EDITORIAL COMMENTARY

Disease Severity and Durability of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antibody Response: A View Through the Lens of the Second Year of the Pandemic

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(See the Major Article by Betton et al on pages e1337–44.)

Our initial lack of understanding of the pathogenesis of coronavirus disease 2019 (COVID-19), a previously unknown viral disease, fueled a devastating pandemic. The development of tools to identify and dissect the immune response to its causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was the first step in contending with the worst humanitarian catastrophe since the 1918 influenza pandemic.

Within months of its emergence, the novel coronavirus now known as SARS-CoV-2 was identified and sequenced. This rapidly led to the development of a multitude of platforms to detect SARS-CoV-2 nucleocapsid protein, spike proteins, and spike protein receptor-binding domain (RBD) antibodies and assess antibody function with live virus and surrogate neutralization assays. Deployment of these platforms led to a steady accumulation of data on the SARS-CoV-2 antibody response. In aggregate, these data associate the magnitude of the antibody response with the severity of COVID-19; hospitalized patients exhibit higher responses than nonhospitalized patients, and severely ill hospitalized patients exhibit higher responses than less critically ill patients [1–4].

A central question about any infectious disease is whether survivors are immune to subsequent infection, and if so, for how long. Population-based analyses of SARS-CoV-2 infection show that previously infected individuals have a markedly reduced risk of infection (84% in 1 study [5]) compared with those without prior infection [5–9]. While the methods, time of sample collection, and documentation of infection in these studies may stimulate debate, they provide an important and biologically plausible link between prior SARS-CoV-2 infection and protection from subsequent infection.

As evidenced by the incontrovertible historical success of convalescent serum for pandemic influenza and meningitis [10] and vaccination to prevent smallpox, polio, measles, mumps, rubella, and varicella, specific antibody has long been recognized as the central mediator of protection against viral infections. For COVID-19, the triumph of SARS-CoV-2 vaccines in preventing severe disease and death [11–13], the ability of monoclonal antibodies to prevent disease progression in individuals with early disease [14, 15], and the promising signals of efficacy of high-titer convalescent plasma used early in disease [16, 17], provide indisputable evidence that specific antibody mediates protection against COVID-19.

The duration (durability) of protection conferred by newly introduced spike protein-based vaccines may depend on their ability to induce lasting T- and B-cell memory. Reassuringly, SARS-CoV-2 infection induced durable spike protein antibody and B- and T-cell memory for ≥8 months across a spectrum disease severity [4]. The stunning success of SARS-CoV-2 vaccines owes to the robust spike protein and neutralizing antibody responses they elicit. In providing an immediate first line of defense, neutralizing antibodies are likely to induce rapid viral elimination. The extraordinary effectiveness of SARS-CoV-2 vaccines provides proof of the concept that SARS-CoV-2 antibodies mediate viral control. This is underscored by accumulating evidence that, compared with seronegative individuals, those who are SARS-CoV-2 immunoglobulin (Ig) G seropositive have substantially reduced rates of subsequent infection [9, 18], albeit for unknown duration.

It is estimated that >2 000 000 people in the United States were hospitalized with COVID-19 between August 2020 and April 2021 (https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions), and new cases and hospitalizations

continue to surge in some areas despite increased vaccine availability and uptake. Patients with COVID-19 who require hospitalization are more likely to be elderly, belong to racial and ethnic minorities, and/or have comorbid conditions that increase the risk of disease progression and death [19, 20]. As such, their SARS-CoV-2 antibody responses may provide new insights into SARS-CoV-2 pathogenesis that may in turn inform vaccine and treatment strategies.

Betton and colleagues investigated the durability of SARS-CoV-2 antibody responses of recovered patients who were hospitalized with COVID-19 pneumonia [21]. The study cohort included 107 patients enrolled in the French Covid Cohort, in whom nucleocapsid protein (NP) IgG, spike protein RBD (S [RBD]) IgG, and SARS-CoV-2 neutralization with the S-fuse platform [22] were measured 3 and 6 months after hospital discharge. The patients had a median age of 58 years; 51% had risk factors for severe COVID-19, 10% were immunosuppressed, 33% required intensive care unit (ICU) care, and 14% required mechanical ventilation. A significantly higher proportion of patients requiring ICU care than those who did not received anti–interleukin 6 antibody (29% vs 10%) or corticosteroids (9% vs 3%). NP IgG, S (RBD) IgG, and SARS-CoV-2 neutralization were significantly higher at 3 than at 6 months. Either NP or S (RBD) IgG was detectable in 104 of 107 patients at 6 months after discharge, and some degree of neutralization was present in all serum samples. However, NP IgG and neutralization were significantly higher in patients who required mechanical ventilation or ICU care than in those that did not require either.

