy to treat the virus. Treatment for the early stages of the disease is focused on adjuvating the immune system with antiviral agents and monoclonal antibodies. Currently, monoclonal antibodies such as bamlanivimab and casirivimab plus imedvimab are recommended in outpatients with a high risk of disease progression [10]. Remdesevir, the only FDA-approved antiviral, is recommended for use in hospitalized patients that require supplemental oxygen; however, remdesevir is not recommended in mechanically-ventilated patients [10, 11]. The later stages, where the immune system dysregulation predominates, is postulated to respond more effectively to immunosuppressive/anti-inflammatory agents. Dexamethasone has been shown to have a survival benefit in hospitalized patients requiring ventilatory support, with the greatest benefit derived by those receiving mechanical ventilation [10, 12].

Still, despite all the resources invested in developing novel pharmacological strategies for managing coronavirus, the most effective measure remains good intensive care. Current guidelines recommend high-flow nasal cannula (HFNC) for adults with COVID-19 and acute hypoxemic respiratory failure who are nonresponsive to conventional oxygen therapy [13]. When/if intubation becomes medically necessary, the procedures should be performed by experienced practitioners, with the use of video laryngoscopy strongly recommended. After intubation, lung-protective ventilation, with low tidal volumes and plateau pressures <30cm H_2O is optimal [13]. As many patients with COVID-19 develop ARDS, long-proven strategies of managing ARDS should be implemented including proning, neuromuscular blockade, and regular recruitment maneuvers [13]. While unique COVID-19 ARDS phenotypes have been proposed, existing evidence does not support these hypotheses [14]. As we mentioned in our previous editorial, the management of COVID-19 has to be centered on high-quality, evidence-based intensive care.

While the vast majority of patients that an intensivist sees are adults, the severe cases of SARS-CoV-2 related disease are not limited to this age group. In fact, pediatric patients originally thought to be at low risk of developing severe complications with SARS-CoV-2 infection have required ICU care—most commonly for a COVID-related Multisystem Inflammatory Syndrome in Children (MIS-C). Cases of this inflammatory syndrome were first widely reported to the scientific community last May by physicians in London, and soon thereafter in Italy, Spain, France, and the United States. The mean age of patients with MIS-C is 8 years old, and while some present with positive SARS-CoV-2 RT-PCR at the time of MIS-C diagnosis, most present with only positive serological antibody tests, suggesting a post-infectious immune pathophysiology [15]. MIS-C most commonly causes high fever, severe illness with multisystem organ involvement, and laboratory evidence of inflammation. When treated early, most patients respond well to intensive supportive care, IVIG, and immunomodulatory therapeutics [15]. Recently, we are also beginning to see reports of a post-infectious MIS-A (Multisystem Inflammatory Syndrome in Adults), a similar COVID-19-related systemic inflammatory condition in patients over the age of 18, although the evidence for is less established [16].

Over the past 12 months, we faced the challenge of containing the pandemic. Now, with two vaccines approved and more under investigation, we face the challenge of vaccinating our population. Few of us could have imagined the scale of the SARS-CoV-2 outbreak, the profound transformation of our society, and the many medical questions that we are continually working to answer.

There are still many unanswered questions as the pandemic continues in full force, from how we can best

treat COVID-19 patients and understand the full clinical picture of the SARS-CoV-2 infection, to how we can manage the new highly infectious SARS-CoV-2 strains and vaccinate our population. Much remains to be learned about SARS-CoV-2, but our medical and scientific community has worked tirelessly to contain the pandemic and treat the affected patients and we will continue to do so.

Conflict of interest

None to declare.

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