Antibody Dynamics and Durability in Coronavirus Disease-19

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KEYWORDS

• COVID-19 • Antibodies • IgG • IgA • IgM • Durability • Germinal center
• Plasma cells

KEY POINTS

- IgM, IgG, and IgA raised to SARS-CoV-2 appear concurrently in most COVID-19 cases by 10 days after symptom onset.
- Antibody titers are highest in subjects with severe COVID-19 and antibody therapeutics are most effective when administered early.
- Although IgM and IgA decline to near baseline levels over 3 months, total IgG raised during acute COVID-19 peaks 1 month following symptom onset then declines to a relatively stable plateau after recovery for at least 6 months.
- Neutralizing antibody responses are frequently lower titer and may reach baseline faster than total antibody responses.

INTRODUCTION

COVID-19 has emerged as the greatest global health threat in generations. An unprecedented mobilization of researchers has generated a wealth of data on humoral responses to SARS-CoV-2 within a year of the pandemic's beginning. The rapidly developed understanding of acute-phase antibody induction and medium-term antibody durability in COVID-19 is important at an individual level to inform patient care and a population level to help predict transmission dynamics. In this brief review,

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we will describe the development and maintenance of antibody responses to immunization and infections generally and the specific antibody dynamics observed for COVID-19. These crucial features of the humoral response have implications for the use of antibody therapeutics against the virus and can inform the likelihood of reinfection of individuals by the virus.

OVERVIEW OF B CELL ACTIVATION AND ANTIBODY RESPONSES

Although there is considerable variation between different infectious diseases and vaccinations, the development of pathogen-specific antibodies follows a similar course in most cases. During a primary exposure, the antibody response is generated through the activation of naïve B cells that have completed development but have not previously been activated. B cell development in the bone marrow produces millions of naïve B cell clones, each bearing a unique antibody generated through a process called V(D)J recombination[1]. Antibodies can be expressed both as secreted molecules and as a membrane form on the surface of B cells called the B cell receptor (BCR). Naïve B cells express antibodies in the form of IgM and circulate through blood to the follicles of secondary lymphoid tissues including lymph nodes, the spleen, and mucosal-associated lymphoid tissues like Peyer's patches. Circulation is continuous until the B cell encounters and binds a foreign antigen recognized by its BCR. After BCR binding, the antigen is internalized, digested, and processed for peptide presentation to CD4 T cells on major histocompatibility II (MHCII) surface proteins. CD4 T cells that recognize the peptide component of the foreign antigen displayed on MHCII will supply "help" in the form of activating cytokines and membrane-expressed ligands for costimulatory receptors on the B cell. Once the B cell receives BCR signal and T cell help, it can follow one of the 2 cardinal paths of differentiation into a dedicated antibody-secreting cell. The first is to migrate out of the follicles and immediately begin producing antibodies by differentiating into plasmablasts and short-lived plasma cells (SLPCs). Plasmablasts and SLPCs relatively rapidly undergo apoptosis and produce a transient "extrafollicular" antibody response. The second is to enter a germinal center, a microanatomical site in the follicle in which an antibody refinement process called affinity maturation occurs. Affinity maturation selects B cells bearing the highest affinity antibodies via competition for T cell help for expansion and differentiation into long-lived plasma cells (LLPCs). LLPCs migrate to the bone marrow, whereby they can survive for years or even decades continuously producing high-affinity antibodies.

Different isotypes of antibody emerge during the B cell activation process via class switch recombination (CSR).[2] In brief, CSR is a DNA recombination process that allows the B cell to convert its antibody from its initial expression as IgM to the other antibody isotypes, IgG, IgE, and IgA. The IgM-encoding exons are excised and replaced with exons for another isotype found downstream on the chromosome. IgM production usually precedes other isotypes from the early extrafollicular antibody responses, as it is the form of antibody expressed by naïve B cells. As B cell activation progresses, CSR occurs, and other isotypes begin to appear. Following the resolution of infection and the death of the SLPCs, pathogen-specific IgM in serum will wane but some pathogen-specific IgG will persist, supplied by the LLPCs in the bone marrow. IgG and other isotype levels thus lag IgM by several days but will eventually rise to become the dominant antibody produced in most cases.

