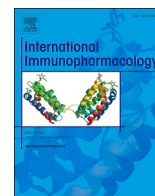




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## Non-neutralizing antibodies: Deleterious or propitious during SARS-CoV-2 infection?

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### ABSTRACT

Antibody-dependent enhancement (ADE) is a complex phenomenon mediated by antibodies, frequently pre-existing non-neutralizing or sub-neutralizing antibodies. In the course of infectious diseases, ADE may be responsible for worsening the clinical course of the disease by increasing the virulence of pathogens (ADE of infection) or enhancing disease severity (ADE of disease). Here we reviewed the mechanisms thought to be behind the ADE phenomenon and its potential relationship with COVID-19 severity. Since the early COVID-19 epidemics, ADE has been mentioned as a possible mechanism involved in severe COVID-19 disease and, later, as a potential risk in the case of infection after vaccination. However, current data do not support its role in disease severity, both after infection and reinfection.

### 1. Introduction

The interaction between humans and viruses (and its outcome) is determined by several factors, which mainly comprise innate and adaptive immunity [1]. Both types of immunity can contribute to the control of viral infections and virus clearance, but also to determine virus pathogenicity and tissue damage.

Virus surface is an antigenic structure that usually triggers cellular and humoral immune responses aimed at eradicating the virus in the host. Among humoral defenses, antibodies, produced after a viral infection, contribute to several levels of antiviral defense, neutralizing the virus and reducing its infectivity by the inhibition of its entry into the host cells. However, in some circumstances, antibodies may potentiate the viral infection of host cells, leading to increased infectivity and promoting inflammation and tissue injury.

Antibody-dependent enhancement (ADE) is a complex phenomenon mediated by antibodies, frequently pre-existing non-neutralizing or sub-neutralizing antibodies (nNAbs), through their fragment crystallizable (Fc) region in their carboxyl-terminal domain. In the course of infectious diseases, ADE may be responsible for worsening the clinical course of the disease by increasing the virulence of the pathogens (ADE of infection) or enhancing disease severity (ADE of disease) (Fig. 1).

ADE of infection has been reported *in vitro* and *in vivo* for several viruses, but ADE of infection observed *in vitro* does not predict ADE of disease in humans [2]. In ADE of infection, pre-existing specific antibodies against a virus serotype do not completely neutralize a different serotype of the same virus, rather facilitating its entrance and replication in phagocytic cells harboring fragment crystallizable gamma (Fc $\gamma$ R) and/or complement receptors, like monocytes, macrophages or granulocyte cells, in this way acting as a “Trojan horse” further allowing the virus to get into permissive cells [3]. Entry of viruses in the host cells occurs through clathrin-coated vesicles, mainly using Fc $\gamma$ R2 receptor [4] (Fig. 1B). By binding to the antibody Fc-portion, Fc $\gamma$ Rs provide a link between the specificity of the adaptive immune system and the effector functions triggered by innate immune effector cells.

ADE of disease is the result of an excessive immune response to pathogens when the antibody-pathogen complex, through the effector functions of the Fc, is able to potentiate the disease by initiating a strong immune cascade that results in a severe pathology. Antibodies still act as a “Trojan horse”, allowing the virus to get into cells and exacerbate the immune response. The outcome of ADE of disease depends on the balance of the activation of the inhibitory Fc $\gamma$ R signaling through the immunoreceptor tyrosine-based activation (ITAMs) and the immunoreceptor tyrosine-based inhibitory (ITIM) motifs. One factor that

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modulates Fc $\gamma$ R signaling is the glycosylation state of the IgG Fc domains within immune complexes [5] (Fig. 1C).

Also based on the main pathogenic mechanism involved, two different types of ADE can develop and are named extrinsic and intrinsic ADE [6]. Extrinsic ADE refers to the increase in the number of cells that are infected due to the binding of the antibody-virus complex to the Fc $\gamma$ Rs, facilitating the virus internalization into host cells. Extrinsic ADE seems to be mediated by IgG type antibodies. The balance of Fc $\gamma$ Rs that are engaged by immune complexes determines the degree of the inflammatory effector cell response [5]. Intrinsic ADE, mainly mediated by IgM type antibodies, refers to the increased production of viral particles per cell as a consequence of the internalized nAb-virus complexes that modulate the innate antiviral response in order to increase virus production. The ADE phenomenon can prompt the massive release of inflammatory and vasoactive mediators that ultimately contribute to disease severity [6]. The two enhancement pathways, IgG- and IgM-related, are independent but not mutually exclusive and can act synergistically.