Given the association between NP IgG, COVID-19 severity, and mortality rates [23], NP IgG in the cohort studied by Betton et al may be a proxy for viral load and nucleocapsid expression. Early in the pandemic, NP IgG was shown to be correlated with disease severity, nasopharyngeal viral load, and prolonged SARS-CoV-2 shedding from multiple tissues [2]. The latter suggests that the marked fall in NP IgG 6 months after discharge reported by Betton et al, especially in previously mechanically ventilated patients, may reflect clearance of persistent virus or viral antigens. Although coronaviruses are not known to exhibit classic latency [24], COVID-19 is too new a disease for us to know whether tissue persistence of SARS-CoV-2 and/or its antigens contributes to serological or B-cell memory. Nonetheless, it is interesting to speculate that antigen persistence in the lungs or gastrointestinal tract may stimulate resident memory B cells to provide a first line of defense against SARS-CoV-2 [25, 26]. Notably, several investigator groups, including a group that identified SARS-CoV-2 in gastrointestinal tissue [27], have reported continued evolution of the SARS-CoV-2 memory B-cell response for months after infection, as evidenced by ongoing somatic mutation, increased neutralization potency, and breadth [27, 28].

Serum S (RBD) IgG from the cohort reported by Betton et al exhibited less change than NP IgG between 3 and 6 months and did not differ as a function of clinical status. Although spike protein is less abundant than nucleocapsid, S IgG was stable up to 8 months after COVID-19 in a cohort of hospitalized and nonhospitalized patients, with levels paralleling disease severity [4]. In an elegant systems serology model, COVID-19 survival was linked to a signature of S IgG functions, including antibody-dependent phagocytosis and cellular cytotoxicity [23]. Thus, in concert with neutralization, S IgG may enhance viral clearance and dampen inflammation [29]. Antibody-mediated immune modulation may be beneficial. A study that linked survival of hospitalized patients to a higher ratio of neutralizing to total RBD IgG [3] found that levels of RBD IgG were lower in patients who received tocilizumab or corticosteroids, and neutralization was reduced in those who received corticosteroids [30]. This raises the concern that immunosuppressants may compound COVID-19 immunosuppression and impair SARS-CoV-2 antibody affinity maturation and the development of durable B-cell memory.

The results of Betton et al extend existing data associating SARS-CoV-2 antibody levels with disease severity to hospitalized patients with COVID-19 pneumonia 6 months after discharge. Reassuringly, they also showed that neutralization of the B1.1.7 and P0.1 variants of concern was comparable to that of the D614G variant, while, as expected, neutralization of B0.1.351 was significantly less. This underscores the fact that the natural polyclonal SARS-CoV-2 antibody response consists of a diverse collection of antibodies recognizing a multitude of SARS-CoV-2 determinants, serving as a reminder that individuals who recover from infection with SARS-CoV-2 variants have antibodies specific to these strains in their serum [31]. Given that seropositive SARS-CoV-2 antibody status is associated with a reduced risk of SARS-CoV-2 infection, it is comforting that S (RBD) IgG and neutralization are durable in serum samples from previously hospitalized patients. However, it must be noted that, at present, we know neither the amount nor the exact function or epitope specificity of SARS-CoV-2 antibodies that mediate protection against SARS-CoV-2 acquisition (infection) or disease. Given animal models showing SARS-CoV-2 antibody protection against pneumonia, but not the nasopharynx [32–34], it should be noted that protection may be tissue specific and certain types of antibodies may mediate protection in one tissue but not another.

It has been more than a year since the emergence and global spread of pandemic SARS-CoV-2, which devastated humanity and overwhelmed healthcare systems worldwide. The staggering amount of new knowledge gained since the onset of the pandemic is a celebration

of humanity and science. We have learned that antibody plays a critical, if not indispensable, role in early viral elimination, and while the magnitude and durability of the response are greatest in those who were the sickest, even mild COVID-19 elicits durable SARS-CoV-2 memory B and T cells, though serum antibody may wane [4, 27, 35]. We now have highly effective vaccines that elicit robust antibody responses and prevent severe disease and death, but treatment options for patients hospitalized with COVID-19 remain extremely limited. While neutralizing monoclonal and vaccine-elicited neutralizing antibodies prevent progression of early COVID-19, antibody functions that induce clearance of viral antigens and dampen inflammation may be needed for efficacy against established disease [29]. Given the continued dearth of treatment options for hospitalized patients with COVID-19 and the diverse functions of SARS-CoV-2 antibodies [23], further analysis of the effect of SARS-CoV-2 antibodies on SARS-CoV-2 pathogenesis and biology are warranted.

Notes

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