A biphasic antibody response emerges from this activation process (**Fig. 1**). For a primary exposure (without preexisting memory), B cell activation takes at least several days to produce measurable antibody following an infectious challenge in all

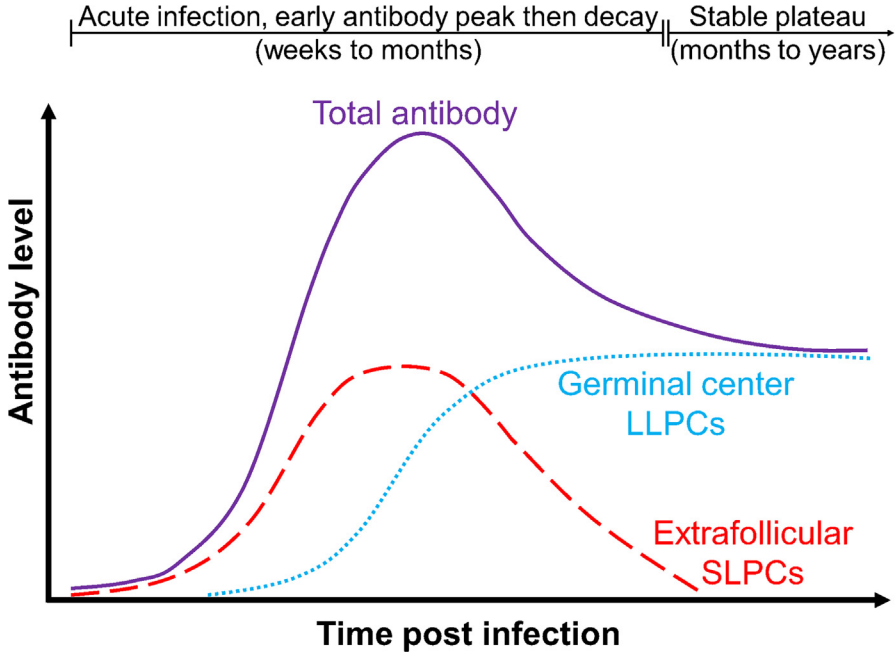

Fig. 1. *Schematic of idealized antibody responses following infection.* A solid purple line represents total antibody levels raised against a pathogen following infection, a dashed red line represents the contribution of extrafollicular SLPCs and plasmablasts and a dotted blue line the contributions of germinal center-originating LLPCs.

circumstances. Peak antibody levels are usually observed several weeks after the initial exposure and are derived from a combination of SLPCs and LLPCs. As the SLPCs undergo apoptosis and the antibodies they produced decay, a stable plateau below the peak is reached representing the contribution of LLPCs. Serum IgG can remain stable for years or even decades with minimal decline assuming robust induction of LLPCs over the course of the infection.

ACUTE PHASE ANTIBODY RESPONSES TO SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Challenges to Severe Acute Respiratory Syndrome Coronavirus 2 Antibody Research

Studies of antibody responses to SARS-CoV-2 have been published at an unprecedented speed since the beginning of the pandemic; however, several factors can somewhat complicate the synthesis of this collected work into a uniform model of SARS-CoV-2 serology. First, most groups studying SARS-CoV-2 antibodies have used custom assays. Commercially available clinical tests could be used as a universal standard, but they have many limitations including poor quantitation, limited availability at the onset of the pandemic, and high cost to implement. The use of lab-specific assays is particularly an issue with different antigens measured between studies. Usually, a combination of nucleocapsid, spike, and receptor-binding domain of spike is used but rarely are studies exactly identical in the antigen(s) deployed. Also, whether or not the assay used is fully quantitative can affect data interpretation. For