nAbs can be naturally acquired by previous infections, passive maternal immunity or acquired with vaccination. ADE was first observed *in vitro* sixty years ago by Hawkes et al., who described an increased infectivity of several viruses, belonging to the Flaviviridae family, which was mediated by specific antisera produced in fowls [7]. Later, Halstead et al. described this process in patients during Dengue fever reinfection. Dengue fever is a mosquito-borne illness caused by the Dengue virus, an RNA virus belonging to the Flaviviridae family with 4

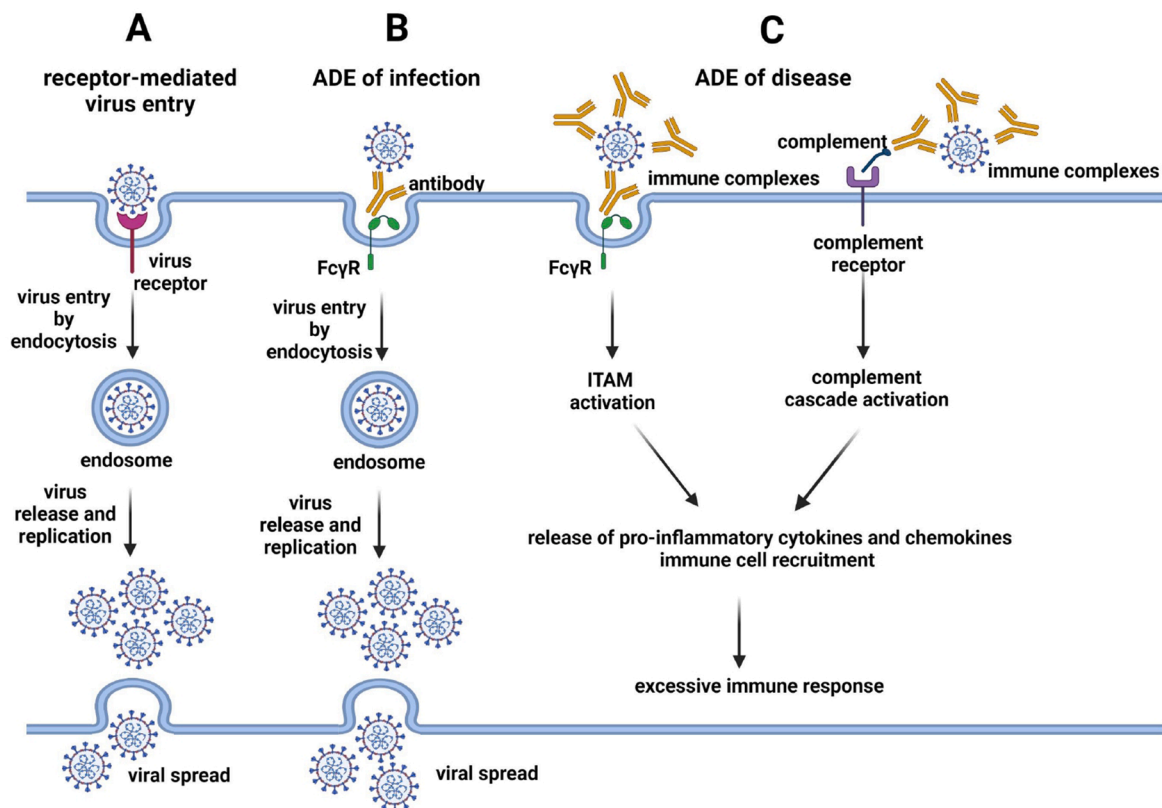
serotypes [8]. The first Dengue fever event can clinically manifest as a mild febrile disease, whilst, during a secondary infection, whether caused by different Dengue virus serotypes, the symptoms can be more severe and characterized by severe thrombocytopenia and increased vascular permeability causing disseminated hemorrhage. The serotype-specific antibodies produced during the first infection cross-react with other virus serotypes but without completely neutralizing them, in turn allowing easier infection of monocytes through antibody-receptor-mediated uptake of the virus.

