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Rostrum

Selective IgA Deficiency May Be an Underrecognized Risk Factor for Severe COVID-19

Rohan Ameratunga, BHB, MBChB, PhD, FRACP, FRCPA, FRCP, FRCPATH, FRCPCH, FFSc, ABMLI[a,b,c], Euphemia Leung, PhD[d,e], See-Tarn Woon, PhD, FFSc[b,c], Edward Lea, MBChB[a], Caroline Allan, MBChB[a], Lydia Chan, MBChB[a], Richard Steele, MBChB, FRACP, FRCPA[a,f], Klaus Lehnert, PhD[f,g], and Hilary Longhurst, MBChB, MA, PhD, FRCP, FRCPATH[a,h] *Auckland and Wellington, New Zealand*

SARS-CoV-2, the agent responsible for COVID-19, has wreaked havoc around the globe. Hundreds of millions of individuals have been infected and well over six million have died from COVID-19. Many COVID-19 survivors have ongoing physical and psychiatric morbidity, which will remain for the rest of their lives.

Early in the pandemic, it became apparent that older individuals and those with comorbidities including obesity, diabetes mellitus, coronary artery disease, hypertension, and renal and pulmonary disease were at increased risk of adverse outcomes. It is also clear that some immunodeficient patients, such as those with innate or T cell−immune defects, are at greater risk from COVID-19.

Selective IgA deficiency (sIgAD) is generally regarded as a mild disorder in which most patients are asymptomatic because of redundancy in protective immune mechanisms. Recent data indicate that patients with sIgAD may be at high risk of severe COVID-19. SARS-CoV-2 gains entry primarily through the upper respiratory tract mucosa, where IgA has a critical protective role. This may underlie the vulnerability of sIgAD patients to adverse outcomes from COVID-19. This perspective highlights the need for ongoing research into mucosal immunity to improve COVID-19 treatments for patients with sIgAD. © 2022

[a]Department of Clinical Immunology, Auckland Hospital, Grafton, Auckland, New Zealand
[b]Department of Virology and Immunology, Auckland Hospital, Grafton, Auckland, New Zealand
[c]Department of Molecular Medicine and Pathology, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
[d]Maurice Wilkins Centre, School of Biological Sciences, University of Auckland, Auckland, New Zealand
[e]Auckland Cancer Society Research Centre, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
[f]Department of Respiratory Medicine, Wellington Hospital, Wellington, New Zealand
[g]School of Biological Sciences, University of Auckland, Auckland, New Zealand
[h]Department of Medicine, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

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Corresponding author: Rohan Ameratunga, BHB, MBChB, PhD, FRACP, FRCPA, FRCP, FRCPATH, FRCPCH, FFSc, ABMLI, Department of Clinical Immunology, Auckland Hospital, Park Rd, Grafton, Auckland 1010, New Zealand. E-mail: rohana@adhb.govt.nz.

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INTRODUCTION

COVID-19 has had a calamitous impact on the global community. The true death toll is likely to greatly exceed the current official number of 6.5 million. Hundreds of millions of patients have been infected and many are experiencing long-term physical and psychiatric morbidity. The pandemic has caused global economic turmoil. Large numbers of individuals have been plunged into poverty caused by the financial devastation of developing nations. The origin of the virus remains to be determined.[1-3]

Three overlapping clinical phases of infection

SARS-CoV-2 infects patients in three overlapping clinical stages (Figure 1).[4] The first nasal phase is asymptomatic. In the second pulmonary stage, the virus enters the lungs, most likely by aspiration from the nose and stomach. Patients may experience fever, myalgia, lethargy, and increasing dyspnea. Inflammatory markers are elevated and computerized tomography scans of the thorax may reveal a ground-glass appearance.

A small number of patients progress to the third systemic phase. These individuals are at risk of multiple organ dysfunction, including acute respiratory disease syndrome. Despite invasive ventilation or extracorporeal membrane oxygenation, mortality is high in patients admitted to intensive care units.

