Vaccines and therapeutics for immunocompromised patients with COVID-19

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Summary

The COVID-19 pandemic has disproportionately impacted immunocompromised patients. This diverse group is at increased risk for impaired vaccine responses, progression to severe disease, prolonged hospitalizations and deaths. At particular risk are people with deficiencies in lymphocyte number or function such as transplant recipients and those with hematologic malignancies. Such patients' immune responses to vaccination and infection are frequently impaired leaving them more vulnerable to prolonged high viral loads and severe complications of COVID-19. Those in turn, have implications for disease progression and persistence, development of immune escape variants and transmission of infection. Data to guide vaccination and treatment approaches in immunocompromised people are generally lacking and extrapolated from other populations. The large clinical trials leading to authorisation and approval of SARS-CoV-2 vaccines and therapeutics included very few immunocompromised participants. While experience is accumulating, studies focused on the special circumstances of immunocompromised patients are needed to inform prevention and treatment approaches.

Keywords: COVID-19; SARS-CoV-2; Immunocompromised; Transplantation; Malignancy

Introduction

The pandemic is an ongoing challenge for immunocompromised patients.[1–3] This heterogenous group, which makes up about 2–3% of the overall population, includes people with human immunodeficiency virus (HIV) infection, cancers, transplants, primary immunodeficiencies and those treated with immunosuppressive biologics and medications. Their underlying etiologies and demographics contribute to multifactorial and interrelated causes for immune compromise. In addition to impaired responses to infection, immunocompromised patients tend to be older, have additional comorbid conditions beyond immunosuppression, and have fewer reserves to recover from the physiological challenges of acute infection. For some (e.g. transplant recipients), the response to vaccination can be significantly impaired, which in turn can contribute to heightened risks for acquiring COVID-19,

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persistent viral shedding and developing severe complications of infection.[4,5]

Some of the highest risks for complications are in transplant recipients, people with metastatic cancer, hematologic malignancies and those receiving cancer chemotherapy.[6,7] Lung transplant recipients, hematopoietic stem cell transplant (HSCT) recipients and patients receiving anti-CD20 therapies are particularly vulnerable to severe and persistent infection and to prolonged viral shedding, which is almost exclusively seen in hematological patients and highly immunosuppressed transplant recipients.

People living with HIV also have increased risk of vaccine breakthroughs and severe presentations.[8–10] While use of antiretroviral therapy (ART) and having HIV infection that is well controlled reduces the risk of poor outcomes, HIV infection itself remains a risk factor for severity and mortality regardless of ART and viral load suppression. For people living with HIV, the risk of severe breakthrough illness is reduced with vaccination, but remains higher for those with CD4 cell counts below 350.[9] While immunocompromised patients are generally at increased risk for severe presentations, hospitalizations, development of persistent infection and deaths one study found that they may be partially protected from acquiring long COVID, except possibly those with underlying HIV infection.[11–13]

Overall, despite vaccinations, COVID-19 remains a threat for immunocompromised patients and their risks for breakthrough infections and severe clinical outcomes remain elevated relative to the rest of the population.[14,15] In solid organ transplant (SOT) recipients for example, outcomes have improved as the virus and prevention and treatment approaches have evolved, however, the risk for hospitalizations and death (~2%) has not completely resolved.[16,17]

An additional problem is that immunocompromised patients frequently constitute an extreme minority of COVID-19 randomised clinical trial (RCT) participants. Immunocompromised patients represented small percentages or were completely excluded from multiple antiviral and immunomodulator COVID-19 randomised clinical trials.[18] When immunocompromised patients are included, the extent or type of their immunosuppression is typically not well documented. This creates challenges, as clinical and policy decisions must be made based on extrapolation of data gathered from populations with more physiologic immunological baselines.

Search strategy and selection criteria

This Review is not systematic literature review with quantitative synthesis of results. It is a critical synthesis and expert viewpoints of the issues related to immunocompromised patients in the COVID-19 pandemic era. Information on prevention and treatment of COVID-19 in immunocompromised patients was sourced by searches of PubMed, Google Scholar and the reference lists of relevant peer reviewed articles and books. Different combinations of multiple search terms relevant to the analysis were used, such as “COVID-19”, “SARS-CoV-2”, “transplant”, “immunocompromised”, “immune compromised”, “hematologic malignancy”, “remdesivir”, “nirmatrelvir”, “molnupiravir”, “monoclonal antibody”, “convalescent plasma”, “treatment”, “prophylaxis”, “prevention”, “Evusheld”, “long covid”. Only articles and books published in English were included.