instance, many studies use single dilution optical density measures from ELISA assays which are insufficient to generate a true antibody titer; all values above or below the upper and lower limits of detection are compressed when using a single dilution approach. Heterogeneity of disease outcomes observed following SARS-CoV-2 infection influences virus-specific antibody dynamics as different patterns of accumulation and decay may be observed depending on the severity of COVID-19. Individuals that develop symptomatic COVID-19 have a range of experiences from a mild, cold-like disease that resolves in days to lethal pneumonia,[3] Furthermore, 40% to 45% of SARS-CoV-2 individuals are asymptomatically infected, manifesting no symptoms at all following exposure.[4] The patient cohorts used in studies of COVID-19 serology are frequently skewed toward individuals falling into one disease category, and conclusions drawn from these studies may not apply broadly to all COVID-19 cases. Apart from challenges to unifying observations from different studies, a further challenge arises when attempting to relate the speed of SARS-CoV-2 antibody emergence to the time of infection. It would be of great interest to correlate the speed of inducing adaptive immunity to viral clearance. Unfortunately, virtually all studies are limited to timing responses based on time after symptom onset, which can be easily determined by surveys in contrast to determining the specific exposure that resulted in an individual's infection. Because the incubation period before symptom onset is relatively lengthy and varied for COVID-19, ranging from 2 to 14 days with a median of 4 to 5 days,[5,6] time after symptom onset has an uncertain relationship with time after infection. With these caveats in mind, a reasonably consistent picture of antibody kinetics following the onset of COVID-19 symptoms has emerged and will be discussed later in discussion.

Antibody Kinetics During Acute-Phase Coronavirus Disease-19

Early SARS-CoV-2 antibody responses are similar between individuals that ultimately suffer mild disease or moderate to severe disease.[7] A majority of individuals seroconvert between 1- and 2-weeks postsymptom onset.[7–14] Some subjects have been shown to seroconvert before 1 week after symptom onset, but this is uncommon.[8,9,11,12,14,15] By 2 to 3 weeks after symptom onset, greater than 85% of subjects are reported to seroconvert across studies, with many studies reporting close to 100% seroconversion among symptomatic subjects.[8,9,11,13,14,16] With respect to the emergence of different antibody isotypes, humoral immunity in COVID-19 presents interesting deviation from the idealized response detailed above. IgM has not been consistently observed to develop before IgG or IgA in COVID-19; most studies show concurrent development of all 3 isotypes. At approximately 1 month after symptom, onset antibody responses peak in convalescent individuals. The peak antibody response can be robust, but convalescent subjects show a broad range of reported peak titers, with individuals recovering from mild infection (which may still be weeks of symptomatic disease) often showing only modest antibody levels.[17–19] Subjects that fail to swiftly resolve SARS-CoV-2 and develop severe disease continue to accumulate antibody. Disease severity is the most frequently reported correlate of the magnitude of antibody response across many independent studies, with hospitalized subjects consistently reported to have high titer antibody responses.[16–21]

Implications of Severe Acute Respiratory Syndrome Coronavirus 2 Antibody Dynamics for the Use of Antibody Therapeutics

Both convalescent plasma and monoclonal antibody therapeutics were rapidly deployed to treat COVID-19 in the early phases of the pandemic. The absence of

anti-SARS-CoV-2 antibodies early after symptom onset and the consistent presence of high titer antibodies in severe COVID-19 suggest that these drugs are most likely to be useful immediately following symptom onset, before endogenous antibody production, and highly unlikely to have a meaningful contribution to disease resolution in individuals with sustained symptoms and/or hospitalization. The available data for both convalescent plasma and monoclonal therapies support this model with the caveat that, in spite of the wide use and reporting on antibody treatment, few rigorous randomized controlled studies (RCTs) have been published. For convalescent plasma, one RCT showed a benefit of treatment within 72 hours after symptom onset to elderly subjects,[22] but 3 other RCTs in which plasma was administered a median of 8 or 9 days after symptom onset showed no difference between control and treatment groups.[23–25] An additional well-conducted retrospective study of convalescent plasma use in COVID-19 supports the administration of high titer plasma to subjects early after symptom onset but found no effect of the treatment later in the disease course.[26] RCT data for monoclonal antibody therapies agree with the results of the convalescent plasma studies. The use of monoclonal therapies for the treatment of hospitalized subjects with severe disease has no demonstrated benefits,[27] whereas the administration of large doses of antibody early following diagnosis has been shown to reduce viral loads and visits to health care facilities.[28–30]