Immunopathology of COVID-19

The molecular events that underlie COVID-19 infection are now better understood. The nasopharynx is the primary route of viral entry. The spike (S) glycoprotein of SARS-CoV-2 binds angiotensin-converting enzyme 2 (ACE2) receptors on epithelial cells in the upper respiratory tract. Host proteases including transmembrane serine protease 2 and furin cleave the S glycoprotein, and the S2 subunit allows the virus to fuse with host epithelial cells.[5] The viral genome enters cells and hijacks intracellular organelles, resulting in the generation of viral progeny.

The immune response to SARS-CoV-2 plays a critical role in the outcome of the infection. High levels of IL-6 and TNF from macrophages and neutrophils underlie the cytokine storm in the third systemic phase of COVID-19. Elevated D-dimers signify an increased risk of thromboembolic disease from endothelial

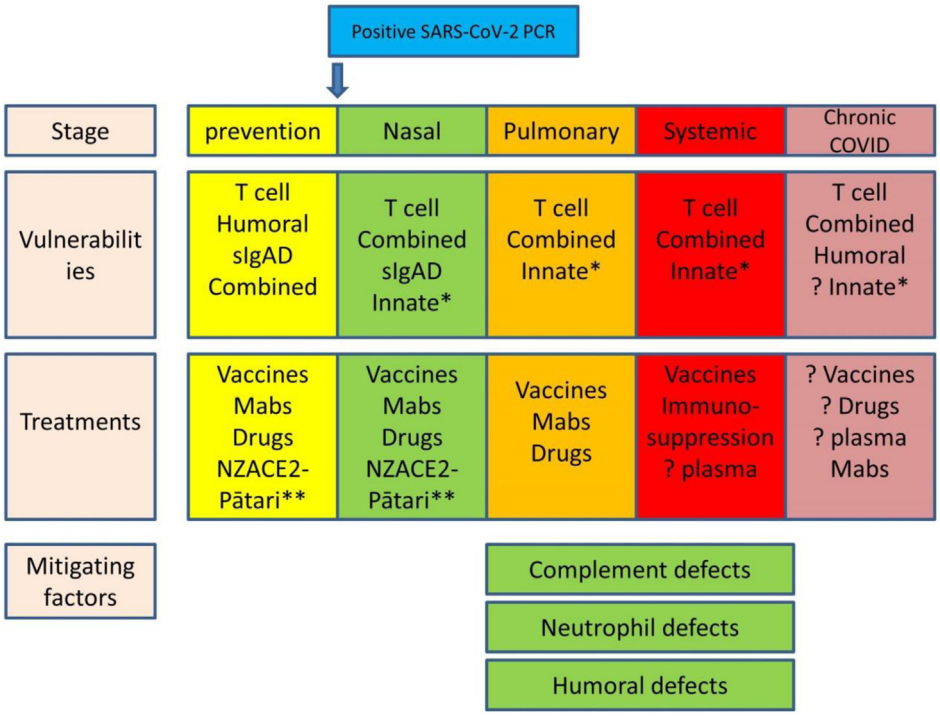

FIGURE 1. Stages of COVID-19, specific vulnerabilities of patients with primary immunodeficiency disorders, and possible treatments. Patients with humoral, cellular, and combined defects may not be optimally protected by COVID-19 vaccines. Patients with selective IgA deficiency (sIgAD) may have a poor mucosal response to vaccines. The systemic phase is caused by an unbalanced immune response, and vaccines reduce the risk of a dysfunctional immune reaction including antibody-dependent enhancement. Because of immune dysregulation in the pulmonary and systemic phases, deficiency of the complement cascade, neutrophils, and humoral immunity may mitigate disease severity. The role of specific treatments for chronic COVID-19 remains to be defined. Convalescent plasma was not successful for previous variants of SARS-CoV-2 but may prove more effective for Omicron and its subvariants. Immunosuppressive drugs include steroids, tocilizumab, and baricitinib. *Innate immune defects include patients with primary immunodeficiency disorders and those with neutralizing anti-interferon antibodies. **The NZACE2-Pātari project has not reached clinical trials. *Mabs*, monoclonal antibodies; *PCR*, polymerase chain reaction.

damage caused by inappropriate activation of neutrophils and the complement cascade.[6]

Patients who die from the infection have a chaotic, destructive immune response often with evidence of antibody-dependent enhancement (ADE).[7] In contrast, most patients with mild disease have an early balanced cellular immune response with high titers of neutralizing antibodies.