Prolonged viral shedding among immunocompromised patients

Relatively longer shedding of the virus in immunocompromised patients is one of the challenges in this group. Immunocompromised patients with hematologic malignancies or transplant recipients can shed viable virus for median 4 weeks.[19] In some patients persistently positive SARS-CoV-2 PCR tests may be a harmless laboratory testing artifact, while in others it represents ongoing infection with the capacity to generate new and more infectious/virulent mutants, serve as a source of ongoing spread of virus and lead to resistance to existing antiviral therapy.[20–23] The terminology and classification of persistent infection remains unsettled and has been variably defined as recurrence, relapse or as a subset of long COVID. Both practically and scientifically, PCR positivity is often insufficiently reliable to establish the diagnosis of persistent infection, viable (or active) culture is the gold standard. However, virus culture is not routinely available and can only be done in research laboratories. Funding to improve accessibility globally for such testing is needed. Standard clinical definitions and diagnostics could be able to inform international guidelines for management, including infection control practices in such patients, which are currently lacking.

Prevention of infections

People who are immunocompromised tend to be more adherent to non-pharmacologic measures than the general population. For example, patients with cancer were found to be more likely to practice preventive behaviors, including social distancing, wearing face masks, and avoiding crowded areas compared to adults without cancer.[24] As a whole immunocompromised patients were also more likely to adhere to recommendations for hand hygiene and social distancing.[25] However, as society opens and pandemic era restrictions ease, the ability of immunocompromised patients to avoid exposure to COVID-19 infected people becomes more challenging. This in turn renders pharmacologic interventions and efficacious algorithms for their use all the more important. These include immunization of household and other routine contacts of immunocompromised patients, a strategy referred to as “cocoon vaccination”, as well as pre-exposure prophylaxis.[26] The

World Health Organization (WHO) recommends that all immunocompromised patients continue with protective measures such as masking and social distancing and that their contacts be vaccinated.[27] To the extent possible, immunocompromised persons should have a care plan that includes prompt testing at the onset of COVID-19 symptoms, rapid access to antivirals if SARS-CoV-2 infection is detected and an assessment of the feasibility of these treatments depending on the context.

Vaccination and pre-exposure prophylaxis

Vaccine responses are often impaired in the immunocompromised patient population. Of particular concern are solid organ transplant recipients, patients with hematologic malignancy, older patients and recipients of corticosteroids, immunosuppressives, or anti-CD20 agents.[28] Vaccination schedules need to be adjusted in the immunocompromised because a primary series of two doses does not generate immune responses of equivalent magnitude compared to the non-immunocompromised.[4] The WHO therefore recommends an additional dose for all immunocompromised patients coined "extended primary series".[27,29] WHO also puts immunocompromised patients under the highest-priority use populations, and recommends two boosters for all immunocompromised patients regardless of age.[30] In some cases even additional doses prove ineffective.[5] Some experts recommend a temporary hold on certain immunosuppressive agents (e.g. mycophenolate) around time of vaccination although data to support the safety and efficacy of this approach is sparse.[31–33] For those not already on immunosuppressive medications, whenever possible, COVID-19 vaccines should be administered at least 2 weeks before initiation or resumption of immunosuppressive therapies.

Pre-exposure prophylaxis is an approach to prevention of infection for immunocompromised patients who may not mount an adequate immune response to COVID-19 vaccination. The only product definitively shown to be effective as pre-exposure prophylaxis is the combination of the two monoclonal antibodies tixagevimab + cilgavimab. The authorisation for the drug, however, was based on RCT data from a group of largely non-immunocompromised patients.[34] Retrospective studies of immunocompromised patients have shown this product to provide protection against COVID-19 complications in immunocompromised patients with suboptimal immune responses to vaccines.[35] This is not available in many countries, leaving immunocompromised patients who do not respond to vaccination and reside in those countries without reliable means of COVID-19 prevention. Additionally, as with other anti-SARS-CoV-2 monoclonal antibodies, tixagevimab + cilgavimab are prone to loss of antiviral activity with emerging variants. For example, activity against Omicron variant BA.4.6 and several of the other commonly circulating variants, is severely reduced rendering the drug ineffective.[36] As a result, considering the SARS-CoV-2 variants projected to make up more than 90% of the variants circulating in the United States, Tixagevimab + cilgavimab is no longer authorised for use in the United States.

