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# Early combined therapy for COVID-19 in immunocompromised patients: a promising approach against viral persistence and drug resistance

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## Abstract

Immunocompromised (IC) patients face significant challenges in managing COVID-19 due to their heightened susceptibility to severe illness, persistent infections, and the potential development of drug resistance. Studies indicate that IC patients, particularly those with hematologic malignancies (HM), hematopoietic stem cell transplants (HSCTR), or solid organ transplants (SOTR), experience higher mortality rates and worse outcomes compared to the general population, even post-vaccination. The persistence of the virus in these patients, combined with its rapid mutation, further complicates treatment. Recent evidence supports the use of combined neutralizing monoclonal antibodies (mAbs) and direct-acting antivirals (DAAs) as a more effective approach to viral clearance, reducing mortality, and preventing relapses. However, the rise of resistant variants, especially to mAbs, and concerns about the safety of prolonged or intensive therapies pose ongoing challenges. Monotherapies often fail short to address these issues, highlighting the need for early combined therapy (ECT) with mAbs and DAAs. ECT has shown promise in managing COVID-19 in IC individuals by targeting multiple stages of the viral lifecycle, reducing viral load, and clearing infections at earlier stages, which helps mitigate the risks of severe disease and drug resistance. Continued research is essential to refine these treatment protocols, especially as the virus evolves. Although further studies are needed, current findings suggest that ECT may become the standard of care for managing COVID-19 in severely IC patients, offering better clinical outcomes and hindering viral persistence.

## Clinical trial

Not applicable.

**Keywords** Immunocompromised, COVID-19, Combined therapy, Monoclonal antibodies, Antivirals

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## Introduction

COVID-19 presents significant risks to immunocompromised (IC) individuals, who are particularly vulnerable to severe disease, prolonged viral shedding, and poor clinical outcomes [1]. IC patients encompass various groups, each with unique challenges. These include individuals with hematologic malignancy (HM), including hematopoietic stem cell transplant recipients (HSCTR), who often have impaired immune responses [2]. Solid organ transplant recipients (SOTR) also represent a high-risk group due to the immunosuppressive therapies required to prevent organ rejection [3]. Additionally, patients receiving therapies like anti-CD20 monoclonal antibodies, are at elevated risk due to both the disease itself and the immunosuppressive treatments used to manage it [4]. Despite widespread vaccination efforts, these patients remain at a high risk due to reduced vaccine efficacy, especially with emerging variants [5, 6]. Standard treatments often fail to address the unique challenges faced by IC individuals, leading to persistent infections and the potential development of drug-resistant strains [7, 8].

Given the inadequacy of monotherapy in such cases, early combined therapy (ECT) with neutralizing monoclonal antibodies (mAbs) and direct-acting antivirals (DAAs) has emerged as a promising strategy [9–11]. This approach targets the virus at multiple stages of its lifecycle, reducing viral load, preventing disease progression, and mitigating the risk of severe outcomes [10, 12].

This review explores the safety and effectiveness of ECT in severely IC patients, highlighting the therapeutic advantages and potential challenges posed by emerging variants and drug resistance.

## Natural history of COVID-19 in immunocompromised patients

At the beginning of the pandemic, when neither vaccines, DAAs, nor mAbs were available, observations quickly revealed unfavorable outcomes in IC patients [13–15]. Among IC individuals, those with HM emerged as one of the groups at highest risk for severe infection, primarily due to their inherent frailty, ongoing immunosuppressive therapies, and frequent hospital visits [15]. An earlier study conducted in Wuhan, China, focused on 13 IC patients diagnosed with COVID-19 who were affected by HM. It revealed that eight of these patients, representing 61.5% of the cohort died. The median time from the onset of symptoms to death was 11 days, with the time range varying between 6 and 29 days [16]. Another study of 35 patients in the United Kingdom found a 40% mortality rate, three times higher than the general population. Older age and comorbidities like hypertension and chronic kidney disease were adjunctive risk factors for worse outcomes. However, no clear association between ongoing cancer treatment and mortality was found, as many patients on active therapy recovered [17]. In a larger cohort of 536 patients, 37% died, with 50% experiencing severe or critical illness. Mortality was nearly four times higher in patients under 70 compared to the general population and 41 times higher than in non-COVID-19 hematological patients [15]. Adult patients with HM, especially those hospitalized and aged ≥ 60 years, were found to be at high risk of dying from COVID-19. Factors such as age, disease status, and specific malignancy subtypes significantly impact survival, while recent systemic anticancer therapy does not appear to substantially increase the risk of death [14, 15]. Overall, these patients were twice as likely to die from COVID-19 as the general population. This elevated risk was even more pronounced among individuals younger than seventy, who had nearly four times the mortality risk compared to their peers in the general population [15].

Studies focusing on unvaccinated, hospitalized HSCTR further highlight the severe outcomes associated with COVID-19 in this vulnerable group. An analysis of 34 hospitalized HSCTR emphasized the significant mortality risks related to advanced age, poor performance status, and the development of acute respiratory distress syndrome (ARDS). Elevated procalcitonin levels emerged as a critical marker of mortality, suggesting a potential for targeted monitoring and intervention. Notably, patients in remission or under a watch-and-wait strategy had better outcomes compared to those undergoing active cancer treatment, reflecting the impact of ongoing therapy on COVID-19 outcomes [18]. Similarly, another study of 25 hospitalized HSCTR reported a 40% mortality rate at one month, reinforcing the finding that advanced age, multiple comorbidities, and the immunosuppressive effects of HM and treatments are key contributors to severe COVID-19 outcomes [19].

Regarding patients treated with anti-CD20 therapies, such as rituximab, initial literature indicates mixed outcomes for patients on anti-CD20 therapies during the COVID-19 pandemic. Some studies have reported favorable outcomes or asymptomatic cases among patients on ocrelizumab [20–22], while others have noted increased of hospitalization and mortality [23]. Indeed, the French Covisep MS registry including 347 patients, found no significant association with anti-CD20 therapies, possibly due to a smaller sample size [20]. By contrast, in the COViMS Registry study including 1626 patients, the use of anti-CD20 therapies, including rituximab and ocrelizumab, showed notable associations with worse COVID-19 outcomes. Rituximab was linked to an increased risk of hospitalization compared to other disease-modifying therapies, and this association was more pronounced than that observed for ocrelizumab. The differences in outcomes between these two anti-CD20 monoclonal antibodies may be attributed to the longer

duration of treatment with rituximab, as ocrelizumab is a more recent addition to MS treatments [23]. Similarly, the COVID-19 Global Rheumatology Alliance registry reported a four-fold increased risk of death for patients on rituximab compared to those on methotrexate among 110 IC individuals [24]. Therefore, these patients are at a significantly increased risk of severe COVID-19, prolonged viral shedding, and relapses. The timing of anti-CD20 therapy relative to COVID-19 infection is a critical determinant of outcomes, with recent therapy associated with higher mortality [25, 26].

