Infection and Drug Resistance

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REVIEW

# On the Use of Immunoglobulins for Pre-exposure Prophylaxis Against COVID-19 in Immunocompromised Patients

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**Abstract:** COVID-19 remains a cause of significant mortality and morbidity for immunocompromised patients. In the current absence of effective monoclonal antibodies to SARS-CoV-2, standard commercial intravenous/subcutaneous immunoglobulin (IVIG/SCIG) lots provide an option for passive immunotherapy since these now consistently contain SARS-CoV-2-reactive antibodies. Strong mechanistic considerations and emerging observational data support the use of IVIG/SCIG as a biologically plausible option for COVID-19 pre-exposure prophylaxis (PreEP) in immunocompromised patients. In this review, we summarize the supporting evidence available and consider optimal use cases. Neutralization capacity against Omicron lineages is consistently reduced and highly variable between lots, and there is an intrinsic several-month lag between donor immunity and product infusion. The available information in literature sources consistently reflects the use of standard replacement dosing of IVIG/SCIG and does not systematically analyze COVID-19-specific safety or outcomes with dose intensification. While the available evidence suggests that IVIG/SCIG may be effective in PreEP, without dedicated randomized or well-controlled human trials, the magnitude of clinical benefit from this intervention remains uncertain, especially against contemporary Omicron sublineages.

**Keywords:** neutralizing antibodies, immunoglobulins, spike, treatment-emergent resistance

## Introduction

Passive immunotherapies, including immunoglobulin replacement therapy (IGRT), remain among the most clinically proven and tolerable antivirals for frail immunocompromised (IC) patients.[1,2] Coronavirus disease 2019 (COVID-19) continues to be a significant cause of mortality and morbidity among IC patients, especially among those with B-cell defects who cannot mount protective neutralizing antibody titers after vaccination. Multiple independent groups have reported that contemporary intravenous/subcutaneous polyclonal immunoglobulin (IVIG/SCIG) lots contain substantial amounts of anti-spike antibodies with neutralizing activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which are transferred to IC patients when IVIG/SCIG is administered at replacement doses[3–9] (Table 1). The presence of antibodies to the spike protein in IVIG/SCIG lots reflects widespread immunity to SARS-CoV-2 in the general population from vaccination and/or infection. Such antibody replacement is especially relevant for pre-exposure prophylaxis (PreEP), considering the current lack of effective long-acting monoclonal antibodies. Nevertheless, despite the theoretical benefits of specific antibody administration, the clinical effectiveness of this approach for PreEP is not yet established. In this review, we summarize the evidence supporting its use and discuss the optimal use cases.

## Mechanistic and Immunologic Evidence

In IC individuals with B-cell defects who have inadequate levels of anti-SARS-CoV-2 antibodies after infection and/or infection, the administration of IVIG/SCIG functions as a type of IGRT. In these individuals, the administered antibody functions as a temporary shield against COVID-19, which lasts as a function of transferred antibody pharmacokinetics.

https://doi.org/10.2147/IDR.S540925
Received: 2 February 2026
Accepted: 18 April 2026
Published: 30 April 2026

