Disease severity and durability of the SARS-CoV-2 antibody response: A view through the lens of the second year of the pandemic

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Introduction

Our initial lack understanding of the pathogenesis of 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, SARS-CoV-2, was the first step in contending with the worst humanitarian catastrophe since the 1918 influenza pandemic.

Text

Within months of its emergence, the novel coronavirus now known as **S**evere **A**cute **R**espiratory **S**yndrome-**Co**ronavirus-**2** (SARS-CoV-2) was identified and sequenced. This rapidly led to the development of a multitude of platforms to detect SARS-CoV-2 nucleocapsid, spike proteins, and spike protein receptor binding domain antibodies, and assess antibody function with live virus and surrogate neutralization assays. Deployment of these platforms led to steady accumulation of data on the SARS-CoV-2 antibody response. In aggregate, these data associate the magnitude of the antibody response with Covid-19 severity; hospitalized patients exhibit higher responses than non-hospitalized 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 one study [5]) compared to those without prior infection [5-9]. While the methodology, 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 sera 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 at least 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 to seronegative individuals, those that are SARS-CoV-2 IgG seropositive have substantially reduced rates of subsequent infection [9, 18], albeit of unknown duration.

It is estimated that > 2,000,000 people in the U.S. 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, racial, and ethnic minorities, and/or have co-morbid 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. The study cohort included 107 patients enrolled in the French Covid Cohort from whom nucleocapsid (NP)-IgG, spike protein RBD (S (RBD))-IgG, and SARS-CoV-2 neutralization using the S-fuse platform [21] were measured 3 and 6 months after hospital discharge. Median age was 58 years, 51% had risk factors for severe Covid-19, 10% were immunosuppressed, 33% required ICU care, and 14% required mechanical ventilation. A significantly higher proportion of patients requiring ICU care than those who did not received anti-IL-6 antibody (29% versus 10%) and corticosteroids (9% versus 3%). NP-IgG, S (RBD)-IgG, and SARS-CoV-2 neutralization were significantly higher at 3 than 6 months. Either NP- or S (RBD)-IgG was detectable in 104 of 107 patients 6 months after discharge and some degree of neutralization was present in all sera. However, NP-IgG and neutralization were significantly higher in patients who required mechanical ventilation or ICU care than those that did not require either.

Given the association between NP-IgG, Covid-19 severity, and mortality [22], NP IgG in the Betton et. al., cohort may be a proxy for viral load and nucleocapsid expression. Early in the pandemic, NP IgG was shown to correlate 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 in the Betton et. al., cohort, especially in previously mechanically ventilated patients, may reflect clearance of persistent virus or viral antigens. Although coronaviruses are not known to exhibit classical latency [23], Covid-19 is too new of a disease to know if tissue persistence of SARS-CoV-2 and/or its antigens contribute 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 [24, 25]. Notably, several groups, including one that identified SARS-CoV-2 in gastrointestinal tissue [26], 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 [26, 27].

Serum S (RBD)-IgG from the Betton et. al., cohort 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 non-hospitalized 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 [22]. Thus, in concert with neutralization, S-IgG may enhance viral clearance and dampen inflammation [28]. 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 RBD-IgG was lower in patients who received tocilizumab or corticosteroids and neutralization was reduced in those who received corticosteroids [29]. 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 that associate 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 P.1 variants of concern was comparable to that of the D614G variant, while as expected, neutralization of B.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 that recognize a multitude of SARS-CoV-2 determinants, serving as a reminder that individuals who recover from infection with SARS-CoV-2 variants have specific antibodies to these strains in their sera [30]. Given that seropositive SARS-CoV-2 antibody status associates with a reduced risk of SARS-CoV-2 infection, durable S (RBD)-IgG and neutralization in sera of previously hospitalized patients are comforting. However, it must be noted that at present, neither the amount, nor the exact function/s, or epitope specificity of SARS-CoV-2 antibodies that mediate protection against SARS-CoV-2 acquisition (infection) or disease are known. Given animal models showing SARS-CoV-2 antibody protection against pneumonia, but not the nasopharynx [31-33], 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 one 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, 26, 34]. 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 [28]. Given the continued dearth of treatment options for hospitalized patients with Covid-19 and the diverse functions of SARS-CoV-2 antibodies [22], further analysis of the effect of SARS-CoV-2 antibodies on SARS-CoV-2 pathogenesis and biology are warranted.

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