Early reports on SOTR highlighted their vulnerability to severe COVID-19 outcomes. One of the first case series reported 10 renal transplant recipients with SARS-CoV-2 infection in Wuhan, China, highlighting their severe COVID-19 pneumonia and prolonged illness. Compared to their infected family members and the general population, these patients experienced more severe disease, with 80% classified as severe versus 19% in the general population. However, despite a higher severity, all but one patient recovered [27]. In another study of 90 SOTR diagnosed with COVID-19 during the first three weeks of the New York City outbreak, 76% were hospitalized, 18% died, and intensive care unit (ICU) patients had a 52% mortality rate. Severe disease and death were more common compared to non-transplant cohorts [3].

A study from United States observed 36 kidney transplant patients. Most were hospitalized with pneumonia, and many showed lymphopenia and elevated inflammatory markers. Immunosuppressive drugs were often reduced, but despite treatment efforts, mortality rates exceeded those of the general population. A 28% mortality rate at three weeks was recorded, especially high among intubated patients (64%) [28]. Kidney transplant recipients had more comorbidities and displayed more frequent acute kidney injury and renal replacement therapy compared to nontransplant patients. These patients showed had a twofold higher risk of COVID-19-related death [29]. In kidney transplant recipients with COVID-19, laboratory findings show varied results, with lymphocytopenia observed in most cases [27, 29]. Notably, alterations in peripheral lymphocyte subsets are strongly associated with the clinical characteristics of COVID-19. Specifically, changes in CD8 + T cells have emerged as a potential independent predictor of disease severity and treatment outcomes [30].

Some experts hypothesized that calcineurin inhibitors (CNIs) might protect against severe COVID-19 by suppressing viral replication [31]. However, the subsequent findings suggest that CNI therapy does not confer a survival benefit. SOTR on chronic CNI treatment had similar in-hospital mortality rates as those not on CNIs, indicating that the clinical concentrations of these drugs might be insufficient to impact SARS-CoV-2 replication significantly [32, 33]. A retrospective, multicenter study including 1,833 SOTR underscores the differential impact of immunosuppressive regimens on COVID-19 outcomes in kidney transplant recipients. While effective in preventing rejection, the use of mycophenolate increased the risk of 30- and 90-day mortality, possibly due to its effects on the immune system [34]. Indeed, in SOTR who are already on mycophenolate, the drug is typically discontinued immediately after a COVID-19 diagnosis. Indeed, mycophenolate can suppress immune function, potentially worsening the viral infection by impairing the body's ability to mount an effective immune response. Additionally, mycophenolate (MPA) is known to cause leukopenia, which can further weaken the immune system and increase the risk of secondary bacterial infections [35].

In summary, SOTR are at increased risk for severe COVID-19, leading to higher hospitalization and mortality rates. CNIs do not significantly improve survival outcomes, whereas MPA use is associated with worsened outcomes, making it advisable to discontinue or reduce MPA upon a COVID-19 diagnosis if rejection is not a concern. Proper management of immunosuppressive therapy in such cases is essential.

Corticosteroids (CS) are commonly prescribed to manage a variety of chronic inflammatory and autoimmune conditions. However, their long-term use can lead to immunosuppression, which may have serious implications for patients with COVID-19. High doses of CS can be harmful, particularly when used during the early stages of infection, where controlling viral replication is essential and the inflammatory response is still minimal [36]. Indeed, administering glucocorticoids too early may hinder the immune system's ability to clear SARS-CoV-2. Thus, glucocorticoid therapy may prove more effective during this later immunopathological phase, when the excessive immune response and inflammation cause damage, rather than in the early, virus-driven phase [37].

The RECOVERY trial, including 6,425 patients, showed that dexamethasone treatment in patients with COVID-19 resulted in lower 28-day mortality in patients who required respiratory support [38]. Therefore the NIH guidelines recommend initiation of systemic CS treatment for patients with severe and critical COVID-19 [39]. By contrast, chronic systemic CS therapy prior to hospital admission has been identified as a major risk factor for increased mortality in COVID-19 patients, particularly those who are immunosuppressed. Patients receiving long-term CS treatment also face heightened risks of severe in-hospital complications such as ARDS bloodstream infections, acute kidney injury, and multiple organ failure [40]. A study from a Danish cohort of 96,526 individuals reinforced this finding, showing that CS use at the time of hospital admission is the strongest

predictor of mortality in immunosuppressed COVID-19 patients [32]. Moreover, a population-based register data study which includes 1,200,153 patients infected with COVID-19 in Sweden from January 2020 to November 2021 shows that 3,378 (6.9%) deaths occurred among overall patients, with 2,023 (15.0%) deaths in the high-exposure group, and 14,850 (1.3%) deaths in the non-exposed group. Deaths from pulmonary embolism, sepsis and COVID-19 were associated with high glucocorticoid exposure. Also, high exposure to CS was associated with increased deaths caused by stroke and myocardial infarction [41].

In summary, chronic CS therapy may be a risk factor for patients with COVID-19, as the resulting IC state can worsen prognosis and increase the risk of systemic complications.

## Reduced efficacy of vaccination in immunocompromised COVID-19 patients

As the world grappled with the unprecedented spread of SARS-CoV-2, the scientific community mobilized to develop effective vaccines to mitigate the impact of the virus and mRNA vaccines, emerged as groundbreaking innovations, demonstrating high efficacy in preventing severe illness and hospitalization [42]. For instance, the EPICOVIDEHA survey revealed a substantial decrease in COVID-19-related mortality following the introduction of vaccines among 1,548 patients with HM. Prior to the availability of vaccines, the mortality rate among patients with HM was alarmingly high, reaching 31%. While, after vaccination became more widespread, this rate dropped to 8% [43].