**Table 1** Study Type, Main Focus, and Direct Relevance to IVIG/SCIG COVID-19 Pre-Exposure Prophylaxis (PreEP)

| Ref | Year | Study Type | Population/Material | Main Focus | Direct Clinical PrEP Outcome Data? | Mechanistic Anti-SARS-CoV-2 Data in Standard IVIG/SCIG? |
|---|---|---|---|---|---|---|
| [1] | 2024 | Registry analysis + lot testing | ESID registry IEI patients (with/without agammaglobulinemia; on vs off IGRT) + 1100 Ig lots | COVID-19 incidence in IEI subgroups and temporal neutralization capacity (Wuhan, Omicron) of Ig lots | Yes, observational: COVID-19 case data across IGRT/no-IGRT groups (not a dedicated PrEP trial, but ongoing IGRT context) | Yes, large-scale neutralization vs Wuhan and Omicron in 1100 lots |
| [3] | 2023 | Prospective clinical + in vitro | 35 antibody-deficient patients on IGRT; 9 with persistent COVID-19; IVIG lots | Spike antibody and neutralization pre/post IVIG; case series of prolonged COVID-19 treated with IVIG + remdesivir | Indirect: describes ongoing IGRT and reports that 9 persistent infections cleared after IVIG + antiviral (treatment, not PrEP) | Yes, pseudovirus + live-virus neutralization (including BQ1.1, XBB) in products and patient sera |
| [4] | 2022 | Serologic study + small transplant cohort | Commercial IVIG (Privigen™ 10%) 2021–2022; kidney transplant recipients | Anti-spike titers in lots and in recipients post-infusion; Omicron neutralization; anecdotal infection data | Limited: notes that none of the described IVIG-treated transplant patients developed COVID-19 during follow-up | Yes, binding and neutralization vs ancestral and Omicron in lots; post-infusion spike IgG kinetics in vivo |
| [5] | 2024 | In vitro + preclinical (mouse) | 198 IVIG/SCIG lots (Dec 2019–Aug 2022) + K18-hACE2 mice | Time-course of anti-spike/neutralization vs multiple variants; mouse protection from XBB challenge at clinically relevant dosing | No human clinical outcomes | Yes, extensive binding and neutralization vs WA1, Delta, Omicron (BA1, BQ.1.1, XBB.1.5); in vivo protection in mice despite poor neutralization |
| [6] | 2022 | Mechanistic + small pharmacokinetic cohort | 60 sequential IVIG/SCIG batches; 4 XLA patients on IGRT | Temporal rise in SARS-CoV-2 antibodies in products and circulating levels in XLA; variant-specific neutralization | No clinical COVID-19 outcome data | Yes, lot-to-lot anti-S1 and live-virus neutralization vs Wuhan and Omicron; in vivo titers in XLA on routine IGRT |
| [7] | 2022 | Preprint; mechanistic + paired patient samples | 35 primary/secondary deficiency patients on IVIG + 7 controls | Pseudovirus neutralization in IVIG products and pre/post infusion sera (WT and an Omicron variant) | No outcome data | Yes, neutralization activity transmitted to patients, with significant product and lot variability |
| [8] | 2023 | Product surveillance | 125 Ig lots (standard IVIG/SCIG) + subset for functional assays | Binding to RBD/spike/N and ACE2-binding inhibition vs multiple variants; manufacturing/aging context | No human clinical outcome data | Yes, detailed serologic and ACE2-inhibition data vs ancestral, Alpha, Beta, Delta, Omicron |
| [9] | 2022 | Brief report; product neutralization | Commercial IVIG (incl. some SCIG) lots from US/EU (Mar–Apr 2022) | Neutralization vs Wuhan and Omicron B.1.1.529; comparison with hyperimmune Ig | No | Yes, μNT50 titers vs Omicron; variation by geography and product; comparison with hyperimmune products |

(*Continued*)

**Table 1** (Continued).

| Ref | Year | Study Type | Population/Material | Main Focus | Direct Clinical PrEP Outcome Data? | Mechanistic Anti-SARS-CoV-2 Data in Standard IVIG/SCIG? |
|---|---|---|---|---|---|---|
| [10] | 2023 | Prospective immunologic vaccine study | 31 adult primary antibody deficiency/ secondary hypogammaglobulinemia patients (30/31 on IGRT) | Longitudinal vaccine-induced humoral and T-cell responses; mentions IGRT anti-SARS-CoV-2 content | No COVID-19 outcome data attributable to IGRT | Indirect, contextual statements that early IGRT lacked protective anti-SARS-CoV-2 levels and Omicron neutralization remained poor. |

**Abbreviations**: ACE2, angiotensin-converting enzyme-2; ESID, European Society for Immunodeficiencies; hACE2, human angiotensin-converting enzyme-2; IEI, inborn errors of immunity; IgG, immunoglobulin G; IGRT, immunoglobulin replacement therapy; IVIG, intravenous immunoglobulin; RBD, receptor binding domain; SCIG, subcutaneous immunoglobulin; WT, wild-type; XLA, X-linked agammaglobulinemia.