DURABILITY OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 ANTIBODY IN CONVALESCENT SUBJECTS

Mixed Longevity of Vaccine- and Infection-Induced Antibodies

The longevity of an antibody response can vary widely. Most infectious challenges or immunizations produce a stable plateau of antibody supplied by LLPCs for many years.[31] However, this durability is not a necessary outcome even following a robust initial antibody response. For example, high titer measles/mumps/rubella (MMR)-vaccine-induced antibodies are estimated to have half-lives in the hundreds or even thousands of years. In contrast, a recent Zika virus vaccine trial showed almost complete loss of initially robust neutralizing antibody responses within 6 months.[32] Understanding whereby COVID-19-induced antibodies fall in this spectrum will influence the interpretation of serology as evidence of past infection and whether herd immunity to SARS-CoV-2 is likely via natural spread alone.

The best viral analogs to help predict COVID-19 antibody durability are related coronaviruses. Seven human disease-causing CoVs have been identified and are divided between 2 genera, the α and β coronaviruses. Two species within each genus are known to cause the common cold, HCoV-229E and HCoV-NL63 among α coronaviruses and HKU.1 and OC43 among β coronaviruses. Insightful data are available for antibody dynamics following HCoV-229E infection from a human challenge study by Callow *and colleagues*.[33] Volunteers were inoculated with HCoV-229E and their antibodies tracked longitudinally, with a secondary viral challenge conducted after 1 year. Antibodies peaked 3-weeks postinfection but then declined to near baseline levels at 1 year. This result suggests that antibody immunity to cold viruses is short-lived, consistent with the reports of rapid reinfection of individuals by these viruses outside of an experimental setting.[34,35] However, a complete loss of antibody to the cold viruses is not likely; in spite of a marked decline. Subjects still had somewhat higher antibody levels 1-year postinfection than in their prechallenge blood draw. Beyond the Callow study, seropositivity for the cold-causing viruses is high across age groups which would be unlikely if antibody was not retained to some extent for greater than 1 year.[36–38]

SARS-CoV and MERS-CoV are β coronaviruses and are the most closely related species to SARS-CoV-2. The available data suggest that antibody durability patterns in both MERS- and SARS-convalescent subjects are similar. Most subjects that have recovered from MERS-CoV-infection seroconvert; however, there is some variability in this regard.[39–42] Individuals that developed pneumonia and recovered display high titer antibody responses, but some individuals with mild or asymptomatic infections fail to produce detectable serum antibody following viral clearance.[39,41] In terms of maintenance of antibody levels, some subjects with mild disease lost detectable serum antibody within a year,[42] but most individuals with symptomatic disease retain detectable antibody for at least 1 year[40–42] and for as long as 3 years.[39] These observations are caveated by a relatively small number of MERS serology studies with low numbers of subjects per study. Seroconversion following SARS-CoV infection occurs between 4 and 14 days after symptom onset for greater than 90% of patients, with subjects developing IgM, IgG, and IgA responses in this window.[43] The durability of SARS-CoV antibodies is well documented,[44–49] with anti-SARS-CoV antibodies peaking 1 to 4 months after symptom onset and decaying to some extent, but not to extinction, by 1 year. Seropositivity is consistently high 2 years following recovery, with studies showing between 88% and 100% IgG positivity in this period.[44–48] However, after 3 years, seropositivity is less reliably observed, ranging from 54% to 100%.[46–48] Antibody levels were low across studies and discrepancies may be explained by differences in assay sensitivity. Additionally, a preprint study has recently reported retention of SARS-CoV antibodies over 12 years, finding that 69% of SARS-convalescent health care worker studies maintained detectable anti-SARS-CoV IgG through this period, albeit at low levels.[49]

