

# Immunological Response of SARS-CoV-2 Infection

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## INTRODUCTION

Coronavirus Disease 2019 (COVID-19) pandemic has devastated the world in 2020. The number of COVID-19 cases has surpassed 62 millions, with over 1.4 million deaths as of 30th November, 2020. COVID-19 has also led to severe disruption in the socioeconomic activity. The World Bank has forecasted a 5.2% reduction in global GDP in 2020<sup>1</sup>.

COVID-19 is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified during a pneumonia outbreak in Wuhan in December 2019. Epidemiological studies showed that SARS-CoV-2 infection has a lower case-fatality rate than that of 2003 SARS-CoV, but can transmit much more efficiently between humans<sup>2</sup>. Seroprevalence studies showed that neutralising antibody against SARS-CoV-2 are not found in blood specimens collected before 2020 in Hong Kong<sup>3</sup>.

Understanding the immune response for COVID-19 is important for clinical practice. First, the correct interpretation of serology results requires a good understanding of the antibody kinetics during infection. Second, although SARS-CoV-2 can infect different organs and can directly cause tissue damage, many complications of COVID-19 are related to the dysregulated inflammatory response or immune-mediated damage. Third, understanding the immune correlates of protection is critical for risk assessment and for determining the immunogenicity of vaccines.

## CYTOKINE AND CHEMOKINE RESPONSE

Similar to other infections, SARS-CoV-2 infection is accompanied by elevated levels of cytokine and chemokines. Studies have shown that the cytokine/chemokine pattern in patients with critical illness is distinct from those with moderate disease severity [4]. Critically ill patients (those who died, required mechanical ventilation or ICU admission) had increased levels of all types of cytokines, including those from type 1 (against virus or intracellular bacteria, such as IFN- $\gamma$ ), type 2 (allergic or anti-helminth immunity, such as IL-5) and type 3 (against fungi or extracellular bacteria, such as IL-17) immunity. Critically ill patients also demonstrated persistently elevated levels of cytokines, while those with less severe disease demonstrated a progressive reduction in cytokine levels after day ten post-symptom onset.

Although the cytokine and chemokine levels are elevated among COVID-19 patients, the level is much lower than in other inflammatory conditions. A meta-analysis showed that the level of IL-6 is much lower among COVID-19 patients than patients with cytokine release syndrome, sepsis or acute respiratory syndrome unrelated to COVID-19<sup>5</sup>. This observation is important and suggests that the use of different cytokine inhibitors should be carefully evaluated.

## ANTIBODY RESPONSE (HUMORAL IMMUNITY)

### How Long Does it Take for Antibodies to Develop After Infection?

During the first week of symptom onset, only <50% of COVID-19 patients have detectable anti-SARS-CoV-2 antibody. The seropositive rate increases to over 95% two weeks after symptom onset<sup>6,7</sup>. Although some studies showed that IgM seroconversion is earlier than IgG, others showed similar timing in seroconversion<sup>7,8</sup>. Hence, antibody testing is not recommended for the diagnosis of COVID-19 during the acute phase of the illness, but it is useful to document infections in a retrospective manner during the convalescent phase of the illness.

### What are the Different Types of Antibody Assays?

Antibodies against specific viral proteins can be measured using enzyme immunoassays, flow-cytometry based assays, or lateral flow assays. The advantage of these assays is that these can be performed in most clinical laboratories, or even at the point of care. But the disadvantage is that these methods cannot differentiate between antibodies that can protect cells from infection and those that merely bind to the viral proteins without neutralising effect.

On the other hand, neutralisation assays measure the antibodies that can protect cells from SARS-CoV-2 infection. Hence neutralisation assays are considered to be the gold standard for determining protective antibody response<sup>9</sup>. However, neutralisation assays are technically demanding, and neutralisation assays with live virus require biosafety level 3 facilities.

Studies have shown that serum collected before the COVID-19 pandemic contains antibodies against



different SARS-CoV-2 proteins due to the cross reaction with proteins from other human coronaviruses, including 229E, OC43, HKU1 and NL63<sup>10</sup>. However, antibodies against the surface spike protein and nucleocapsid protein are mainly found in COVID-19 patients<sup>10</sup>. Hence, current antibody assays usually target the spike protein (either the entire spike protein, or only the receptor binding domain [RBD]) or the nucleocapsid protein. Furthermore, antibodies against the ORF8 and ORF3b are also detected at higher levels among COVID-19 patients than controls<sup>11,12</sup>, but their roles in antibody testing require further evaluation.