Unlike vaccines and oral antivirals, monoclonal antibodies for immune-compromised patients such as tixagevimab + cilgavimab were purchased by governments and health systems in much smaller quantities (e.g. 1.2 million treatment courses by the US). Such therapeutics remained in extremely short supply throughout the period they were authorised (i.e. while they could neutralise the predominant variants in circulation). Unlike vaccines and nirmatrelvir/ritonavir, the criteria/ethical prioritisation framework was not well established for such therapeutics. As a result, in the US the allocations were by federal government agencies to states, and from states to medical centers to determine how to best allocate scarce stock. With development of next generation pre-exposure prophylaxis products, future efforts should create explicit prioritisation frameworks for therapeutics for the immunocompromised, and better communicate the framework to healthcare professionals globally, as has been done for vaccines and oral antivirals.

Antiviral therapy

Nirmatrelvir dramatically reduces risk of hospitalization and death in high-risk outpatients with COVID-19.[37,38] It is co-packaged with the pharmacologic booster ritonavir (nirmatrelvir/ritonavir; Paxlovid). Ritonavir is a strong inhibitor of CYP3A4 and as such significantly and dangerously increases the serum levels of drugs such as cyclosporin, tacrolimus, everolimus and sirolimus, which are frequently used in immunocompromised patients (particularly transplant recipients). Use of nirmatrelvir/ritonavir should be approached with extreme caution in transplant recipients.[39]

Molnupiravir is the other major orally available antiviral agent. It does not have the drug interactions associated with ritonavir, but is contraindicated in patients under 18 and in pregnancy as it may harm bone and cartilage growth and can cause embryo-fetal toxicities. Molnupiravir efficacy is uncertain. There are also concerns that this drug may drive evolution of SARS-CoV-2 mutations to potentially generate variants of concern, and have long-term risk for mutagenicity in humans.[40] Both of these concerns are heightened in immunocompromised patients. In unvaccinated outpatients with COVID-19, its use was associated with moderate reductions in hospitalizations and deaths but its efficacy in vaccinated people is less clear.[41,42] An open labeled study of over 25,000 vaccinated outpatients (about 9% of which were immunocompromised), which compared molnupiravir to usual care, showed that molnupiravir treatment resulted in more rapid time to recovery, but did not reduce need for hospitalization (1% in both groups).[43] Of

note, the highest risk patients in either arm were eligible to also receive mAb, nirmatrelvir/ritonavir and those in the usual care arm could even receive molnupiravir. Although no head-to-head RCTs have been performed comparing the two orally available drugs, response rate outcomes from an observational comparative study in Hong Kong suggest that nirmatrelvir/ritonavir is the more effective of the two drugs.[44]

Remdesivir is an option for early treatment of COVID-19 and is used as an option for people at risk for progression in place of nirmatrelvir/ritonavir.[45] It is also widely used for patients who are hospitalised with COVID-19. The drug has been tolerated in SOT recipients.[46]

Passive immunization is an important intervention for immunocompromised patients. Early administration of monoclonal antibodies (mAbs) directed against SARS-CoV-2 spike protein had been effective at reducing progression of disease and mortality in high-risk patients. Their use in immunocompromised patients is safe but only effective when variants are susceptible. Monoclonal antibodies had been a cornerstone of antiviral therapy at many transplant centers.[47–49] Due to mutations at the mAb target sites, all of the authorised agents are no longer reliably effective.

COVID-19 convalescent plasma (CCP) is another form of passive immunotherapy. This product has the advantage of being able to keep with changing variants as it is polyclonal and periodically refreshed providing that stocks are replenished from individuals who have recovered from circulating variants. Antibody levels in those who have both been vaccinated and recovered from COVID-19 have high levels of neutralization ability including against Omicron variants.[50–53]

CCP may be helpful in circumstances where the product has high levels of neutralizing antibodies and given at a time when there is high viral load and inadequate immune response.[54–57] This is particularly relevant for people with abnormalities in lymphocyte number or function, who are not able to receive nirmatrelvir/ritonavir or a mAb effective against the viral variants circulating in their community. Among the patients with of abnormal lymphocyte number and function, B-cell depleted patients may most benefit from CPP for COVID-19 treatment.[58] In the United States, CCP is authorised by the Food and Drug Administration (FDA) for use in immunocompromised patients with COVID-19 and supported in certain circumstances by recommendations from multiple organizations.[59–62] CCP remains controversial, however, and the National Institutes of Health (NIH) neither recommends for or against CCP in immunocompromised patients while the WHO recommends against its use.[63–65] There are regulatory and logistical barriers to use of CCP. With increasing number of donors who are vaccinated and/or have a history of natural SARS-CoV-2 infection, there is a need for updating the regulatory requirements for donation and qualification of CCP.