Whether antibodies raised during COVID-19 are more similar to responses elicited by common cold-causing HCoVs or SARS-CoV and MERS-CoV is of consequence for projecting the maintenance of immunity and transmission patterns of the virus. However, it should be noted that antibody declines are not always a clear measure of loss of protection. Even if SARS-CoV-2 serum antibody wanes to baseline as observed for HCoV-229E, preexisting antibodies are not the exclusive source of the protection provided by adaptive immunity. Adaptive immune responses also expand pathogen reactive memory B and T cells that can rapidly reactivate upon secondary exposure. In fact, when the Callow HCoV-229E human challenge subjects described above were re-challenged with virus an asymptomatic infection resulted in contrast to their first symptomatic infection, suggesting that memory responses were sufficient to control disease without retention of serum antibody.

Durability of Total Anti-Severe Acute Respiratory Syndrome Coronavirus 2 Antibodies

By the summer of 2020, only a few months into the COVID-19 pandemic, reports of purportedly “rapid” decay of anti-SARS-CoV-2 antibodies were published or posted to the BioRXIV preprint server and widely covered by the popular media. These studies suggested the potential for transient immunity to SARS-CoV-2 following infection, analogous to common cold-causing HCoVs.[33–35] Data are consistent with the biphasic antibody response for anti-SARS-CoV-2 described above in which an initial decay from peak is followed by a lower but stable plateau of IgG.[7,14,18,20,21,50–57] Many studies have tracked the difference between antibody levels at peak, approximately 1 month after symptom onset, and 3 to 4 months later.[18,20,55–57] As expected, IgM rapidly decays in the months following the clearance of SARS-CoV-2, often below the limits of detection, with IgA following a similar trend, suggesting weak induction of IgA-producing LLPCs.[7,9,52,55,56] The IgG response falls from the initial peak to a

lower level but very rarely to baseline.[18,20,55–57] Although less data are available for antibody secretion at mucosal sites, one study of antibody levels in saliva suggests that antibodies produced at mucosal surfaces follow a similar pattern to the trends observed in serum.[56] Fewer studies are available looking at later timepoints, but the available data are consistent with stable total anti-SARS-CoV-2 antibody levels after the initial decay, including one rigorous study of adaptive immunity up to 8 months following disease onset.[50,51]

Durability of Severe Acute Respiratory Syndrome Coronavirus 2 Neutralizing Antibody Responses

Antibody levels against viral pathogens can be measured using 2 criteria: the total antibody that binds to viral antigens, most frequently as determined by ELISA, and virus-neutralizing antibody, measured by a neutralization assay. A virus-neutralizing antibody prevents infection by binding to the capsid or envelope proteins on the surface of the virion that facilitates attachment and entry into the host cell. Whereby an ELISA measures the simple binding of an antibody to antigens immobilized on plastic, a neutralization assay measures the capacity of antibodies to block the virus from entering live cells. Neutralization is a more stringent measure than binding alone. Only a subset of the total antibody produced against a virus contributes to neutralization; nonneutralizing antibodies can bind to regions of the viral proteins that do not impact its ability to enter cells. Neutralizing antibody titers correlate strongly with vaccine efficacy against other pathogens. If neutralizing antibodies prove to be critical to protection from SARS-CoV-2 reinfection, tracking retention of neutralizing antibody responses will be key to understanding the persistence of humoral immunity to SARS-CoV-2. Total anti-SARS-CoV-2 antibodies are retained with some decay for at least 6-months postsymptoms onset as described above. However, neutralization may show greater susceptibility to decay as neutralizing antibody levels are lower than total antibody level.[58] Indeed, several studies show a subset of COVID-19 convalescent subjects dropping below the limit of detection for neutralizing antibody as early as 3-months postinfection, while overall seropositivity is almost universally retained.[20,50,51,55,57]