Prevention and treatment of COVID-19

Because of an unprecedented global effort, effective vaccines and therapeutics against SARS-CoV-2 have been rapidly developed. However, vaccine hesitancy and vaccine inequities in large regions of the world have resulted in reduced global vaccine uptake.[8] This has allowed ongoing viral circulation resulting in the selection, emergence, and global spread of increasingly infectious strains. These variants of concern (VOCs) have presented as successive waves of infection. Omicron (B.1.529) and its subvariants (BA.1, BA.2, etc) are the latest SARS-CoV-2 strains to dominate global infections.

Newer antiviral agents, including Paxlovid (Pfizer, NY), molnupiravir, and remdesivir, remain effective for the treatment of COVID-19. However, there are important differences in the therapeutic efficacy of monoclonal antibodies, depending on the specific Omicron subvariant. It is imperative for countries and regions to monitor VOCs infecting local communities, because this will inform therapeutic options.

Antiviral drugs should be administered early in the course of infection. Later in the disease, immune dysregulation features prominently and immunomodulatory treatments including dexamethasone, baricitinib, and tocilizumab are more effective (Figure 1).[9]

Host susceptibility

Soon after the pandemic began, it was apparent there were several host factors predisposing to severe disease. There is a steep age-related mortality gradient with high fatality rates in people aged greater than 80 years.[10] Older persons with neutralizing anti-interferon antibodies are at greater risk of adverse outcomes from COVID-19.[11] The prevalence of anti-interferon antibodies increases with age, which may partly explain the steep age-related mortality gradient.

In addition, patients with obesity, diabetes mellitus, coronary artery disease, hypertension, and renal and respiratory disease are at risk of poor outcomes.[10,12,13] The immunologic basis of these host susceptibilities remains to be defined. Individuals of Black, Hispanic, Māori, Pasifika, and South Asian origin are also at

increased risk of death.[14] These ethnic vulnerabilities are also poorly understood, but a higher prevalence of comorbidities and inequitable access to health care at least partially underlie these disparities.[15]

There is increasing evidence that some patients with primary and secondary immunodeficiency disorders are at risk of severe COVID-19 (Figure 1). Patients with innate or T cell−immune defects are at increased risk of poor outcomes.[16] Although healthy children are generally protected from severe disease, some with these immune deficiencies have been hospitalized for COVID-19. In contrast, most patients with X-linked agammaglobulinemia (XLA), without comorbidities, seem to be protected from severe disease. However, patients with XLA may be at risk for chronic COVID-19.[17-20] Chronic COVID-19 is a stalemate between SARS-CoV-2 and a suboptimal immune response, which can result in prolonged viral shedding.[21] These observations underscore the uncertain nature of humoral immunity in protecting against COVID-19.[7]

IgA deficiency may be a risk factor for severe COVID-19

Selective IgA deficiency (sIgAD) is the most common primary immunodeficiency disorder (PID).[22] It is defined as IgA levels of less than 0.07g/L, with normal (other) immunoglobulin isotype levels and absence of T-cell defects in an individual aged 4 years and greater. Partial IgA deficiency (IgAD) is defined as IgA levels more than 2 SDs below the mean.

Only about 30% of sIgAD patients have symptoms attributable to PID. Symptomatic sIgAD patients may have recurrent upper respiratory tract infections and sometimes develop allergic or autoimmune disorders, including celiac disease.[23-26] There is a well-recognized but small risk of adverse blood transfusion reactions in sIgAD, consequent to anti-IgA antibodies.

There are important ethnic differences in the prevalence of sIgAD. Studies suggest that it may be as high as 1:163 in persons from Europe.[27] It also appears to be more common in consanguineous societies.[28] In contrast, the prevalence of sIgAD is much lower in East Asia.[29] Because most patients with sIgAD are asymptomatic, there may be ascertainment bias.