Infection in immunocompromised patients is often characterised by high viral loads, longer times to virologic clearance and occasionally transition to chronic infection. Treatment paradigms developed for the general population can result in suboptimal virologic suppression, prolonged illness or rebound and higher probability of emergence of drug resistance. Combination drug therapy using antiviral agents from different classes may address some of these issues. For example, CCP in combination with remdesivir has been used in immunocompromised patients with acute and persistent infections. Such approaches should be tested in adequately powered clinical trials in the target population of immunocompromised patients.[66] There are multiple antiviral agents in various stages of development. These including an oral version of remdesivir which could be particularly useful for people who cannot take nirmatrelvir/ritonavir due to drug interactions and pegylated interferon lambda. Those drugs, alone or in combination with other antivirals will also need to be tested in immunocompromised patients.

Treatment of immune mediated injury

The understanding that severe COVID in the population at large is in large part driven by an overexuberant immune response has led to development and deployment of many anti-inflammatory approaches to therapy. These have included broad spectrum agents such as glucocorticoids and more narrowly focused interventions such as IL-1, IL-6 and Janus kinase (JAK) inhibitors. Trials of these agents in COVID-19 have been conducted in largely non-immunocompromised patients although some observational data exists for their use in immunocompromised patients.[67–71] Immune compromised patients have a broad range abnormalities in their immune responses, owing to the underlying illnesses, immunosuppressive regimen or a combination of both. Hence the use of anti-inflammatory therapies in such patients is more complicated, requires an individualised approach and must be inferred from studies that were not specifically done in the target population. Some children with COVID-19 have developed clinical syndromes resembling Kawasaki disease and toxic shock syndrome. These constellations of symptoms have been collectively referred to as multisystem inflammatory syndrome in children (MIS-C) and treatments include intravenous immunoglobulin (IVIG), corticosteroids, IL-1 inhibitors and TNF-a inhibitors.[72] Data regarding management of MIS-C in children who are immunocompromised is sparse.[73] Immune mediated injury is seen much less frequently in the omicron era, but it is unknown whether this will remain the case with future variants.

Co-infections and secondary infections

Additional infections can further complicate the course of immunocompromised patients with COVID-19. Bacterial and fungal co-infections are a major problem in patients with more severe manifestations of COVID-19, including bacterial pathogens with the potential for antimicrobial resistance and invasive aspergillosis, respectively.[74,75] Immunocompromised patients are especially vulnerable to developing such complications due to their underlying conditions and impaired ability to opportunistic infections and their elevated risk for developing more severe COVID-19.[76,77] In India rates of mucormycosis in COVID-19 infected kidney transplant recipients reached astounding level with incidence ranging from 4.4 to 10% during a peak in the pandemic.[78,79] Still another interesting observation is the potential to reactivate Epstein–Barr viral infections, which may contribute to the pathogenesis of long COVID, although whether immunocompromised patients with COVID-19 are at higher risk for EBV reactivation is unknown.[12,74]

Conclusions

Owing to their heightened susceptibility to developing complications from COVID-19 is a major challenge for immunocompromised patients. The margin for error is often narrow and appropriate prevention and treatment can be highly impactful. Much of the data to inform decisions in such patients is extrapolated from studies in non-immunocompromised patients and derived from observational experiences. The WHO recently called on "research funding agencies to prioritise and fund clinical trials that are well-designed and well-implemented, conducted in diverse settings and include all major population groups."[80] Immunocompromised patients are one such group. Studies to better understand the efficacy of currently available antiviral agents alone and in combination, including use at times in their disease later than in the general population are needed.

Contributors

All authors contributed to the conceptualization and formal analysis of the manuscript. SS wrote the first draft. All authors contributed to the review and editing of the first and subsequent drafts.