However, despite vaccination, IC individuals remain at a higher risk of SARS-CoV-2 infection. Real-world data from a cohort of 664,722 vaccinated individuals in the United States revealed that those with immune dysfunctions —such as HIV infection, rheumatoid arthritis, SOTR or HSCTR—experienced significantly higher rates of infections despite vaccination. This risk was particularly pronounced following the emergence of the Delta variant [5]. Moreover, a large population-based study including 20,910 individuals in England highlighted the disproportionate impact of COVID-19 on IC. Although over 80% of these individuals had received at least three vaccine doses, they accounted for over 20% of COVID-19 hospitalizations, ICU admissions, and deaths, despite comprising only 3.9% of the population studied [6]. Indeed, efficacy COVID-19 vaccines are less effective in generating robust immune responses in IC individuals compared to immunocompetent people. This issue is particularly concerning in certain high-risk groups, such as patients with HM, SOTR, individuals receiving immunosuppressive treatments, including CS, anti-CD20 monoclonal antibodies, or other immunosuppressive therapies, and older adults whose immune function naturally declines with age (i.e., immunosenescence) [44–47]. In particular, in a systematic review of 162 studies ($n = 25,209$) assessing vaccine-induced immunity across different groups, SOTR, particularly lung and kidney recipients, and patients with HM exhibit the highest non-response rates [44]. In another systematic review and meta-analysis of 82 studies, was examined the seroconversion rates after COVID-19 vaccination among different IC groups compared to immunocompetent controls. SOTR had the lowest seroconversion rates, with a pooled risk ratio of 0.06 after the first dose and 0.39 after the second dose. Patients with HM had risk ratios of 0.40 and 0.63, respectively. For those with immune-mediated inflammatory disorders, the risk ratios were 0.53 and 0.75, while patients with solid cancers had ratios of 0.55 and 0.90. In contrast, people with HIV had a comparable immune response after the second dose [48]. A systematic review and meta-analysis of 16 studies involving 1,186 HSCTR patients found a 24% prevalence of severe or critical disease and a 17% mortality rate. Allogeneic HSCTR patients showed higher mortality (17%) compared to autologous HSCTR patients (14%) [47]. Another study reported data from 66 cases of COVID-19 in SOTR who received COVID-19 vaccinations, with 78.8% of infections occurring after the second vaccine dose and 82.7% of those happening at least 14 days post-vaccination. Despite vaccination, 60.5% of patients were hospitalized, and 20.9% experienced critical disease. There was no significant difference in outcomes between fully and partially vaccinated individuals, and three fully vaccinated patients died [46]. Even in patients undergoing anti-CD20 therapy the response to vaccination is significantly impaired compared to those who are not with the seroconversion rates for patients on active anti-CD20 therapy were reported to be very low, often ranging from 0 to 25% [45]. As a consequence, patients treated with anti-CD20 monoclonal antibodies experience a significantly higher rate of worse COVID-19 outcomes, including increased mortality and a more prolonged and complicated clinical course compared to the general population. Additionally, these patients are more prone to frequent relapsing infection [25].

Therefore, despite IC benefit from COVID-19 vaccination in terms of mortality, they remain at significantly higher risk for severe outcomes despite vaccination [6]. While vaccines offer some protection, IC individuals remain highly affected by COVID-19 underscoring the importance of additional preventive measures, personalized vaccination strategies, and the continued development of evidence-based guidelines to protect this vulnerable population [6, 49]. Immune responses to COVID-19 vaccines may vary among IC due to different underlying conditions and medications [50–52]. A

deeper understanding of how disease mechanisms, medications, and vaccine formulations interact is crucial to personalize vaccination plans [50, 53, 54]. Overall, when selecting a COVID-19 vaccine formulation for IC, factors such as disease state, treatment regimen, and vaccination history should be considered [53]. Evidence-based guidelines for IC vaccination are needed, along with further research to address gaps and explore new vaccine formulations and dosing strategies.

## Monotherapy falls short in immunocompromised COVID-19 patients

As the medical community was still trying to understand the best therapeutic approaches for COVID-19, the limited effectiveness of early treatments in patients with weakened immune systems became apparent [9]. These patients, already at higher risk due to their compromised ability to fight infections, were among the first to experience severe complications. The initial reliance on drugs like hydroxychloroquine, which later proved to be largely ineffective against COVID-19, highlighted the urgent need for more effective therapies, especially for vulnerable populations such as the IC [13, 55]. Moreover, as the COVID-19 pandemic evolved, it became clear that immunosuppression can lead to prolonged and complicated infections in IC patients.

A study examined the effectiveness of mAbs in treating COVID-19 among 88 hematological patients. Key findings show that 17% of patients progressed to severe or critical COVID-19, nine deaths (10%) were recorded with 8% attributed to COVID-19. Progression to severe/critical disease was observed in 29% of myeloma cases, 17% of lymphoma cases, and 18% of acute leukemia cases. COVID-19 mortality was significantly lower in the mAb-treated group compared to the untreated hematological patients [56]. Receiving anti-SARS-CoV-2 treatment, either with mAbs alone or in combination with DAAs, was independently associated with a significantly lower mortality risk [43]. In another study, a total of 143 outpatients were included, 106 of whom were immunocompromised. Adverse drug reactions (ADRs) were reported in 16.1% of cases, with no significant difference between IC and non-IC groups. Within 14 days after treatment, eight (7.8%) IC patients visited the emergency department, and five (5.8%) were hospitalized due to COVID-19, with one COVID-19-related death [57]. In a retrospective cohort study including 331 IC inpatients with COVID-19, was found that the incidence of severe COVID-19 was significantly lower in patients treated with remdesivir or mAbs (38%) compared to those who received no therapy (59%). Interestingly, the combination of remdesivir and mAbs was even more effective, reducing the incidence of severe COVID-19 to 11% [58].

In IC patients, treating COVID-19 with a single therapeutic agent often proves insufficient due to the virus's capacity to adapt and develop resistance, thereby diminishing treatment efficacy. SARS-CoV-2 demonstrates a notable propensity for mutation, particularly under the selective pressure of a single drug. Consequently, employing a combination of therapies has become critical. This approach may reduce the likelihood of resistance development and enhance infection control [9]. Persistent SARS-CoV-2 infections in IC individuals are associated with a higher mutation rate, leading to increased viral diversity and the emergence of drug-resistant strains [9, 59]. This increased mutation rate can contribute to the development of resistance against both mAbs and DAAs. In such patients, several mutations associated with treatment-resistant viral strains have been identified. Particularly in the receptor-binding domain, which constitutes less than 2% of the genome but accounts for 17% of all detected de novo mutations [60]. For example, a case study over seven months in an IC patient demonstrated the evolution of 17 non-synonymous intra-host mutations, with 88.2% of these mutations having been previously identified as significant immune escape mutations [61]. This high frequency of mutations suggests multiple events of convergent evolution, where specific mutations confer a fitness advantage to the virus. Moreover, it was suggested that these persistent infections are characterized by an accelerated viral evolution compared to acute infections [59]. This rapid intra-host diversification, particularly in patients who had not been vaccinated or in those who are non-responsive to the vaccine due to immunosuppression, underscores the role of selective pressure in driving the virus to adapt and evade host immune responses [62]. The findings also suggest that the prolonged evolution of SARS-CoV-2 within these hosts could lead to the emergence of new variants that are not only more transmissible but also potentially resistant to existing therapies and vaccines.