IgA deficiency can also occur in the context of other PIDs, such as common variable immunodeficiency disorders (CVIDs), CVID-like disorders are conditions presenting with a CVID phenotype, where the causative mutation is identified.[30-32] Although the molecular basis of IgAD and CVID is unknown, the genetic basis of IgAD in CVID-like disorders, XLA, and X-linked hyper IgM syndrome is understood.[33,34] In the latter disorders, IgAD is a relatively small part of the PID, because deficiencies of other components of the immune repertoire dominate the clinical presentation.

Selective IgAD may be an important risk factor for severe COVID-19. There was an early suggestion that countries such as Japan, with low rates of sIgAD, had less severe outcomes.[35] However, the older age-related demographics are likely to be confounded by the reduced prevalence of comorbidities and societal factors in Japan. A more recent study suggested a high risk of severe COVID-19 in sIgAD patients, which is much stronger evidence of disease susceptibility.[36] This essay explores emerging evidence that sIgAD may be an important but underrecognized risk factor for severe COVID-19.

DISCUSSION

Primary immunodeficiency disorders have been termed experiments of nature.[37] Previous studies of PID patients with defects of the immune response demonstrated specific host vulnerabilities to pathogens. Patients with T-cell deficiency are at risk of viral, fungal, and bacterial infections. Those with humoral immune defects are predisposed to bacterial, protozoal, and selected viral infections. Patients with innate immune defects are at risk of *Salmonella*, mycobacterial, and viral infections. Individuals with terminal complement defects are susceptible to recurrent *Neisseria* infections. These host vulnerabilities illustrate the role of specific immune components in normal protective responses to pathogen groups.

IgA plays a critical role in protecting mucosal surfaces, including the upper respiratory tract, which is the primary route of SARS-CoV-2 entry. Relatively few patients with sIgAD have been included in recent case series of PID patients infected with SARS-CoV-2.[38-41] In one large series, only seven of 961 sIgAD patients contracted COVID-19 and there were no fatalities.[41] Because sIgAD is more highly prevalent than other PIDs, it is unclear why so few sIgAD patients contracted SARS-CoV-2 in these case series. It is possible that individuals effectively sheltered in place or had higher COVID-19 vaccination rates. However, most of these PID case series were published before the widespread availability of COVID-19 vaccines.

Because most patients with sIgAD are asymptomatic, ascertainment of IgA levels of patients with severe COVID-19 may be more informative than case series of PID patients. A recent publication containing a larger number of sIgAD patients infected with SARS-CoV-2 showed a much greater risk of adverse outcomes.[36] Of 424 patients admitted to the hospital, 11 who were infected with SARS-CoV-2 had sIgAD. Those individuals had a 7.7-fold increased risk of severe COVID-19 compared with patients with normal IgA levels (odds ratio = 7.789; 95% CI, 1.665-36.690; $P = .008$). In this group of hospitalized patients, the prevalence of sIgAD was one in 38, compared to one in 188 in the general Turkish population. This is important evidence that patients with sIgAD are at increased risk of severe COVID-19.

In another study, there was a gradient of risk for severe COVID-19, based on levels of IgA and IgG in the serum.[42] In a third study, protective vaccine responses may have been less effective in patients with reduced IgG and IgA compared with healthy controls.[43] Selective IgAD is at the extreme end of this gradient of host susceptibility, supporting a causal relationship between the severity of COVID-19 and reduced IgA levels. These observations are also evidence that mucosal SARS-CoV-2 IgA levels after vaccination have an important role in protecting against COVID-19 in healthy individuals (Figure 1).

The potential vulnerability of patients with sIgAD to COVID-19 illustrates the importance of research into the role of mucosal immunity in protecting against SARS-CoV-2.[44] Saliva is a readily accessible source of mucosal IgA for research. Unsurprisingly, children prefer saliva tests to venipuncture. Children generally have much milder COVID-19 than do adults; a possible explanation is robust mucosal immunity. This possibility needs to be investigated.