A caveat to these results is that surveys of SARS-CoV-2 neutralizing antibody responses tend to rely on pseudovirus neutralization assays rather than measuring neutralization against authentic SARS-CoV-2 virus. SARS-CoV-2 is designated a biosafety level 3 pathogen, demanding specialized laboratory facilities available only to a few research groups. Pseudoviruses or pseudotyped viruses are chimeric virus particles that bear the surface envelope proteins of one virus, for example, SARS-CoV-2 spike, assembled into a secreted particle using components of another viral species, for example, VSV or HIV. Pseudoviruses do not necessarily incorporate the genetic material needed to replicate and can be used to measure the inhibition of a single round of entry into cells as a surrogate of authentic virus neutralization without posing a risk to researchers. Titers determined using pseudovirus neutralization and live virus neutralization tend to correlate, but are not necessarily identical. An excellent example of discordance between pseudovirus and live virus neutralization can be seen in trial data for the Moderna mRNA-1273 SARS-CoV-2 vaccine for which pseudovirus neutralization seems to underestimate the true neutralizing antibody titer induced by the vaccine as measured using authentic virus assays.[58,59] Additionally, stark discrepancies between pseudovirus- and live virus-measured neutralization for neutralizing monoclonal antibodies targeting the N-terminal domain of the spike protein have been reported, with high potency authentic virus-neutralizing antibodies failing to inhibit pseudovirus entry into cells.[60]

This decay in neutralization occurs in tandem with the emergence of new SARS-CoV-2 variants bearing mutations which reduce the potency of antibody responses raised against the original strain.[61–66] The combination of reduced neutralizing titers and variant strains resistant to antibodies raised against a historically circulating virus may reduce immunity to the virus sufficiently to allow for reinfection, analogous to what has been observed for cold-causing HCoVs.[34,35] The course of the pandemic in the city of Manaus in Brazil may lend credence to this scenario. Manaus had an exceptionally high rate of infection during the first phase of the pandemic in May 2020, with infection rates estimated to be 76% based on a serologic survey.[67] With this infection level, Manaus would be predicted to have achieved herd immunity. However, 8 months following the initial peak, a second COVID-19 wave has leveled a comparable morbidity and mortality burden on the city as a new SARS-CoV-2 variant, P1, swept through Brazil.[68] P1 is known to bear mutations that impact the efficacy of neutralizing antibodies raised against the original Wuhan strain of SARS-CoV-2.[61,63] Further study is necessary to better understand transmission dynamics of SARS-CoV-2 variants through putatively immune populations. Regardless, the prudent course is to deploy the highly efficacious COVID-19 vaccines as widely as possible to ensure robust adaptive immunity is widespread and maintained.

SUMMARY

In summary, antibody responses to SARS-CoV-2 follow a typical biphasic response pattern, reaching a peak approximately 1-month postsymptom onset followed by a period of decay to a stable, months-long plateau. Even following mild COVID-19, SARS-CoV-2 immunity follows a similar pattern to that observed for MERS-CoV or SARS-CoV, reducing the risk of reinfection and disease recurrence upon reexposure to homologous strain virus, as observed for common cold-causing HCoVs. However, genetic drift-driven emergence of new viral variants in tandem with frequently weak neutralizing antibody responses conspires to make reinfection risks with heterologous strains a continued concern. An important goal for future work will be to fully understand heterologous strain reinfection frequencies and to identify the degree to which antibody measurements such as neutralizing levels and SARS-CoV-2 variant cross-reactivity inform predictions and gauge risk levels for disease recurrence.

CLINICS CARE POINTS

- Neutralizing antibody function correlates with total anti-spike IgG levels.
- Neutralizing antibody levels correlates with immune fitness against SARS-CoV-2.
- Assays differ in standardization–requiring caution in interpretation across platforms.
- Protection from SARS-CoV-2 variants likely require greater anti-original-spike antibody levels.

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