Apart from some Flavivirus like Dengue virus, ADE has been described for few other human viruses, like Human Immunodeficiency Virus-1 (HIV1) [9], West Nile virus [10], Zika virus [11] or Ebola virus [12]. ADE has also been described for some respiratory infections like Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) or Human Influenza virus [13–19] and it has been reported both *in vivo* and *in vitro* [20]. In these respiratory infections, nAbs enhance viral entry into lung phagocytic cells, disseminating the infection and initiating a powerful immune cascade that results in lung pathology.

Recently, ADE has also been described for multiple bacterial infections in both animal models and humans [21].

## 2. SARS-CoV-2 and ADE: mechanisms and evidence

Since the emergence of the SARS-CoV-2 pandemic in the Chinese city of Wuhan in December 2019, concern of ADE for SARS-CoV-2 were



**Fig. 1.** (A) Viruses initiate infection through the interaction of viral proteins with virus-specific receptors on host cells. Viruses enter the host cells mainly through endocytosis, virions are uncoated, viral genome is replicated, viral proteins are produced and new virions are assembled for their final spread. (B) In ADE of infection, pre-existing non-neutralizing or sub-neutralizing antibodies bind to the virus and interact with the fragment crystallizable gamma receptors (Fc $\gamma$ ) mainly present on the surface of myeloid cells, facilitating the internalization of the virus into host cells by endocytosis. If the virus can productively infect these cells, it replicates and spread like in (A), increasing the production of viral particles per cell or/and increasing the number of infected cells. (C) In ADE of disease, pre-existing non-neutralizing or sub-neutralizing antibodies can form immune complexes with viral particles. These immune complexes may interact with the Fc $\gamma$  receptors of host myeloid cells, activating the immunoreceptor tyrosine-based activation motifs (ITAMs) of these receptors. Alternatively, immune complexes, through the activated complement components, interact with the complement receptors of host cells, activating the complement cascade. In both cases, the activation results in the release of pro-inflammatory cytokines and chemokines and recruitment of immune cells, exacerbating the immune response.

raised based on preliminary data on previous outbreaks of coronaviruses like SARS-CoV in 2002 and MERS-CoV in 2012 and 2015 [18,20,22–24]. ADE was related to both viruses, as an alternative mechanism of infection of host cells and the cause of abnormal cytokine production. Among the four major structural SARS-CoV2 proteins, the Spike envelope glycoprotein (S) has been identified as the most important antigen inducing neutralizing and protective antibodies. Entry of SARS-CoV-2 into the cells of infected individuals has been shown early on to depend on the receptor-binding domain (RBD) of the S protein. Accordingly, much of the research on SARS-CoV-2 has focused on the epitopes of the RBD recognized by antibodies to learn more about viral pathogenesis, to find an effective treatment and build a vaccine.

Neutralizing antibodies bind to viral protein epitopes that interact with host cell receptors which are crucial for viral infection. Therefore, antibodies against SARS-CoV-2 RBD are considered as neutralizing [25]. RBD interacts with the human receptor angiotensin-converting enzyme 2 (ACE2) to enter susceptible cells. ACE2 is mainly expressed in the cells of the respiratory tract and its expression is regulated by interferons [26]. ACE2 and Fc $\gamma$ R concomitant expression in respiratory cells is scarce, so the ADE mechanism caused by SARS-Cov-2 via the dual-receptor mechanism in lung could be mediated by cells of the immune system expressing Fc $\gamma$ R and ACE2 [2,27].

The mechanism of the damaging inflammatory response characteristic of severe coronavirus disease 19 (COVID-19) is still unclear. Discordant data have been published regarding ADE-mediated interleukin-6 (IL-6) aberrant production as the cause of severe COVID-19 [28–30]. Furthermore, Multisystem Inflammatory Syndrome in children (MIS-C) has been hypothesized to be mediated by ADE although this speculation remains to be demonstrated [31]. Recent studies have suggested that non-neutralizing afucosylated IgG-Fc $\gamma$ R interactions could trigger an abnormal cytokine response in myeloid cells in the lung of patients with severe COVID-19 [32]. In contrast, BNT162b2 SARS-CoV-2 messenger RNA vaccine-elicited IgG are highly fucosylated and enriched in Fc sialylation. Interestingly, these Fc glycoforms seem to have reduced inflammatory potential [32]. Previously, the presence of afucosylated Fc glycans ( $\geq 10\%$ ) on maternal anti-Dengue virus IgG has been shown to be a risk factor for susceptibility of infants to disease during primary Dengue virus infections [33]. IgG glycosylation is a mechanism not completely understood but it seems regulated mainly by heritable factors and related to better clinical prognosis of infections [34].