Breast milk from lactating mothers is another source of secreted IgA that could be investigated.[45] Anti-SARS-CoV-2 IgA in breast milk may protect infants against COVID-19.[46] Orally

administered breast milk was successfully used to treat an adult immunodeficient patient with chronic COVID-19.[47]

Potential immunologic mechanisms underlying severe COVID-19 in sIgAD remain to be defined. During the incubation period of COVID-19, the viral load reaches high levels in the nasal mucosa before aspiration into the lungs. Owing to the mucosal defect, it is unknown whether sIgAD patients have higher viral loads compared with those with normal IgA levels. This is an important research question, because there is evidence that a higher initial viral inoculation, as judged by the reverse transcriptase quantitative polymerase chain reaction cycle threshold, is associated with worse outcomes.[48,49] Early studies from China showed that even young health care workers were at risk of death from COVID-19.[50] Before the use of personal protective equipment, those health care workers were exposed to high viral concentrations, presumably resulting in heavy inoculation. Thus, a high mucosal viral load might explain severe COVID-19 in sIgAD patients.

A second possibility for severe COVID-19 in sIgAD patients is systemic autoimmunity triggered by SARS-CoV-2.[51] Patients with sIgAD are predisposed to autoimmunity, which could contribute to adverse outcomes.[51] Patients with sIgAD have altered T-cell subsets, which could trigger autoimmunity after COVID-19.[52] The potential role of neutralizing anti-interferon antibodies in exacerbating autoimmunity in sIgAD is not known.

A third, non−mutually exclusive possibility is increased intestinal viral entry in the absence of gut SARS-CoV-2 neutralizing IgA or alterations in the gut microbiome caused by sIgAD.[53] The gut is a secondary route of entry for SARS-CoV-2 and may contribute to a higher systemic viral load in sIgAD patients.[54]

It is interesting to compare the COVID-19 risk profiles of patients with XLA and those with sIgAD. Both groups of patients are unable to produce mucosal IgA, yet the risk profiles seem to differ. There are conflicting data about the protective role of the systemic humoral immune response.[7] Some studies indicate ADE in severe COVID-19.[55] Perhaps the absence of ADE in patients with XLA compensates for the lack of mucosal IgA, mitigating their risk. Patients with XLA may be predisposed to chronic COVID-19. It is unknown whether patients with sIgAD are at increased risk of chronic COVID-19.

Potentially severe outcomes in sIgAD patients suggest that targeting the nasal phase may reduce the risk for severe pulmonary and systemic disease in other vulnerable patients.[56] New vaccines and therapeutics impeding SARS-CoV-2 nasal mucosal entry may improve the prognosis for high-risk patients.[57] Nasal vaccines are being studied in animals as well as in human phase 1 to 3 trials.[58,59] Systemic primary vaccination with nasal boost strategies may prove to be effective in the future.[60] The efficacy of nasal vaccines in sIgAD patients would need to be determined separately.

Some current COVID-19 vaccines induce mucosal IgA antibodies, which may provide protection against SARS-CoV-2. There are important differences between vaccines. The Janssen (Johnson and Johnson, NJ) (Ad26.COV2.S) and CoronaVac (inactivated SARS-CoV-2 virus) vaccines seem to stimulate less salivary SARS-CoV-2 IgA than does the AstraZeneca (Cambridge, UK) (ChAdOx1) vaccine and much less than the mRNA vaccines (Pfizer (New York, NY) BNT162b2 and Moderna (Cambridge, MA) mRNA-1273).[44,61] How mRNA vaccines that are administered intramuscularly induce mucosal IgA responses is unclear, but this mechanism may at least partly underlie their efficacy.[62]

Current data indicate that heterologous booster doses are more effective in countering new SARS-CoV-2 VOCs.[63,64] Future studies will indicate whether the superiority of heterologous vaccination with mRNA and subunit or adenovirus-based vaccines results from higher protective mucosal SARS-CoV-2 IgA levels. Saliva (and breast milk) neutralizing IgA antibody studies can similarly be undertaken for VOCs. Future vaccine-efficacy studies should measure both systemic and mucosal immunity to SARS-CoV-2. Most studies have focused on the systemic adaptive immune response to SARS-CoV-2. This is understandable, because a dysregulated cellular immune response is associated with severe outcomes.[9]

The NZACE2-Pātari project seeks to intercept and block SARS-CoV-2 in the nasal mucosa.[65] Pātari is the Māori verb for decoy, leading to interception. This project uses modified ACE2 molecules to intercept SARS-CoV-2 in the nasal phase of COVID-19 to mitigate the severity of the pulmonary and systemic phases. Because the project uses modified ACE2 molecules, viral evolution to evade these molecules will result in loss of virulence.[66] NZACE2-Pātari is likely to be effective against current and future VOCs.