New mutations that confer resistance to SARS-CoV-2 therapeutics have significant clinical implications. Despite vaccination, IC individuals, such as SOTR, are at increased risk for developing these mutations following treatment with DAAs [8, 63]. In a prospective multicenter analysis conducted during the Omicron period with a cohort of 150 IC patients, several key findings emerged regarding treatment-related mutations. All four patients treated with molnupiravir exhibited a high number of nucleotide substitutions which highlights the drug's mutagenic effects. Among those treated with mAbs, 38% developed new non-synonymous mutations in the spike protein, some of which are associated with resistance to these treatments. Patients who received remdesivir showed de novo mutations in 25% of cases, though these mutations were generally present at very

low frequencies. In contrast, nirmatrelvir–ritonavir did not result in notable mutations and convalescent plasma had minimal impact on mutation rates [64]. In a recent study of 15 immunocompromised COVID-19 patients, all treated with remdesivir, with three also receiving nirmatrelvir/ritonavir and four receiving monoclonal antibodies at different timepoints, significant antiviral resistance mutations were observed. Nine patients developed mutations in the nsp12 gene, targeted by remdesivir, while four had mutations in the nsp5 gene, targeted by nirmatrelvir. Notably, one patient developed a viral variant that became dominant, acquiring dual mutations (nsp5 T169I and nsp12 V792I), resulting in a multidrug-resistant strain. This variant showed reduced sensitivity to both remdesivir and nirmatrelvir when used individually. However, in vitro, combination therapy with both drugs significantly suppressed viral replication, highlighting that dual simultaneous antiviral therapy is more effective at overcoming resistance than monotherapy [65].

In summary, the lessons learned highlight the importance of using combination therapies to prevent resistance, closely monitoring long-term patients—especially those who are IC—to avoid the accumulation of mutations and recognizing the critical role of vaccination and prophylaxis in reducing initial viral load and infection risk, thereby limiting the opportunities for the virus to mutate. Managing COVID-19 requires a holistic and adaptable approach that accounts for the virus's ability to evolve and the specific conditions of each patient.

## Convalescent plasma against emerging SARS-CoV-2 variants

Convalescent COVID-19 plasma (CCP) from recovered patients has been considered a therapeutic option for the treatment of COVID-19, especially in the early stages of the pandemic when pharmacological alternatives were limited [66]. Indeed, compared to mAbs, plasma is more affordable, available in low-income countries, and less susceptible to emerging resistant variants [67]. However, results from randomized clinical trials have shown conflicting data, raising questions about the actual effectiveness and the optimal criteria for the use of convalescent plasma. These studies have produced mixed outcomes, likely due to the inclusion of a broad range of patient populations at various stages of COVID-19, without specifically focusing on IC patients [68–70]. For example, a systematic review and meta-analysis of 33 randomized controlled trials involving 24,861 participants—11,432 of whom received CCP—suggested that CCP in patients with moderate to severe COVID-19 does not reduce mortality and has minimal impact on clinical outcomes [71]. In contrast, a retrospective cohort study by Thompson MA et al. analyzing 966 patients with HM and COVID-19—143 of whom received CP—found significantly lower mortality rates in CCP recipients compared to nonrecipients. The 30-day death rate was 13.3% for CCP recipients versus 24.8% for controls, with this survival benefit observed consistently in mechanically ventilated patients [72].

Later during the pandemic, several studies have suggested a potential benefit, particularly in IC patients treated early or with moderate forms of the disease. For instance, Ripoll et al. [73] reported on a large observational cohort of 386 patients, 58% of whom received vax-plasma treatment (i.e., convalescent plasma obtained from donors who had received COVID-19 vaccination) in addition to standard-of-care, while 42% received only standard-of-care. The results showed that the 28-day hospitalization rate was significantly lower in the vax-plasma group (2.2%) compared to the standard-of-care group (6.2%), with no ADRs recorded in the vax-plasma group. The study concluded that vax-plasma transfusion, when combined with standard-of-care treatments, reduced the incidence of hospitalization, which is consistent with previous studies on antibody-based therapies for IC patients [73]. Dequidt T et al. investigated the impact of CCP therapy in a homogeneous cohort of 92 IC patients with inflammatory demyelinating diseases receiving anti-CD20 monoclonal antibodies. The overall survival rate at 30 days was 97%, with all deaths attributed to worsening COVID-19. Two relapses occurring on days 20 and 82. Clinical improvement was observed in 77% of patients by day 7 and in 93% by day 30. Of the 75 patients initially admitted to general wards, 11% required ICU transfer. Notably, symptoms resolved in most patients within two days following CCP administration [74]. In the COVIC-19 randomized trial included 117 IC patients to compare COVID-19 CCP and standard of care in the control group, with 59 in the CCP group and 58 in the control group. In this trial, the median time from symptom onset to randomization was 3 days. Almost all patients had received at least three doses of COVID-19 vaccine but exhibited low baseline antibody levels. Although viral load reduction and genomic evolution patterns did not differ between groups, overall, CCP showed a protective effect in IC patients, with no patients in the CCP group who were hospitalized or died within 28 days, compared to five (8.6%) in the control group. Serious adverse events were less frequent in the CCP group (20% vs. 34%) [75].

Therefore, recent evidence suggests that CCP may be particularly beneficial in IC population, especially when administered early in the disease course. Unlike monoclonal antibodies, which may lose efficacy as new resistant strains emerge, CCP retains broad neutralizing activity and remains a viable treatment option, particularly in pazienti recentemente guariti (vedi revisore). However, further research is needed to refine selection

criteria, optimize administration timing, and assess the durability of immune responses in IC patients.

## Effectiveness of combined therapy for persistent COVID-19

The use of combination therapies involving mAbs and DAAs is not a novel concept, and it has garnered increasing interest in the management of various viral infections, particularly in IC patients facing severe or life-threatening conditions. For instance, combined therapy has been explored to improve outcomes in hCMV pneumonia in HSCTR, where hCMV infections can result in significant morbidity and mortality [76]. Recently, treatment with vaccinia immune globulin and DAAs has been proposed as a potential strategy for managing severe Mpox infections in IC patients [77].