The virus-(neutralizing or non-neutralizing)antibody complex binds to the Fc $\gamma$ R on the surface of immune cells such as monocytes and macrophages, possibly allowing SARS-CoV-2 entry also without the usage of ACE2 (Fig. 1B). The family of Fc $\gamma$ Rs is broadly expressed in immune cells, however, only FcII $\gamma$ R and FcIII $\gamma$ R have been described to be involved in ADE [30]. The concern about a potential role of ADE for severe COVID-19 pathogenesis was early raised during pandemic, but currently there is no data confirming this hypothesis. Positive correlation between the titer of antibodies against SARS-CoV-2 [35,36] and COVID-19 severity initially supported this hypothesis, posing a problem for vaccine development and therapeutic approaches in patients infected with different SARS-CoV-2 variants [20]. By the use of convalescent-phase plasma from COVID-19 patients, Maemura et al. have recently shown that SARS-CoV-2 induces antibodies that can elicit ADE of infection *in vitro* as for 6 months after infection, but these antibodies do not facilitate or exacerbate abnormal cytokine production by macrophages [30]. Convalescent plasma from patients recovered from COVID-19 was initially used as therapy in several trials with suboptimal results, but ADE was not considered as a cause of progression to severe disease or all-cause mortality in treated patients [37,38].

Cross-reactivity of pre-existing antibodies with SARS-CoV-2 proteins may have important consequences both on virus neutralization and on ADE. Cross-reactivity may be determined by the presence of glycans on viral proteins. Glycosylation of viral proteins is observed for envelope protein (Env) of HIV-1, hemagglutinin protein (HA) of influenza virus,

coronavirus Spike protein (S) and envelope proteins of many other viruses [39]. Since glycosylation of viral proteins mainly occurs through the host-glycosylation pathway [39], it is possible that different viruses present similar glycosylation pattern and antibodies elicited by one virus may cross-react with another virus. An antibody targeting the glycosylated Env protein of HIV-1 (2G12) has recently been shown to also neutralize influenza virus, due to the presence of similar oligomannose-type clusters on HA [40]. The same 2G12 antibody, together two further antibodies directed against glycans of the HIV-1 Env glycoprotein (PTG126 and PTG128) have been shown to display high cross-reactivity with the S protein of SARS-CoV-2, but they are incapable of neutralizing pseudoviruses expressing SARS-CoV-2 S protein and most probably do not mediate ADE [41].

Epidemiological studies have shown the presence of pre-existing antibodies cross-reactive with SARS-CoV-2 in the serum of sub-Saharan African patients. This presence has been related to a lower COVID-19 morbidity/mortality in this populations [42,43]. Plasmodium and human immunodeficiency virus (HIV), both microorganisms being endemic in Africa, have been shown to induce in patients nNABs that can cross-react with SARS-CoV-2, but these antibodies do not correlate with more severe forms of COVID-19 disease [44–46]. Polyclonal plasma from HIV-infected children cross-reacts with SARS-CoV-2 but, to our knowledge, there are no data in the literature on their possible involvement in ADE [47]. Moreover, cross-reactivity of SARS-CoV-2 antigen/antibodies can lead to HIV-antibody false positive results in chemiluminescent HIV immunoassays [48].

More recently, pre-existing IgG targeting several seasonal coronavirus-conserved SARS-CoV-2 spike subdomains have been correlated with differential COVID-19 disease outcomes and authors suggested that the severity of disease depend on epitope targeting by humoral recall response. Pre-existing IgG targeting the S2'FP region of SARS-CoV-2 are predictors of more severe COVID-19 than IgG targeting HR2, 5'fHR" or RDB region [49]. More studies are necessary to understand if ADE is involved in these effects.

Influenza vaccination is associated with reduced susceptibility to or decreased COVID-19 severity in a recent meta-analysis [50] and sera from convalescent COVID-19 patients and from SARS-CoV-2 spike immunized mice showed cross-reaction with the Influenza virus HA protein *in vitro* [51].