These drugs may compensate for the mucosal defect in sIgAD. They may also be valuable for elderly people and those with comorbidities, who are at high risk for adverse outcomes. NZACE2-Pātari may have synergistic therapeutic benefits with other COVID-19 treatments such as protease inhibitors and monoclonal antibodies.

Future research will indicate whether patients with sIgAD should undergo robust immunologic evaluation. Vaccine challenge responses are not typically undertaken in patients with sIgAD unless there is concern that the disease is evolving into another, more severe disorder such as CVID.[67,68] In the absence of IgA, other secreted immunoglobulin isotypes such as IgG or IgM may compensate for mucosal protection.[69] This redundancy in mucosal immune protection is presumably why most patients with sIgAD are asymptomatic. Future studies may indicate whether measuring salivary SARS-CoV-2−specific IgG or IgM after COVID-19 vaccination is of prognostic value in sIgAD patients.[69]

Given the importance of cellular immunity, prospective studies may also indicate whether *in vitro* T-cell responses to SARS-CoV-2 are a surrogate marker for protection against COVID-19 in patients with PIDs, including sIgAD.[70,71] The outcomes of such studies will enable personalized medicine for COVID-19 in patients with PIDs, including sIgAD.[72]

At the time of writing, SARS-CoV-2 Omicron and its subvariants are dominating global COVID-19 infections. Previously ineffective treatments such as convalescent plasma infusions may be more effective for Omicron and its subvariants. Omicron appears to provoke less severe perturbations of cellular immunity, and protection could be more reliant on antibodies.[73] If this hypothesis is accurate, therapeutic plasma infusions from sIgAD Omicron survivors may reduce the risk for severe COVID-19 in sIgAD patients.[73] Younger sIgAD convalescent plasma donors are preferred because they are less likely to have anti-interferon antibodies, which could aggravate disease. The immunopathology of COVID-19 (and therapeutics) will need to be reviewed for each successive SARS-CoV-2 VOC.

Patients with sIgAD may be in good health until they contract SARS-CoV-2 and experience severe COVID-19. Future studies

will confirm whether patients with sIgAD have a specific pathogen vulnerability to SARS-CoV-2. There are many other examples of critical pathogen vulnerabilities in patients with PIDs, including X-linked lymphoproliferative disease.[74] Patients with this disease are mostly in good health until they contract Epstein-Barr virus, which can lead to fulminant infection, lymphoma, or bone marrow failure.[74]

Preliminary data presented here indicate that patients with sIgAD may need to be considered severely immunecompromised in the context of COVID-19, similar to patients with innate or cellular immune defects (Figure 1). Patients with sIgAD should be encouraged to receive three or four primary vaccine doses and heterologous boosters. Moreover, sIgAD patients should be offered other prophylactic therapeutics such as sotrovimab or Evulsheld (Astra Zeneca, Cambridge, UK) (tixagevimab and cilgavumab), depending on the sensitivity of VOCs circulating in the community.

These observations may also have important clinical implications for the treatment of SARS-CoV-2−infected patients with sIgAD. Because most sIgAD patients are asymptomatic, they may be unaware of their potential vulnerability to COVID-19. Immunoglobulin levels should be routinely measured in patients admitted to the hospital with severe COVID-19. SARS-CoV-2−infected sIgAD patients should receive priority for early treatment with monoclonal antibodies and antiviral drugs such as Paxlovid, molnupiravir, or remdesivir.[75]

According to precautionary principles, pending further data, previously diagnosed sIgAD patients should be preemptively recalled from case notes and other databases (including PID registries and blood bank data) to receive relevant clinical advice. Further research into the vulnerability of sIgAD patients to COVID-19 is a high priority.[44] A recent study showed health care workers with higher mucosal anti-SARS CoV-2 IgA levels were protected from breakthrough COVID-19 infections, epitomizing the importance of mucosal immunity.[76] Enhancing mucosal protection against SARS-CoV-2 with vaccines and therapeutics may be the key to ending the pandemic.

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