Regarding COVID-19, persistent infections can significantly impact the timing and effectiveness of essential treatments for patients with compromised immune systems. For example, in individuals with HM, ongoing COVID-19 infections can delay crucial therapies such as chemotherapy or stem cell transplantation since managing COVID-19 becomes a priority to reduce the risk of severe complications [78, 79]. Similarly, for SOTR on immunosuppressive medications like mycophenolate, persistent COVID-19 can complicate their treatment regimens. These patients are already at a higher risk for infections due to their immunosuppressive therapy, and a protracted COVID-19 infection can further hinder their ability to manage their primary condition. The need to balance effective management of the viral infection with the continuation of immunosuppressive therapy adds a layer of complexity to their care [78, 80]. Additionally, persistent infection in IC individuals has significant public health implications. These patients can act as reservoirs for the virus, contributing to its spread within healthcare settings and the community. Moreover, the potential for viral evolution in this group highlights the need for ongoing surveillance and targeted treatment strategies to prevent the emergence of new variants that could threaten broader public health efforts [81]. Indeed, these individuals with IC not only experience higher mortality rates and more severe illness but also face a significantly increased risk of persistent SARS-CoV-2 infections compared to the general population [7]. As a result, these infections can last longer, heightening the risk of complications and the emergence of resistant viral variants [9, 59]. Viruses may evade the immune system by replicating in immune-privileged sites or through antigenic variation. This risk is particularly pronounced among hospitalized patients with underlying immunocompromising conditions, who are more likely to test positive for viral RNA and remain viral culture positive for more than 21 days [81].

Therefore, the first studies on IC patients with COVID-19 regarded persistent positive patients who failed to clear SARS-CoV-2 infection despite an initial DAA treatment. The early findings on combination therapies for COVID-19 persistent infected patients have shown significant potential in improving patient outcomes [10, 12, 82–84]. These reports collectively underscore the efficacy of combination DAA therapies, particularly the pairing of remdesivir and nirmatrelvir/ritonavir with or without mAbs, in managing persistent COVID-19 infections, especially in IC patients with HM. These therapies, involving multiple drugs with distinct mechanisms of action, aim to address various target of SARS-CoV-2, potentially offering improved efficacy compared to monotherapy [84]. The use combination therapy where initial treatment with a 10-day course of remdesivir have failed to clear SARS-CoV-2 infection were suggest, making it a critical tool in managing these challenging COVID-19 cases [12].

A 54-year-old female with multiple sclerosis and a 54-year-old male with stage 4 follicular lymphoma both experienced persistent SARS-CoV-2 infections. The female, on ocrelizumab, had persistent symptoms despite negative swabs, with SARS-CoV-2 detected in bronchoalveolar lavage. Treated with remdesivir, CS, and mAbs, she recovered by day 45. The male, post-chemotherapy and rituximab, developed severe respiratory symptoms and was treated with remdesivir, CS, and mAbs. He improved and recovered by day 60. Both patients achieved high levels of neutralizing antibodies and reduced T-cell activation with combined therapy [85]. A study evaluated the treatment of 14 IC patients with or at risk for persistent COVID-19, using a combination of DAAs and mAbs. Eleven patients showed complete recovery, while three had partial responses. Non-responders were infected with the BA.5 variant, less responsive to tixagevimab/cilgavimab [82]. In another analysis of 31 patients with primary or secondary immunodeficiencies and persistent COVID-19, the median duration of symptoms was 62 days, with a range extending up to 300 days. Viremia was common (58.3%), and most patients (97%) required hospitalization. Combination therapy with remdesivir and antibody-based treatments (e.g., mAbs or convalescent plasma) was the most effective in clearing the virus, achieving a 92.8% success rate, while remdesivir monotherapy cleared the virus in 30.4% of cases [86]. In a cohort of 44 B-cell lymphoma patients with COVID-19, prolonged viral shedding was associated with prior bendamustine use, recent immunosuppressive treatment, and multiple lymphoma therapies. Despite these challenges, all patients survived, with tailored DAA regimens and mAbs guided by genomic analysis, leading to successful viral clearance [56]. In a study, 22 severely IC patients with persistant SARS-CoV-2 infections were

treated with a combination of two DAAs, and in most cases mAbs. The combination therapy proved highly effective, with a 75% early virological response and a 73% clinical and virological response at 30 days. Notably, patients receiving mAbs in addition to DAAs showed better outcomes [10]. Pasquini et al. provided a series of 14 patients, all of whom had B-cell malignancies and/or were undergoing B-cell-targeting therapies, leading to persistent SARS-CoV-2 infections. These patients were treated with a combination of remdesivir and nirmatrelvir/ritonavir, resulted in both virologic and clinical recovery across all cases in the series [12]. In a large survey from the EPICOVIDEHA registry ($n = 1,548$), the combination of mAbs and DAAs in hematological patients lowered the mortality risk of death by more than 80% while mAbs monotherapy reduced the risk by about 60% [43]. This study also highlighted that the combination of mAbs with DAAs showed a better outcome primarily in severe or critical cases, which may further underline that the patient's baseline condition plays a significant role in determining the outcome. Moreover, the study indicates that underlying health conditions, specifically the status of the HM and the presence of comorbidities, play a significant role in the outcomes of patients with COVID-19. However, it does not explicitly discuss how these factors influence the choice between using DAAs plus mAbs versus mAbs alone [43].

In response to these promising results, the Israeli Society of Infectious Diseases (ISID) has developed a consensus statement on diagnosing and managing persistent COVID-19 in IC patients that emphasizes the use of a combination of therapies for persistent COVID-19, involving antibody-based treatments and DAAs administered for 5–10 days [87]. In contrast, the NIH guidelines no longer recommend mAbs due to their reduced effectiveness against emerging SARS-CoV-2 variants [39]. At this regard, a recent study including 52 IC outpatients with mild-to-moderate COVID-19 identified that enrolling patients more than 180 days after the study began was an independent risk factor for the failure of this combination therapy, indicating that the therapy's effectiveness declines as the virus evolves [88]. This suggests that while the strategy was promising, it may no longer be effective until new mAbs capable of neutralizing the latest variants are developed As mAbs lose efficacy over time, relying on them as a therapy may fail to achieve early viral clearance, potentially limiting their ability to prevent COVID-19 progression. Notably, preliminary results from the SUPERNOVA Phase III trial have shown positive outcomes for sipavibart (formerly AZD3152), a long-acting antibody that is well-tolerated and currently in discussions with regulatory authorities for approval. The trial demonstrated that sipavibart significantly reduced symptomatic COVID-19 incidence in IC patients, including those with HM, SOTR, and individuals receiving anti-CD20 monoclonal antibodies, when compared to the control group (tixagevimab/cilgavimab or placebo). These findings suggest that sipavibart could serve as an effective prophylactic treatment, offering much-needed protection for these high-risk groups [89]. Additionally, this trial could pave the way for the use of sipavibart in early treatment, much like tixagevimab/cilgavimab was used after its initial approval as pre-exposure prophylaxis. Future studies may also explore its combination with DAAs to further enhance treatment efficacy. Thus, the continuous evolution of the virus challenges the sustainability of current treatment strategies, highlighting the urgent need for updated therapeutic approaches tailored to emerging variants.