Since IVIG preparations contain primarily immunoglobulin G (IgG), which has a half-life in serum ranging from 15 to 30 days depending on isotype,[11] repeated dosing can theoretically maintain a level of protection against COVID-19 provided that sufficient antibody to SARS-CoV-2 is administered. While pre-COVID-19 immunoglobulin pandemic lots contained essentially no SARS-CoV-2–reactive antibodies,[5,6,8,9] after 2021 IVIG/SCIG lots from the US and Europe began to contain substantial anti-spike/receptor binding domain (RBD) binding and neutralizing activity against the ancestral (WA1) virus, often reaching levels comparable to vaccinated healthy donors for ancestral strains[4–6,8,9] (Table 2). As more individuals acquired humoral immunity from vaccination and/or infection, and donated blood, there was a consistent time-dependent rise in commercial immunoglobulin titers from 2020 to at least mid-2022.[1,5,6,8] Nevertheless, given the inevitable variability in humoral immunity among donor populations, there is lot and brand variation in anti-SARS-CoV -2 titers. This is evident in marked heterogeneity in anti-S1 titers and neutralization levels across 60 lots in Sweden,[6] 125 lots in North America,[8] 198 US lots,[5] and lots from US/EU fractionators.[9] Differences in specific antibody composition reflect donor immunization history, geography, and the time window for lot production.[5,8,9] This variability means that IVIG/SCIG is a dynamic product, which reflects the population-level SARS-CoV-2 immunity at the time of collection, and its composition thus reflects immunity to whatever viral strain was prevalent in the months prior to its collection. Consequently, IVIG/SCIG; potency cannot be assumed across products or time, and requires periodic testing to ascertain its anti-SARS-CoV-2 titers and neutralizing capacity.

Today, the levels of neutralizing antibody titers in IVIG/SCIG preparations against ancestral SARS-CoV-2 strains are robust in most contemporary lots, often at levels projected to transfer protective humoral immunity comparable to that achieved in immunocompetent hosts after vaccination.[3–6,8,9] However, for the latter SARS-CoV-2 variants the neutralizing activity Is more variable. Against Omicron BA.1 variants, neutralization is detectable but is significantly lower in multiple series.[4–6,8,9] However, of greater concern is that neutralization against the later, currently circulating, highly immune-evasive Omicron sublineages (eg, BQ.1.1, XBB.1.5) is frequently poor or low, with substantial lot-to-lot variability.[3,5] This makes clear that lot efficacy is very dependent on the timing of lot production relative to variant circulation.

Administration of IVIG to patients with either primary or secondary antibody deficiencies receiving IGRT revealed five-fold increases in anti-spike IgG levels, with serum IgG rising from approximately 2100 to 10,600 U/mL immediately after IVIG infusion.[3] Kidney transplant recipients infused with a high-titer product (IVIG 2022 lots) manifested increases in serum levels from approximately 500 to 8900 AU/mL.[4] These levels paralleled post-infusion rises in pseudovirus and live virus neutralization titers that were comparable to those of healthy donors for ancestral strains, but with variable degrees of Omicron neutralization, depending on product/lot.[3,7] X-linked agammaglobulinemia (XLA) patients on continuous IGRT given IVIG manifested steady-state circulating anti-S1 IgG and Wuhan neutralization levels, but Omicron neutralization was limited at trough levels.[6]

While anti-spike levels and neutralization titers are the parameters most commonly measured and reported, antibody-mediated protection against SARS-CoV-2 is also mediated by several Fc-dependent functions, such as phagocytosis of