Declaration of interests

The authors report the following potential competing interests: PH and MEB are co-inventors of a COVID-19 recombinant protein vaccine technology owned by Baylor College of Medicine (BCM) that was licensed by BCM non-exclusively and with no patent restrictions to several companies committed to advancing vaccines for low- and middle-income countries. The co-inventors have no involvement in license negotiations conducted by BCM. Similar to other research universities, a long-standing BCM policy provides its faculty and staff, who make discoveries that result in a commercial license, a share of any royalty income. To date, BCM has not distributed any royalty income to the co-inventors on the COVID-19 recombinant protein vaccine technology. Any such distribution will be undertaken in accordance with BCM policy. MH is Founder and Managing Director of SaudiVax. GK is a member of the WHO SAGE Working Group on COVID-19 vaccines. GK is independent director appointed by the Wellcome Trust, MSD Wellcome Trust Hilleman Laboratories Private Limited and Vice Chair of the Board, Coalition of Epidemic Preparedness Innovations (CEPI). HL reports grants and honoraria from GlaxoSmithKline for training talks and from Merck as a member of the Merck Vaccine Confidence Advisory Board, grants from J&J outside the submitted work. AWS serves as Consultant to WHO. The views presented here reflect her views and not necessarily those of WHO. TS reports grants from National Institute of Allergy and Infectious Disease and Fast Grants and research contracts from GlaxoSmithKline, and ViiV Healthcare. SS reports grants or contracts made to institution from U.S. Department of Defense (Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense), Defense Health Agency, Shionogi, Shire, Ansun, Cidara, Zeteo Tech Inc., F2G, Emergent Biosolutions, Bloomberg Philanthropies, the State of Maryland, NIH National Center for Advancing Translational Sciences, Mental Wellness Foundation, Moriah Fund, Octopharma, Shear Family Foundation, HealthNetwork Foundation, Mayo Clinic, University of Nebraska; consulting fees made directly to author from Immunome, Adagio Therapeutics, Celltrion Healthcare, Karius; payment or honoraria to author for lectures, presentations, speakers bureaus, manuscript writing or educational events from Prime Inc. and Peerview; travel support from Peerview for American Transplant Congress 2022, from NCCN for NCCN Guideline meeting, and from ACP for ACP board of governors meeting; paid participation on a Data Safety Monitoring Board or Advisory Board for Intermountain Health, Karyopharm, Adamis Health; a role on guideline panels for NCCN, IDSA, MSG/EORTC, on RSV vaccine workgroup for ACIP/CDC, as Governor of Washington DC Chapter of ACP, and as member of Board of Governors of ACP; stock or stock options from Immunome. JHK reports personal fees from SK biosciences. CB, YBA, OE, BL, DN, NSW, SOS, and PY declare no conflict of interests. The authors views and opinions in the Review do not necessarily represent the views, decisions, or policies of the institutions, universities, or health systems with which they are affiliated.

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Appendix A. Supplementary data

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References

1 Harpaz R, Dahl RM, Dooling KL. Prevalence of immunosuppression among US adults, 2013. *JAMA*. 2016;316(23):2547–2548.
2 Belsky JA, Tullius BP, Lamb MG, Sayegh R, Stanek JR, Auletta JJ. COVID-19 in immunocompromised patients: a systematic review of cancer, hematopoietic cell and solid organ transplant patients. *J Infect*. 2021;82(3):329–338.
3 Cravedi P, Mothi SS, Azzi Y, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant consortium. *Am J Transplant*. 2020;20(11):3140–3148.
4 Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325(21):2204–2206.
5 Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. *Ann Intern Med*. 2021;174(9):1330–1332.
6 Chavez-MacGregor M, Lei X, Zhao H, Scheet P, Giordano SH. Evaluation of COVID-19 mortality and adverse outcomes in US patients with or without cancer. *JAMA Oncol*. 2022;8(1):69–78.
7 Miarons M, Larrosa-García M, García-García S, et al. COVID-19 in solid organ transplantation: a matched retrospective cohort study and evaluation of immunosuppression management. *Transplantation*. 2021;105(1):138–150.
8 Coburn SB, Humes E, Lang R, et al. Analysis of postvaccination breakthrough COVID-19 infections among adults with HIV in the United States. *JAMA Netw Open*. 2022;5(6):e2215934.
9 Lang R, Humes E, Coburn SB, et al. Analysis of severe illness after postvaccination COVID-19 breakthrough among adults with and without HIV in the US. *JAMA Netw Open*. 2022;5(10):e2236397.