## Effectiveness of early combined therapy for immunocompromised COVID-19 patients

The early use of combination therapy in IC patients may be beneficial because it addresses COVID-19 while the infection is still manageable, potentially leading to better outcomes from a more robust treatment strategy tailored to their specific needs with fewer side effects. The potential for ECT lies in several reasons. First, the combined use of mAbs and DAAs ensures a broad-spectrum antiviral effect by targeting different stages of the viral replication cycle, which is particularly beneficial for IC patients who might otherwise experience a more severe or prolonged illness [10]. Second, early intervention can be crucial in preventing the progression of the disease to more severe stages [11, 79, 88]. Indeed, administering treatment as soon as possible, when the infection is still in its initial stage, takes advantage of the relatively low viral load because the virus has not yet had time to replicate extensively [11, 79, 90]. These patients often have uncontrolled viral replication, creating an environment where the virus can mutate and adapt, potentially compromising the effectiveness of DAA therapies currently approved against COVID-19 [8]. Third, when therapy is initiated early, shorter and potentially less toxic combination regimens can be employed. This is because a lower viral load allows for the use of combination therapies that do not need to be as prolonged or intensive. Shorter regimens were found to be associated with reduced risk of side effects [11]. In the largest cohort published to date of 304 IC COVID-19 patients including those vaccinated with low anti-Spike IgG titers and prior anti-CD20 treatments, combination therapy demonstrated effectiveness across various SARS-CoV-2 variants. It was associated with a lower risk of progression (0% in combination therapy vs. 4.6% in monotherapy), though this difference was not statistically significant, with no patients in the combination therapy group experienced COVID-related deaths or severe progression, while there were two deaths

in the monotherapy group. ADRs were mild and did not occur significantly more frequently with combination therapy compared to monotherapy [91]. In 144 primarily IC patients receiving ECT for COVID-19, clinical courses were found to be mild to moderate. In contrast, 7.8% of patients on monotherapy experienced treatment failure, defined as severe COVID-19 or related death. Prolonged viral shedding was observed in 14.6% of patients, predominantly those with HM, highlighting the ongoing vulnerability of this group. SOTR patients also faced prolonged viral shedding, though less frequently [79]. Regular assessment of spike-specific antibody responses and Ct values, which serve as surrogate markers for viral load, is essential for guiding treatment decisions and evaluating patient responses. This monitoring allows for timely adjustments in therapy, was suggested that may improve outcomes, particularly when initial treatments are ineffective [92]. Despite the limitations of a retrospective design and the absence of a control group, these results suggest that dual anti-SARS-CoV-2 therapies may be safe and effective in IC patients with COVID-19 given the low toxicity and high viral clearance rates [11, 79].

There are only a few studies assessing the clinical outcome of IC patients with COVID-19 who received ECT versus monotherapy [58, 88, 90, 91, 93, 94]. In a single-center experience the use of ECT with mAbs and DAAs in cohort of 331 hospitalized COVID-19 patients, including older and IC individuals, resulted in a significant reduction in the duration of SARS-CoV-2 infection. A significant impact on preventing disease progression primarily in older with metabolic comorbidities, IC, and those with ineffective vaccination was found. No serious ADRs leading to discontinuation or medical interventions were registered, Additionally, no patients required intensive care or experienced COVID-19-related deaths [58]. A study involving 60 high-risk patients with HM and SARS-CoV-2 Omicron infection highlighted the benefits of early DAA treatment administered after a median time of 2 days from symptom onset. Of these patients, despite prior vaccination in 95% of patients, only 41.7% had positive SARS-CoV-2 serology at admission. All patients received remdesivir, with 53.3% also receiving hyperimmune plasma. Key findings included a median viral shedding of 20 days, with only 10% experiencing viral persistence after 6 weeks. ICU admission was required for 6.7% of patients, and mortality was 5%, contrasting with higher mortality rates in other studies [90]. Similarly, another study found that ECT was associated with high viral clearance, minimal risk of hospitalization, and no COVID-19-related deaths in a cohort of 55 IC patients with mild-to-moderate disease. Notably, none of the patients required hospital admission or oxygen therapy, and the median duration of SARS-CoV-2 infection was 10.5 days. A key finding from this research was that delayed therapy (more than three days after symptom onset) significantly increased the risk of prolonged infection [88]. A study assessed the efficacy and safety of remdesivir in combination with mAbs compared to remdesivir alone in 68 IC patients with mild-to-moderate COVID-19, with 35 receiving combination therapy and 51 receiving remdesivir monotherapy. While combination therapy was associated with earlier fever resolution and greater viral load reduction, it did not result in significant differences in COVID-19 exacerbation, death due to COVID-19, or 30-day all-cause mortality between the two groups. ADRs were rare in both groups, with no significant differences observed in liver or kidney dysfunction or infusion reactions [93]. A single-center study including 81 severely IC individuals assessed the early treatment of SARS-CoV-2 in using combination therapy (DAA plus mAbs) versus monotherapy (DAA alone). The analysis, after applying inverse probability of treatment weighting, showed that combination therapy was associated with improved outcomes, including reduced hospitalizations, ICU admissions, and mortality rates [94].

Therefore, while existing studies suggest that ECT might offer enhanced viral clearance [79, 88], faster symptom resolution [93] and prevent disease progression [58, 94] compared to monotherapy in IC individuals, the data is not yet robust enough to draw definitive conclusions. Indeed, the level of evidence remains relatively low due to several factors. These include the limited number of cases studied, significant variability among patients, and differences in timing and therapeutic regimens across studies. As a result, further research with larger, more homogeneous groups and standardized treatment protocols is needed to better establish the efficacy and safety of these combined regimens. It is still notable the lack of clinical trials specifically targeting IC patients. While DAA drug trials have shown the efficacy of monotherapy in the general population, these studies often underrepresented IC individuals, leaving a gap in understanding the optimal treatment strategies for this high-risk group [1, 94, 95]. Given these limitations, there is still much to learn about the optimal therapeutic approach for IC patients with COVID-19. More extensive, targeted research is necessary to better understand the comparative benefits and potential risks of combination therapy versus monotherapy in these patients. Trials with larger, more homogeneous cohorts and standardized treatment protocols are essential to establish clearer guidelines and improve clinical outcomes for such frail population. Table 1 presents a summary of various studies evaluating the efficacy and safety of combined therapies in IC patients with COVID-19 conducted between 2021 and 2024.