https://doi.org/10.2147/IDR.S540925

**Table 2** Evolution of SARS-CoV-2 Antibody Content and Variant Neutralization in Commercial Immunoglobulin Lots

| Ref | Lots Tested (n) | Time Window /Geography | Assays | Main Findings on Antibody Levels and Variant Coverage |
|---|---|---|---|---|
| [1] | 1100 | Over 3 years (approx. 2020–2023; Europe) | Neutralization vs Wuhan and Omicron | Pre-pandemic/early lots lacked activity; marked increase in anti-SARS-CoV-2 neutralization over time. Omicron neutralization detectable but lower than Wuhan and variable between lots. Used to interpret registry outcomes |
| [5] | 198 | Dec 2019–Aug 2022 (US products) | Binding (anti-spike) and neutralization vs WA1, Delta, BA.1, BQ.1.1, XBB.1.5 | Prepandemic lots non-reactive. Binding and neutralization vs WA1 increased steadily, reaching levels comparable to vaccinated donors ~18 months after first US case. Neutralization vs Delta and Omicron sublineages often poor and highly variable. Estimated ~8-month lag from plasma collection to infusion, limiting contemporaneous variant coverage |
| [6] | 60 | Sequential batches to Jan 2022 (Europe; 3 manufacturers) | Anti-S1 IgG and live-virus neutralization (Wuhan and Omicron) | SARS-CoV-2 antibody content rose over the pandemic, but lot-to-lot variability was large. Lots with strong Wuhan neutralization gave limited or insufficient neutralization of Omicron, demonstrating early Omicron escape |
| [8] | 125 (48 for functional assays) | North American products; pandemic period not fully specified but includes pre- and post-vaccination lots | Binding to RBD/spike/N; ACE2–spike binding inhibition vs ancestral, Alpha, Beta, Delta, Omicron | Pre-pandemic lots lacked SARS-CoV-2 antibodies. Post-pandemic lots contained robust anti-spike and anti-RBD binding, plus ACE2-blocking activity against multiple variants, though Omicron inhibition was reduced relative to earlier variants. Emphasizes manufacturing timescale (up to a year) and 3-year shelf life |
| [9] | Contemporary lots; number not fully specified in summary | Lots released Mar–Apr 2022 (US and Europe) | μNT50 neutralization vs Wuhan and Omicron B.1.1.529 | Standard IVIG/SCIG lots contained detectable Omicron-neutralizing antibodies, but titers were well below hyperimmune Ig. Yield and potency differed by geography and product, reflecting donor infection/ vaccination patterns |
| [4] | Multiple lots | 2021–2022 (US-manufactured) | Binding to spike RBD and neutralization vs ancestral and Omicron | 2021 lots had minimal spike-RBD activity; 2022 lots showed strong spike binding even at 1:1000 dilution and measurable neutralizing activity to ancestral and Omicron variants. Anti-N also detected, indicating donor infection contributions |
| [7] | Multiple commercial IVIG products; distinct lots | 2022 (UK) | Luminescence-based pseudovirus neutralization vs WT and Omicron | Many products contained neutralizing anti-spike antibodies, with substantial variability between brands and lots. Omicron neutralization detectable but often lower than WT |

(*Continued*)

**Table 2** (Continued).

| Ref | Lots Tested (n) | Time Window /Geography | Assays | Main Findings on Antibody Levels and Variant Coverage |
|---|---|---|---|---|
| [3] | Same or overlapping IVIG products as Ref[7] | 2022 (UK) | Pseudovirus + live-virus neutralization vs early and contemporary variants (incl. BQ.1.1, XBB) | Confirms that current IVIG lots can achieve neutralization titers in vitro comparable to vaccinated healthy donors for some variants, but neutralization of contemporary Omicron lineages BQ.1.1/XBB is reduced and product-dependent |

**Abbreviations**: ACE2, angiotensin-converting enzyme-2; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; RBD, receptor binding domain; SCIG, subcutaneous immunoglobulin; WT, wild-type.

viral particles, complement activation, and antibody-dependent cellular cytotoxicity (ADCC).[12] Unfortunately, measuring these activities is more complex than measuring titer and neutralization, and consequently this information is not usually available for IVIG/SCIG preparations. In fact, such Fc-dependent effector functions (ADCC/ADCP, complement) may contribute disproportionately to the efficacy of IVIG/SCIG in limiting disease severity rather than infection acquisition. In this regard, clinically relevant dosing of immunoglobulin protected K18 hACE2 mice against XBB challenge by preventing disease, lung infection, and inflammation, despite poor in vitro neutralizing activity.[5] Overall, these observations fit well with historical evidence that IVIG reduces the incidence/severity of respiratory viral infections in primary immunodeficiencies.[2] However, given the dynamic nature of IVIG/SCIG composition, inferences about efficacy from past studies require caution since the product changes with time, and measuring titers and neutralizing capacity does not measure all the variables that contribute to antibody-mediated protection, including Fc-related functions.