10 Bertagnolio S, Thwin SS, Silva R, et al. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: analysis of data from the WHO Global Clinical Platform of COVID-19. *Lancet HIV*. 2022;9(7):e486–e495.
11 Kuczborska K, Buda P, Książyk J. Long-COVID in immunocompromised children. *Eur J Pediatr*. 2022;181(9):3501–3509.
12 Peluso MJ, Deveau TM, Munter SE, et al. Chronic viral coinfections differentially affect the likelihood of developing long COVID. *J Clin Invest*. 2023;133(3):e163669.
13 Peluso MJ, Spinelli MA, Deveau TM, et al. Postacute sequelae and adaptive immune responses in people with HIV recovering from SARS-COV-2 infection. *AIDS*. 2022;36(12):F7–F16.
14 Yek C, Warner S, Wiltz JL, et al. Risk factors for severe COVID-19 outcomes among persons aged ≥18 years who completed a primary COVID-19 vaccination series - 465 health care facilities, United States, December 2020-October 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(1):19–25.
15 Sun J, Zheng Q, Madhira V, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. *JAMA Intern Med*. 2022;182(2):153–162.
16 Vinson AJ, Anzalone AJ, Sun J, et al. The risk and consequences of breakthrough SARS-CoV-2 infection in solid organ transplant recipients relative to non-immunosuppressed controls. *Am J Transplant*. 2022;22(10):2418–2432.
17 Cochran W, Salto-Alejandre S, Barker L, et al. COVID-19 outcomes in solid organ transplant recipients who received tixagevimab-cilgavimab prophylaxis and/or bebtelovimab treatment in a nurse-driven monoclonal antibody program during the omicron surge. *Transplantation*. 2022;107(2):e60–e61.
18 Trøseid M, Hentzien M, Ader F, et al. Immunocompromised patients have been neglected in COVID-19 trials: a call for action. *Clin Microbiol Infect*. 2022;28(9):1182–1183.
19 Kang SW, Kim JW, Kim JY, et al. Characteristics and risk factors of prolonged viable virus shedding in immunocompromised patients with COVID-19: a prospective cohort study. *J Infect*. 2023;86(4):412–414.
20 Gandhi S, Klein J, Robertson AJ, et al. De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. *Nat Commun*. 2022;13(1):1547.
21 Hogan JI, Duerr R, Dimartino D, et al. Remdesivir resistance in transplant recipients with persistent COVID-19. *Clin Infect Dis*. 2023;76(2):342–345.
22 Corey L, Beyrer C, Cohen MS, Michael NL, Bedford T, Rolland M. SARS-CoV-2 variants in patients with immunosuppression. *N Engl J Med*. 2021;385(6):562–566.
23 Fourati S, Gautier G, Chovelon M, et al. Persistent SARS-CoV-2 alpha variant infection in immunosuppressed patient, France, February 2022. *Emerg Infect Dis*. 2022;28(7):1512–1515.
24 Islam JY, Camacho-Rivera M, Vidot DC. Examining COVID-19 preventive behaviors among cancer survivors in the United States: an analysis of the COVID-19 impact survey. *Cancer Epidemiol Biomarkers Prev*. 2020;29(12):2583–2590.
25 Islam JY, Vidot DC, Havanur A, Camacho-Rivera M. Preventive behaviors and mental health-related symptoms among immunocompromised adults during the COVID-19 pandemic: an analysis of the COVID impact survey. *AIDS Res Hum Retroviruses*. 2021;37(4):304–313.
26 Woodfield MC, Pergam SA, Shah PD. Cocooning against COVID-19: the argument for vaccinating caregivers of patients with cancer. *Cancer*. 2021;127(16):2861–2863.
27 *Global COVID-19 vaccination – strategic vision for 2022 technical document*. Geneva: World Health Organization; 2021.
28 Galmiche S, Luong Nguyen LB, Tartour E, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. *Clin Microbiol Infect*. 2022;28(2):163–177.
29 *Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons*. Geneva: World Health Organization; 2021.