**Table 1** Efficacy and safety of combined direct-acting antiviral (DAA) and monoclonal antibody (mAb) therapies in immunocompromised patients with COVID-19

| Reference | Author, year | Design, country | Population (study timeframe) | Combined therapy | Safety | Effectiveness |
|---|---|---|---|---|---|---|
| **Efficacy and safety of combined antiviral and monoclonal antibody therapies in immunocompromised patients with persistent COVID-19** | | | | | | |
| [86] | Brown LAK et al., 2022 | Retrospective, United Kingdom | 31 antibody-deficient patients with persistent or relapsing COVID-19, 62 episodes of illness (Jan 2022 - Jun 2022) | Remdesivir (≤ 10 days and > 10 days) and antibody-based therapy (casirivimab/imdevimab, convalescent plasma) | No severe ADRs | Higher viral clearance (92.8%) with combination therapy; remdesivir monotherapy achieved viral clearance in 50% of cases. No untreated patients cleared the virus. Three deaths occurred, one unrelated to COVID-19 |
| [92] | Wada D et al., 2022 | Single-center, Japan | 10 immunocompromised COVID-19 patients with persistent SARS-CoV-2 infection, all under immunosuppressive agents (Feb 2022 - Sep 2022) | Remdesivir or switch to other antiviral, mAbs, monitoring spike-specific antibodies and Ct as a surrogate for viral load | No severe ADRs reactions occurred | Effective viral clearance in all patients, with no cases of viral relapse |
| [10] | Mikulska M et al., 2023 | Retrospective, Italy | 22 severely immunocompromised patients with presistent COVID-19 (Feb 2022 - Oct 2022) | Triple therapy with remdesivir, nirmatrelvir/ritonavir (or molnupiravir if contraindicated), plus mAbs when available | Severe ADRs in 2 patients (bradycardia and myocardial infarction); other side effects mild and manageable | High response rate: 75% virological response at day 14; 73% clinical and virological response at day 30; 82% response at last follow-up; higher efficacy when mAbs included |
| [96] | Gentile I et al., 2023 | Retrospective, Italy | 4 immunocompromised patients with persistent COVID-19 (Apr 2023 - Jun 2023) | Remdesivir 10 days plus nirmatrelvir/ritonavir for 5 days and sotrovimab | One patient experienced bradycardia, led to remdesivir discontinuation | 50% viral clearance by day 30, 75% alive and well at follow-up. Patients treated late had prolonged infection, higher need for oxygen and steroids, and worse severity |
| [82] | Brosh-Nissimov T et al., 2024. | Retrospective, Israel. | Severely immunocompromised COVID-19 patients: renal transplant recipients, B-cell lymphoproliferative diseases, rheumatoid arthritis (Starting in March 2022) | Tixagevimab/cilgavimab (prophylaxis and treatment), antivirals, corticosteroids, a median of 28 days after symptoms onset. | Two non-responder patients developed opportunistic infections, suggesting that immunomodulatory treatment for severe COVID-19 may enhance susceptibility to secondary infections. | Subjective symptomatic improvement for all patients at the end of treatment. 11/14 with complete response, 3 with clinical relapse. |
| **Efficacy and safety of early combined antiviral and monoclonal antibody therapies in immunocompromised patients with COVID-19** | | | | | | |
| [9] | Scaglione V et al., 2022 | Retrospective, Italy | 18 COVID-19 patients, predominantly immunocompromised or with high-risk comorbidities (Apr 2021 - Apr 2022) | Combination of mAbs plus DAAs (remdesivir, molnupiravir, nirmatrelvir/ritonavir), a mean of 3 days from symptoms onset | No serious ADRs; minor ADRs, such as rash, observed in few cases | Patients with high-risk conditions who received combination therapy avoided hospitalization; early treatment within a dedicated territorial center improved accessibility and outcomes |
| [90] | Aiello TF et al., 2023 | Prospective, Spain | 60 high-risk adults with hematologic malignancies, SARS-CoV-2 Omicron (Dec 2021 - Mar 2022) | Remdesivir, hyperimmune plasma, sotrovimab; applied according to national treatment regulations. | No severe ADRs | Short viral shedding duration (median 20 days), 95% survival rate. Three patients died |
| [96] | Gentile I et al., 2023 | Retrospective, Italy | 7 immunocompromised patients with early COVID-19 (Apr 2023 - Jun 2023) | Remdesivir 10 days plus nirmatrelvir/ritonavir for 5 days; Sotrovimab added in most cases | No severe ADRs | 100% viral clearance by day 30, 100% alive and well at follow-up |