Overall, these studies suggest that cross-reactive non-neutralizing responses across several infections and SARS-CoV-2 infection do not drive ADE phenomena in COVID-19.

### 3. Omicron and ADE: foreseen risks

The RBD and the N-terminal domain (NTD) of SARS-CoV-2 S protein have accumulated mutations overtime as evidenced by several variants of concern (VOC) and the sequential waves of infection around the world. Currently, the epidemic curve of SARS-CoV-2 is silently raising again with the surge of a new SARS-CoV-2 variant (Omicron BA.2-lineage).

Omicron, the last identified VOC, contains 15 mutations in the RBD and 11 mutations in the NTD, respectively, and its RBD binds to ACE2 with a  $\sim 2.4$  fold enhanced affinity compared to the original Wuhan-Hu-1 strain, possibly explaining only partially the increased transmissibility of the variant [52,53].

Currently, no variant of SARS-CoV-2 has accumulated as many mutations as the Omicron variant. This variability is likely related to immune evasion, as evidenced by the increase in reinfections during the last wave and the detection of new infections in vaccinated patients, mainly attributed to Omicron variant. The antigenic shift led to severe damping of the neutralizing activity of antibodies which are present in patients with a previous SARS-CoV-2 infection (possibly with a different variant) or in vaccinated individuals. Several studies in infected or vaccinated individuals based on the humoral antibody SARS-CoV-2 responses have reported a reduction in the neutralizing antibody titers to

the Omicron variant in comparison to the wild-type SARS-CoV-2 [54,55]. Moreover, SARS-CoV-2 reinfections seem to be less severe than the first one both in children [56] and adults [57] and even in solid organ transplant (SOT) patients [58].

Among all therapeutic monoclonal antibodies (mAbs) approved against SARS-CoV-2, the only ones with neutralizing activity against the Omicron variant are sotrovimab and the cilgavimab/tixagevimab cocktail. Even these mAbs experienced respectively a 2–3-fold and 12–200-fold reduced potency against the Omicron variant, using both pseudovirus and authentic virus assays [59]. LY-CoV1404, a new mAb recently approved by the U.S. Food and Drug Administration (FDA) has demonstrated to potently neutralize almost all circulating SARS-CoV-2 variants, including B.1.1.7, B.1.351, B.1.617.2, B.1.427/B.1.429, P.1, B.1.526, B.1.1.529 and the BA.2 subvariant [60]. Available data fail to demonstrate that mAbs or convalescent plasma from COVID-19 patients can facilitate SARS-CoV-2 D614 infection in human blood monocyte-derived macrophages inducing ADE *in vitro* [61].

Today, with the neutralizing antibody response induced by vaccination or previous SARS-CoV-2 infection weakening over time, whether non-neutralizing or sub-neutralizing antibodies would lead to enhanced viral invasion or proinflammatory damage upon reinfection is becoming a serious concern. The risk of SARS-CoV-2 reinfection and COVID-19 hospitalization in individuals after a previous SARS-CoV-2 infection or after SARS-CoV-2 vaccination remained low and it seems less severe [62].

The initial alarm raised about the possible emergence of ADE with the use of convalescent sera for the treatment of COVID-19 [63], and then after vaccination, is today weakening. Recent research has described a reduced cross-neutralization against VOCs (especially for Omicron BA.2) in plasma of patients infected with Omicron BA.1 and without history of vaccination, with opposite results reported in vaccinated patients [64]. While authors comprehensively highlight the potential implications of the study for the introduction of omicron-based vaccines, theoretically the reduced cross-reactive neutralization could rise the risk of ADE, which is not currently confirmed in the many data available about both SARS-CoV-2 reinfections and infections after vaccine [65].

Probably, the mechanism of ADE is not completely known and there are no markers to certainly predict or identify the possible benefit or risk of the presence of non- or sub-neutralizing antibodies coming from natural infection, vaccines or specific mAbs. Clinical data has not yet established a role for ADE in human COVID-19 pathology. It has been suggested that assays verifying early antibody quality/quantity, the expression of cognate FcγR on phagocytic cells or the presence of Fc glycoforms within antibodies could be used to anticipate COVID-19 outcomes.

In the meantime, vaccines and mAbs are considered optimal therapies, regardless the potential role of ADE in COVID-19 severity, which so far seems not to be confirmed in the most recent VOC waves.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial

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