30 *Good practice statement on the use of second booster doses for COVID-19 vaccines*. Geneva: World Health Organization; 2022.
31 Curtis JR, Johnson SR, Anthony DD, et al. American College of Rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 5. *Arthritis Rheumatol*. 2022;75(1):E1–E16.
32 Connolly CM, Chiang TP, Boyarsky BJ, et al. Temporary hold of mycophenolate augments humoral response to SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal diseases: a case series. *Ann Rheum Dis*. 2022;81(2):293–295.
33 *Summary document for interim clinical considerations for use of COVID-19 vaccines currently authorized or approved in the United States*. Centers for Disease Control; 2022.
34 Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for prevention of Covid-19. *N Engl J Med*. 2022;386(23):2188–2200.
35 Al-Obaidi MM, Gungor AB, Kurtin SE, Mathias AE, Tanriover B, Zangeneh TT. The prevention of COVID-19 in high-risk patients using tixagevimab-cilgavimab (evusheld): real-world experience at a large academic center. *Am J Med*. 2022;136(1):96–99.
36 Wang Q, Li Z, Ho J, et al. Resistance of SARS-CoV-2 omicron subvariant BA.4.6 to antibody neutralisation. *Lancet Infect Dis*. 2022;22(12):1666–1668.
37 Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;386(15):1397–1408.
38 Trinkl J, Bartelt K, Joyce B, et al. Paxlovid significantly reduces COVID-19 hospitalizations and deaths. *Epic Res*. 2022.
39 Avery RK. Update on COVID-19 therapeutics for solid organ transplant recipients, including the omicron surge. *Transplantation*. 2022;106(8):1528–1537.
40 Focosi D. Molnupiravir: from hope to epic fail? *Viruses*. 2022;14(11):2560.
41 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med*. 2022;386(6):509–520.
42 Khoo SH, FitzGerald R, Saunders G, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Infect Dis*. 2022;23(2):183–195.
43 Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 2023;401(10373):281–293.
44 Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *Lancet*. 2022;400(10359):1213–1222.
45 Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med*. 2022;386(4):305–315.
46 Buxeda A, Arias-Cabrales C, Pérez-Sáez MJ, et al. Use and safety of remdesivir in kidney transplant recipients with COVID-19. *Kidney Int Rep*. 2021;6(9):2305–2315.
47 Yetmar ZA, Khodadadi RB, Seville MT, et al. Outcomes of B-cell-depleted patients with coronavirus disease 2019 treated with anti-spike monoclonal antibodies. *Open Forum Infect Dis*. 2022;9(7):ofac204.
48 Yetmar ZA, Beam E, O'Horo JC, et al. Monoclonal antibody therapy for COVID-19 in solid organ transplant recipients. *Open Forum Infect Dis*. 2021;8(6):ofab255.
49 Fernandes G, Devresse A, Scohy A, et al. Monoclonal antibody therapy in kidney transplant recipients with Delta and omicron variants of SARS-CoV-2: a single-center case series. *Kidney Med*. 2022;4(6):100470.
50 Sullivan D, Franchini M, Joyner M, Casadevall A, Focosi D. Analysis of anti-SARS-CoV2 Omicron neutralizing antibody titers in different vaccinated and unvaccinated convalescent plasma sources. *Nat Commun*. 2022;13(1):6478.
51 Li M, Beck EJ, Laeyendecker O, et al. Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern. *Blood Adv*. 2022;6(12):3678–3683.
52 Vickers MA, Sariol A, Leon J, et al. Exponential increase in neutralizing and spike specific antibodies following vaccination of COVID-19 convalescent plasma donors. *Transfusion*. 2021;61(7):2099–2106.
53 Leon J, Merrill AE, Rogers K, et al. SARS-CoV-2 antibody changes in patients receiving COVID-19 convalescent plasma from normal and vaccinated donors. *Transfus Apher Sci*. 2022;61(2):103326.