**Table 1** (continued)

| Reference | Author, year | Design, country | Population (study timeframe) | Combined therapy | Safety | Effectiveness |
|---|---|---|---|---|---|---|
| [93] | Hirai J et al., 2023 | Retrospective, Japan | 86 immunocompromised patients with mild-to-moderate COVID-19 (Jul 2021 - Mar 2023). | Remdesivir plus mAbs, initiated within 7 days of symptom onset | No severe ADRs | Improved outcomes in the combined therapy group, with faster reduction in viral load (Ct), faster fever resolution, and higher discharge rates compared to remdesivir monotherapy. No disease progression in the combined therapy group |
| [91] | Calderón-Parra J et al., 2024 | Prospective, Spain | 304 immunocompromised patients with mild-to-moderate SARS-CoV-2 infection (Jan 2022 - Oct 2022) | Sotrovimab plus DAA (remdesivir or nirmatrelvir/ritonavir), timing based on risk and clinical assessment | No hospital admissions or deaths due to ADRs; 6.9% of patients had mild ADRs | Combination therapy reduced COVID-19 progression compared to monotherapy (0% vs. 4.6%). Significant reduction in progression for patients with anti-S IgG < 750 BAU/mL and/or prior anti-CD20 treatment |
| [88] | Gentile I et al., 2024 | Prospective, Italy | 52 immunocompromised adult patients with COVID-19 (May 2023 – Dec 2023) | Sotrovimab plus nirmatrelvir/ritonavir (64%) or remdesivir (36%) | No severe ADRs, no patients discontinued treatment | No hospitalizations, reinfections, or deaths within the first 60 days. Prolonged infection in 33% of patients |
| [79] | Orth HM et al., 2024. | Multicenter, retrospective, Germany | 144 high-risk immunocompromised patients with COVID-19. (Mar 2022 - Apr 2023) | Remdesivir, nirmatrelvir/ritonavir, molnupiravir ± mAbs, early treatment within 5 days | No severe ADRs, minor ADRs (diarrhea, nausea) | 85.4% avoided prolonged viral shedding. Best outcomes in early-treated patients. Patients with hematologic malignancies and late treatment had longest viral shedding |
| [11] | Rotundo S et al., 2024 | Single-center, retrospective study, Italy | 48 immunocompromised adult patients with COVID-19 (hematologic, transplanted, or treated with anti-CD20 monoclonal antibodies). (Jan 2022 - Jan 2023) | DAAs plus mAbs, a median of 2 days after diagnosis | No severe ADRs | 2 patients admitted before viral clearance; One patient died. No relapses or prolonged viral shedding |
| [94] | Mazzitelli M et al., 2024 | Single-center, retrospective study, Italy | 81 severely immunocompromised patients (hematologic, advanced HIV, or treated with anti-CD20 monoclonal antibodies), (Jan 2022 - Dec 2023) | 39 receiving early combination therapy vs. 42 receiving DAA monotherapy. | No severe ADRs | After applying inverse probability of treatment weighting, the rates of mortality, hospitalizations, and access to the emergency department were lower with combination therapy |

ADRs: adverse drug reactions; mAbs: monoclonal antibodies against SARS-CoV-2; Ct: cycle threshold; BAU/mL: binding antibody units per milliliter

## Safety considerations

While the benefits of combined therapy are evident, safety concerns remain, particularly regarding ADRs. Both mAbs and DAAs can cause side effects, and the combination may increase the risk of certain reactions. Moreover, longer courses of treatment and combined therapy with two DAAs and mAbs could present safety risks. For instance, severe side effects in 9% of patients undergoing such treatments were reported [10, 96]. In the report by Gentile et al. [96] one patient in the experienced an ADR in the form of symptomatic bradycardia, which led to the discontinuation of remdesivir after 8 days of therapy. In the cohort by Mikulska et al. [10] severe ADRs were observed in two patients undergoing combination therapy for persistent SARS-CoV-2 infection. The first case involved asymptomatic bradycardia, which resolved after discontinuing remdesivir. The second case involved a patient who developed a myocardial infarction. Although this patient had no known cardiac comorbidities other than non-Hodgkin lymphoma, the association with the use of mAbs could not be excluded. The potential for drug interactions is a significant concern, especially in patients who are already on multiple medications [39] since IC patients often take multiple medications for various conditions, including underlying chronic illnesses, infections, and side effects of other treatments. Each additional drug increases the potential for interactions that can alter the safety of the treatment regimen [97].

Therefore, despite combined therapy may offer benefits for IC COVID-19 patients, safety concerns persist, particularly regarding longer course regimens. Moreover, long-term safety remains unclear, necessitating ongoing research to optimize treatment and minimize

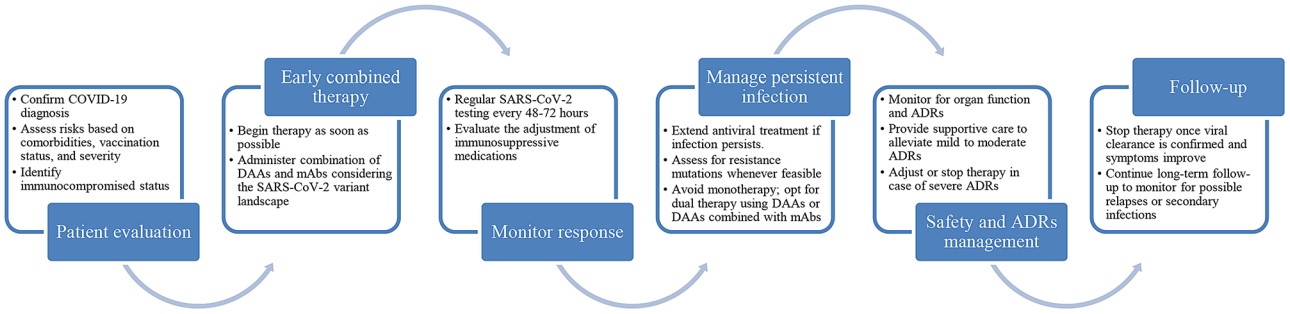


**Fig. 1** Proposed management strategy for immunocompromised patients with COVID-19. DAAs: Direct Acting Antivirals; mAbs: monoclonal antibodies against SARS-CoV-2; ADRs: adverse drug reactions

risks. Further distinguishing between different groups of IC patients will allow for more precise and individualized treatment plans. Additionally, it is important to explore the effects of various combination treatment strategies (e.g., combining mAbs and DAAs vs. combining two DAAs) to better understand their combined efficacy across different IC populations. This approach will help tailor treatments to the specific needs of each subgroup, ultimately improving outcomes for IC patients. Figure 1 presents a proposed management strategy for IC patients with COVID-19, highlighting the essential steps in patient identification, assessment, and treatment, tailored to the stage of infection.

## Conclusion

Although ECT with mAbs and DAA agents holds significant promise for improving outcomes in severely IC outpatients with COVID-19, its true effectiveness remains a topic of ongoing debate within the scientific community. Therefore, the conclusions drawn in this description of the available evidence should be interpreted with caution, as it is not a systematic review. While the current evidence supports the effectiveness of this approach, safety concerns and challenges such as resistance and drug interactions must be carefully managed. However, the evidence suggests that ECT with mAbs and DAAs is a highly effective and safe approach for managing COVID-19 in severely IC patients. This strategy not only enhances viral clearance but also reduces the likelihood of severe outcomes, supporting its use as a first-line treatment in this high-risk population. Ongoing research and clinical trials will be crucial in refining these therapies and ensuring their long-term success in this high-risk population.

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**Author contributions**
SR: conceptualization, investigation, methodology, writing – original draft preparation; FS: visualization, validation; LB: investigation, writing – original draft preparation; SM: visualization, validation; SPG: investigation, writing – original draft preparation; MTT: investigation, writing – original draft preparation; EMT: validation, supervision, writing – review and editing; AR: validation, supervision, writing – review and editing.

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**Data availability**
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**Consent for publication**
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**Competing interests**
The authors declare no competing interests.

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