## What is the Duration of Antibody Response?

There is conflicting data regarding the duration of antibody response among recovered COVID-19 patients. While some studies showed a rapid decline in antibody titers<sup>13-16</sup>, others showed sustained antibody response for a few months<sup>17,18</sup>. IgA and IgM decrease more rapidly than IgG<sup>19</sup>. The rapid decline in antibody levels in some patients may be due to the defective T follicular cell differentiation and the lack of germinal centre formation in the lymph nodes<sup>20</sup>.

Understanding the longevity of antibody response is important for several reasons. First, a rapid decline in antibody response may render recovered COVID-19 patients to be susceptible to reinfection. This was documented in our previous patient with reinfection, for whom neutralising antibody was not detected at the beginning of the second episode<sup>21,22</sup>. Second, if vaccine-induced antibody response is short-lasting, vaccination will need to be repeated. Third, seroprevalence studies are widely used to estimate the true burden of COVID-19 infection. If many recovered patients are seronegative due to antibody decay, the estimation of the burden of disease would be falsely low.

## What are the Factors Associated with Antibody Response?

Several factors affect the antibody response. Patients with severe disease have a higher antibody response, while mildly symptomatic or asymptomatic patients have the poorest antibody response<sup>16,23,24</sup>. Disease severity is also a major factor associated with the duration of antibody detection. In one study, 40% of asymptomatic patients become seronegative during the early convalescent phase<sup>25</sup>.

Age also plays an important role in the antibody response. Adults have been shown to have higher neutralising antibody titer than children<sup>26</sup>. One study showed that adult patients generate antibodies against both nucleocapsid protein and spike proteins, while pediatric patients generate much weaker antibody response against the nucleocapsid protein than the spike protein<sup>27</sup>.

Symptom duration correlates with the sustainability of antibody titers. Those who recover more quickly are more likely to have sustainable titers of antibodies, while who takes longer to recover is more likely to have decline in antibody level<sup>16</sup>.

## Does Antibody Titre Correlate with Protection?

It is generally believed that a higher antibody titre correlates with protection. During an outbreak involving a fishing vessel, three members with pre-existing neutralising antibody were not infected, while 88% of people without pre-existing neutralising antibody were infected<sup>28</sup>.

The S protein receptor binding domain (RBD) is responsible for binding to the host cell surface receptor. Hence, antibodies against the spike protein are considered to be most important for protection. Antibody against the spike protein RBD correlates well with neutralising antibody titre<sup>29</sup>. Although the N terminal domain (NTD) of the spike protein does not bind to the host cell receptor, monoclonal antibodies against NTD have also been found to have neutralising activity<sup>30</sup>. Monoclonal antibodies against either the RBD or NTD have been shown to be protective in animal studies<sup>30</sup>.

## Will Antibody-based Treatment Work?

Monoclonal antibody therapy is a promising treatment strategy. Several studies showed that monoclonal antibodies targeting the surface spike protein of SARS-CoV-2 reduce viral load and improve outcomes in animal models<sup>30,31</sup>. A phase 2 clinical trial showed that fewer out-patients treated with monoclonal antibody LY-CoV555 required hospitalisation or visited the emergency department than those treated with placebo<sup>32</sup>.

One potential problem with monoclonal antibody therapy is the emergence of escape mutants. Mutations in the RBD and NTD of the spike protein have been shown to confer resistance to monoclonal antibodies<sup>33</sup>. Recently, in a patient with severe disease, we have identified the emergence of a mutation located at the epitope of the target of a monoclonal neutralising antibody<sup>34</sup>. Therefore, several groups have used a cocktail of antibodies for treatment<sup>31</sup>.

## Autoantibodies

In addition to antibodies against SARS-CoV-2, autoantibodies are also found in many COVID-19 patients, and some autoantibodies have been found to be associated with disease severity. Higher titres of antiphospholipid autoantibodies are associated with more severe respiratory disease<sup>35</sup>. Autoantibodies are also believed to play a role in pediatric multisystem inflammatory syndrome (PIMS) (also known as multisystem inflammatory syndrome in children [MIS-C])<sup>36</sup>.