## Clinical Evidence for PrEP-Like Effects

Unfortunately, no dedicated PreEP trials (randomized, prospective, or even rigorous matched cohort designs) are available. In the absence of randomized controlled trials (RCTs), evidence for IGIV/SGIV efficacy must be sought in observational and historical studies with awareness of the limitations inherent in such data, which generally preclude establishing causal associations. The European Society for Immunodeficiencies (ESID) registry data on immunoglobulin efficacy against COVID in patients with inborn errors of immunity (IEI) were made available by Karbiener et al in 2024.[1] Among 981 agammaglobulinemia patients on continuous IGRT, 8960 IEI patients on IGRT, and 14,428 IEI patients without IGRT receiving 1100 immunoglobulin lots between 2021 and 2022, COVID-19 case numbers increased with Omicron, but the pattern of infection differed between IGRT and non-IGRT groups. While there were no differences in COVID-19 incidence between groups in the 2020/2021 and 2021/2022 cold seasons, for the 2022/2023 season there were approximately 30- and six-fold declines for patients with agammaglobulinemia and non-agammaglobulinemia, respectively, relative to those not receiving IGRT. In addition to the epidemiologic evidence, two other factors argue for a cause-and-effect relationship between administering IGRT and reduced COVID-19: 1) during the time of the study there was an increase in the titer of antibody against Omicron variants, which was associated with efficacy; and 2) the effect was greater in the agammaglobulinemia group, which would be expected to receive greater benefit from receiving some antibody over those who had baseline antibody. Dose–response effects are strongly suggestive of a causal association between IGRT and reduced COVID-19. Although this study is observational and lacks randomization to avoid confounding effects from vaccination, behavioral precautions, and differences in disease severity, it included a large number of participants who experienced large effects, and thus represents the most directly relevant human dataset for assessing standard IGRT as quasi-PreEP.

In addition, there are small series that have been published for different cohorts that provide additional suggestive evidence for IVIG/SCIG efficacy. In 2022, Jordan et al[4] reported no SARS-CoV-2 infections among kidney transplant recipients receiving high-titer standard IVIG for usual clinical indications during the observation period. Although a non-PreEP scenario, in 2023 Upasani et al reported nine patients with persistent SARS-CoV-2 infection (median duration 189

days, one >900 days) in whom the introduction of IVIG alongside remdesivir was associated with viral clearance within approximately 20 days.[3]

Agammaglobulinemia patients constitute a uniquely informative population for evaluating IGRT efficacy, since they have essentially no endogenous antibodies to SARS-CoV-2, and protection coming from IGRT must come from transfused antibodies. Lindahl et al reported that routine IGRT in XLA patients resulted in titers that neutralized the Wuhan strain and mediated limited Omicron neutralization.[6] These patients are the clearest testbed for IVIG/SCIG PreEP; the combination of high dependence on passive immunity and available registry data[1] suggests that any observed protection is highly attributable to IGRT. In contrast, patients with common variable immune deficiency (CVID), who are also typically on continuous IVIG/SCIG, represent a more heterogeneous group, with poor or absent humoral responses but often preserved T-cell responses to spike.[10] IGRT in patients with CVID supplies antibodies with limited neutralization against recent variants.[3,6,8,10] Patients with secondary hypogammaglobulinemia secondary to B-cell-depleting therapies or bone marrow transplantation[4] are likely to have similar responses and experience comparable benefits from IGRT,[3,10] but formal outcome data are lacking, and in this group considerations of thrombotic and renal risk events are particularly important.

## Safety and Tolerability in the COVID-19 PreEP Context

Although none of the studies identified in this review provided a systematic safety analysis specifically for IVIG/SCIG when used for COVID-19 PrEP, we did not identify any safety signals of concern. All clinical uses are at standard replacement doses for IEI/primary antibody deficiency or transplant indications.[1,3,4,6,10] Importantly, no sign of unusual COVID-19-related safety concerns is reported, but adverse events (infusion reactions, headache, rare thrombosis/renal injury, hemolysis) are not systematically captured in relation to SARS-CoV-2. Dose-escalation strategies to increase anti-SARS-CoV-2 titers have not been evaluated for safety, and hence there is a need for careful pharmacovigilance should IVIG/SCIG be repurposed or intensified for COVID-19 PreEP.