54 Rodionov RN, Biener A, Spieth P, et al. Potential benefit of convalescent plasma transfusions in immunocompromised patients with COVID-19. *Lancet Microbe*. 2021;2(4):e138.
55 Thompson MA, Henderson JP, Shah PK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. *JAMA Oncol*. 2021;7(8):1167–1175.
56 Senefeld JW, Klassen SA, Ford SK, et al. Use of convalescent plasma in COVID-19 patients with immunosuppression. *Transfusion*. 2021;61(8):2503–2511.
57 Sullivan DJ, Gebo KA, Shoham S, et al. Early outpatient treatment for Covid-19 with convalescent plasma. *N Engl J Med*. 2022;386(18):1700–1711.
58 Hueso T, Godron AS, Lanoy E, et al. Convalescent plasma improves overall survival in patients with B-cell lymphoid malignancy and COVID-19: a longitudinal cohort and propensity score analysis. *Leukemia*. 2022;36(4):1025–1034.
59 Estcourt LJ, Cohn CS, Pagano MB, et al. Clinical practice guidelines from the association for the advancement of blood and biotherapies (AABB): COVID-19 convalescent plasma. *Ann Intern Med*. 2022;175(9):1310–1321.
60 Cesaro S, Ljungman P, Mikulska M, et al. Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9). *Leukemia*. 2022;36(6):1467–1480.
61 Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis*. 2022:ciaa478.
62 Franchini M, Casadevall A, Joyner MJ, Focosi D. WHO is recommending against the use of COVID-19 convalescent plasma in immunocompromised patients? *Life (Basel)*. 2023;13(1):134.
63 CDC. Interim clinical considerations for COVID-19 treatment in outpatients. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/outpatient-treatment-overview.html; 2022. Accessed November 4, 2022.
64 NIH. COVID-19 treatment guidelines. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/; 2022. Accessed November 4, 2022.
65 *Therapeutics and COVID-19: living guideline, 16 september 2022*. Geneva: World Health Organization; 2022.
66 Hentzien M, Owen A, Strub-Wourgaft N, Pérez-Casas C, Trøseid M, Calmy A. Rethinking treatment paradigms for the deployment of SARS-CoV-2 antiviral drugs on the shifting landscape of new variants. *Front Microbiol*. 2022;13:998287.
67 Yamani AH, Alraddadi BM, Almaghrabi RS, et al. Early use of tocilizumab in solid organ transplant recipients with COVID-19: a retrospective cohort study in Saudi Arabia. *Immun Inflamm Dis*. 2022;10(3):e587.
68 Bodro M, Cofan F, Ríos J, et al. Use of anti-cytokine therapy in kidney transplant recipients with COVID-19. *J Clin Med*. 2021;10(8):1551.
69 Trujillo H, Caravaca-Fontán F, Sevillano Á, et al. Tocilizumab use in kidney transplant patients with COVID-19. *Clin Transplant*. 2020;34(11):e14072.
70 Ringer M, Azmy V, Kaman K, et al. A retrospective matched cohort single-center study evaluating outcomes of COVID-19 and the impact of immunomodulation on COVID-19-related cytokine release syndrome in solid organ transplant recipients. *Transpl Infect Dis*. 2021;23(2):e13556.
71 Pereira MR, Aversa MM, Farr MA, et al. Tocilizumab for severe COVID-19 in solid organ transplant recipients: a matched cohort study. *Am J Transplant*. 2020;20(11):3198–3205.
72 Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 3. *Arthritis Rheumatol*. 2022;74(4):e1–e20.
73 Petters LM, Vogel TP, Munoz FM, et al. Multisystem inflammatory syndrome in children associated with SARS-CoV-2 in a solid organ transplant recipient. *Am J Transplant*. 2021;21(7):2596–2599.
74 Kurra N, Woodard PI, Gandrakota N, et al. Opportunistic infections in COVID-19: a systematic review and meta-analysis. *Cureus*. 2022;14(3):e23687.
75 Clancy CJ, Schwartz IS, Kula B, Nguyen MH. Bacterial superinfections among persons with coronavirus disease 2019: a comprehensive review of data from postmortem studies. *Open Forum Infect Dis*. 2021;8(3):ofab065.
76 Gudiol C, Durà-Miralles X, Aguilar-Company J, et al. Co-infections and superinfections complicating COVID-19 in cancer patients: a multicentre, international study. *J Infect*. 2021;83(3):306–313.
77 Cataño-Correa JC, Cardona-Arias JA, Porras Mancilla JP, García MT. Bacterial superinfection in adults with COVID-19 hospitalized in two clinics in Medellín-Colombia, 2020. *PLoS One*. 2021;16(7):e0254671.
78 Bansal SB, Rana A, Babras M, et al. Risk factors and outcomes of COVID associated mucormycosis in kidney transplant recipients. *Transpl Infect Dis*. 2022;24(2):e13777.
79 Meshram HS, Kute VB, Yadav DK, et al. Impact of COVID-19-associated mucormycosis in kidney transplant recipients: a multicenter cohort study. *Transplant Direct*. 2022;8(1):e1255.
80 Organization WH. *Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination: seventy-fifth world health assembly WHA75.8*. Geneva: WHO; 2022.