## T CELL IMMUNITY

T cell immunity is identified among patients without prior SARS-CoV-2 infection. CD4+ T cells against SARS-CoV-2 epitopes can be identified in 20-60% of healthy blood donors<sup>37-39</sup>. After infection, T cell immunity is induced. However, by the end of the second week



after symptom onset, only about 50% and 25% of patients develop T cell response against nucleocapsid protein and RBD, respectively<sup>40</sup>. Furthermore, there is functional impairment of both CD4 and CD8 T cell subsets during the acute phase<sup>40</sup>.

SARS-CoV-2-reactive CD4+ T cells can be found in almost all recovered COVID-19 patients, including those who were asymptomatic or mildly symptomatic<sup>38,41</sup>. The duration of T cell immunity appears to be long-lasting<sup>42</sup>.

T cell response is associated with disease severity. A lower frequency of naïve CD8 or CD4 T cells are associated with more severe disease<sup>4,43</sup>. Patients with severe disease had robust CD4 T cell activation, while those with less severe disease had less CD4 T cell activation<sup>44</sup>. Mild disease is associated with a coordinated CD4 and CD8+ T cell response. However, the uncoordinated response was found in patients older than 65 years old<sup>43</sup>.

## OTHER IMMUNE CELLS AND COMPLEMENT ACTIVATION

During acute infection, the frequency of natural killer cells, monocytes, and dendritic cells are reduced<sup>40</sup>. The function of dendritic cell is impaired<sup>40</sup>. The complement pathways are triggered during infection, and are associated with lung injury. The triggering of the complement pathways has been associated with severe disease<sup>45</sup>. Patients with severe disease have higher levels of C5a. The anti-C5aR1 antibody has been shown to ameliorate lung damage in animal models.

## DOES INTERFERON PLAY A ROLE IN IMMUNE RESPONSE AGAINST SARS-CoV-2?

Interferon is a key antiviral cytokine. Interferon  $\beta$  inhibits viral replication in airway cell lines<sup>46</sup>. SARS-CoV-2 suppresses interferon  $\beta$  response in order to replicate in host cells<sup>46,47</sup>. The importance of interferon during COVID-19 is well illustrated by patients having autoantibodies or genetic defects that affect the function of type I interferon. Autoantibodies against type I interferons are found in 10% of severe patients but not among asymptomatic or mildly symptomatic patients<sup>48</sup>. Genetic defects in the type I interferon-related pathways are also present at a higher frequency among severe cases than those with milder illness<sup>49</sup>.

## TREATMENT MODALITIES TARGETING THE IMMUNE SYSTEM

Several drugs targeting the host immune system have been evaluated in clinical trials. The most successful is steroid-based therapy. In a large randomised controlled trial in England, the incidence of death was significantly lower among severe patients receiving intravenous dexamethasone 6 mg once daily than those receiving usual care<sup>50</sup>. In a subsequent meta-analysis conducted by the World Health Organization, several corticosteroids have been shown to reduce mortality, including dexamethasone, hydrocortisone, and methylprednisolone<sup>51</sup>.

Interferon  $\beta$ -1b, as part of a triple combination therapy with lopinavir-ritonavir and ribavirin, shortens the duration of symptoms in COVID-19 patients<sup>52</sup>. Inhaled nebulised interferon  $\beta$ -1a has also been shown to achieve faster recovery in a phase 2 randomised controlled trial<sup>53</sup>. However, intravenous interferon  $\beta$ -1a was not beneficial<sup>54</sup>.

Tocilizumab is an anti-IL-6 receptor antibody. Early use of tocilizumab in the first two days of ICU admission was shown to reduce the risk of mortality<sup>55</sup>. However, no benefits were shown in two randomised controlled trials<sup>56,57</sup>. Anakinra, an IL-1 receptor antagonist, has been used in a case series of 8 patients with haemophagocytic lymphohistiocytosis and these patients showed improvement<sup>58</sup>.

## CONCLUSION

COVID-19 is a novel disease. Despite intensive research, there are still many unknowns on this disease. Further research on the immunology of COVID-19 will have a major impact on diagnostics, patient management and vaccine development.

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