## Key Knowledge Gaps and Priorities for Future Research

Based on the available information, it is reasonable to posit that standard IVIG/SCIG contributes some level of protection against COVID-19, particularly in patients with absent or severely impaired humoral immunity. Nevertheless, clinicians should recognize that protection is partial and variant dependent, especially against contemporary Omicron sublineages. Furthermore, there is likely to be a time dependence for protective efficacy, being highest shortly after immunoglobulin infusion and waning as antibody levels naturally decline. IGRT should not replace vaccination, early antiviral treatment, or non-pharmacologic measures to prevent infection. Where serologic data are available, clinicians should preferentially use higher titer lots/products. The value of monitoring post-infusion anti-spike titers in the highest risk patients is debatable, given that correlates of protection are not firmly defined. Given these uncertainties, regulatory and funding bodies should recognize that IVIG/SCIG is already being administered to many of the highest risk patients, and should support the continued gathering of registry information, as well as focused measurement of antibody efficacy parameters in commercial lots, as these interventions could yield high-value data at relatively modest incremental cost.

No trials so far have quantified the risk reduction in infection, hospitalization, or deaths attributable to IVIG/SCIG PreEP in any IC subgroup. Without these data, it is not possible to establish the cost–efficacy ratio of this intervention. Prospective, ideally randomized, or carefully controlled cohort studies in agammaglobulinemia or B-cell-depleted malignancy patients are likely to be informative, with integrated lot characterization (neutralization and Fc effector profiling) to link product potency with outcomes. However, there are likely to be ethical concerns in assembling non-treated control groups among these vulnerable populations, given the likelihood that such interventions are effective and have relatively low toxicity. Correlates of protection are also poorly defined in IC hosts, who may require higher and more sustained titers than immunocompetent hosts to achieve protection. Given the IVIG/SCIG production and shelf-life lag (~6–12 months) and rapid SARS-CoV-2 variant evolution, any PreEP strategy needs ongoing surveillance of immunoglobulin lot anti-S/neutralization titers against currently circulating variants.[1,5,8,9] Furthermore, PreEP strategies require a decision framework that can switch brands, adjust dosing or infusion frequency, or de-emphasize IVIG/SCIG PreEP when neutralization against prevailing variants is negligible. Dose-escalation and pharmacokinetic/

pharmacodynamic studies with integrated safety monitoring are also needed, focusing on the long-term cumulative risk of thrombosis, hemolysis, and renal impairment, especially in populations with high baseline thrombotic/renal risk (eg, multiple myeloma, solid organ transplantation, hematopoietic stem cell transplantation).

## Hyperimmune Immunoglobulins

COVID-19 convalescent plasma (CCP) represented the frontline response to the pandemic and was deployed for therapy in over 50 countries.[13] As the pandemic evolved, several countries began to direct CCP donations towards plasma manufacturers to produce hyperimmune polyclonal IgG formulations.[14] The large-scale production of anti-SARS-CoV -2 hyperimmune IVIG (hIVIG), aimed at marketing a plasma-derived product with a high and standardized neutralizing antibody titer against SARS-CoV-2 (IVIG being approximately 10-fold more concentrated than CCP) in a smaller volume, would probably have encountered similar obstacles to those that we have already discussed for IVIG. Nowadays, any strategy to produce a hyperimmune immunoglobulin product would find that the main hurdle is competition from standard IVIG manufacturing, some of which already has high titers of IgG to SARS-CoV-2. Production of hyperimmune IgG requires several months between the initiation of CCP collection and the distribution of lots. This time delay, combined with the rapid evolution of SARS-CoV-2 strains, would pose a formidable logistical problem for any plans to test these products in well-designed RCTs. Another issue of equal importance is the economic sustainability related to the high costs of production of IVIG, the price of which is noticeably higher than that of CCP. This has led many manufacturers to consider investments on hIVIG as being economically non-advantageous.[14] The results of RCTs on the clinical use of hIVIG for the treatment of COVID-19 have been inconsistent.[14] In a phase I/II RCT by Ali et al in 50 patients with severe and critical COVID-19 and randomized to receive hIVIG or standard of care, the administration of anti-SARS-CoV-2 specific immunoglobulins was associated with a reduction in mortality (25% in the intervention group versus 60% in the control group).[15] In another study, the administration of hIVIG to 60 hospitalized COVID-19 patients, randomized to receive hIVIG or standard care, was found to be safe and well tolerated, resulting in a shorter time to viral clearance and an early reduction in inflammatory biomarkers in treated patients relative to controls.[16] Another RCT enrolled 18 severely IC patients hospitalized for COVID-19 to receive either hIVIG (10 patients) or standard IVIG (eight patients) and showed that hIVIG significantly reduced the incidence of severe COVID-19 (20% versus 88%, $p = 0.015$).[17] By contrast, the ITAC RCT enrolled 593 participants, of whom 301 received hIVIG and 292 placebo,[18] and found that the hIVIG group did not have significantly greater odds of a more favorable outcome at day 7 than the placebo group (adjusted OR: 1.06; 95% CI 0.77–1.45; $p = 0.72$). A 2023 Cochrane systematic review identified five RCTs evaluating hIVIG efficacy involving 947 participants (688 treated with different formulations of hIVIG) hospitalized with moderate or severe COVID-19.[19] With the limitations derived from the great heterogeneity (differences in dosing, and human or animal origin) of marketed hIVIG formulations, there was no impact of this treatment on patients' mortality or clinical improvement. Notably, in a recent head-to-head comparative RCT (hIVIG versus CCP), treatment outcomes were better in patients treated with hIVIG on day 28, but not on day 14.[20] Overall, although limited, the available literature data indicate no benefit to hIVIG therapy in immunocompetent individuals hospitalized with COVID-19, but there may be a potential role in improving outcomes in severely IC patients. In the current era, where many individuals have had both vaccination and COVID-19, there is high-titer heterologous immunity against SARS-CoV-2, which provides efficient cross-protection against most variants, including Omicron sublineages. Within this new context, currently available standard IVIG, originating mostly from CCP donations, equates to hIVIG in terms of anti-SARS-CoV-2 neutralizing antibody content, and renders the creation of a dedicated manufacturing chain poorly cost-effective and probably unnecessary.

# Conclusions

Standard commercial IVIG/SCIG has evolved into a mechanistically credible, widely available, but incompletely characterized option for COVID-19 PreEP in IC patients. Current mechanistic and observational data justify serious consideration and formal testing, but do not yet support complete reliance on IVIG/SCIG as a standalone PreEP strategy in the Omicron era. Before 2021, standard IVIG/SCIG were essentially devoid of anti-SARS-CoV-2 antibodies as they originated from plasma donors who had not experienced COVID-19 or vaccination; as such, the focus was on CCP,

hyperimmune serum, and anti-spike monoclonal antibodies. IGRT was mostly seen only as non-specific background protection for IC patients. However, by early 2022, as the prevalence of COVID-19 infection and vaccination in the donor population increased, there were the first clear demonstrations of rising anti-SARS-CoV-2 activity in IVIG/SCIG lots, with early recognition of Omicron escape and lot variability;[4,6,9] in addition, there was the first evidence of post-infusion serology in transplant and PID patients.[4] In 2023, patient-level neutralization and serology firmly established that routine IGRT confers substantial anti-spike titers and measurable neutralization in vivo,[3,7] and broader lot surveillance[8] extends our mechanistic understanding.[8] In 2024, Fc-mediated and immunomodulatory mechanisms were shown in addition to neutralization,[5] and registry data supported clinical benefit in agammaglobulinemia patients.[1] Despite all of this encouraging evidence, the field now sits stuck at the threshold of formal clinical evaluation of IVIG/SCIG as COVID-19 PreEP. While the available observational evidence is encouraging, the benefit of IVIG/SCIG in secondary antibody deficiencies will likely remain uncertain unless properly randomized controlled trials are undertaken.

## Abbreviations

CCP, COVID-19 convalescent plasma; IC, immunocompromised; IEI, inborn errors of immunity; IgG, immunoglobulin G; IGRT, immunoglobulin replacement therapy; IVIG, intravenous immunoglobulin; PrEP, pre-exposure prophylaxis; RBD, receptor binding domain; RCT, randomized controlled trial; SCIG, subcutaneous immunoglobulin; XLA, X-linked agammaglobulinemia

## Disclosure

The authors report no conflicts of interest in this work.

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