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COVID-19 in the Immunocompromised Host, Including People with Human Immunodeficiency Virus

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KEYWORDS

• HIV • Immunocompromise • CD4 • COVID-19 • SARS-CoV-2
• Solid organ transplant • Immunosuppression • Hematopoietic stem cell transplant

KEY POINTS

- Persons with immunocompromising conditions are at elevated risk of severe outcomes, hospitalization, and death from severe acute respiratory distress syndrome (SARS)-coronavirus 2 (CoV-2) infection.
- Immunocompromising conditions are associated with decreased protective immunity after an initial infection with SARS-CoV-2 and decreased efficacy of COVID-19 vaccines.
- Persons with certain immunocompromising conditions should receive an additional dose(s) of initial vaccine series and should be prioritized for receipt of therapeutics and consideration of other preventive interventions.

HUMAN IMMUNODEFICIENCY VIRUS

Epidemiology

Incidence of COVID-19 in people with human immunodeficiency virus

There is conflicting evidence regarding whether COVID-19 incidence is higher in people with human immunodeficiency virus (HIV) (PWH) compared with people without HIV, after controlling for medical and structural risks that increase exposure to severe acute respiratory distress syndrome (SARS)–coronavirus 2 (CoV-2) and affect likelihood of progression to detected disease. A large study using linked clinical data from adults attending public sector health facilities from March 2020 to June 2020 in South Africa found a similar crude prevalence of laboratory-diagnosed COVID-19

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in PWH compared with people without HIV but was unable to control for age and immune status.[1] By contrast, public health surveillance data in San Francisco found an increased proportion of positive tests among PWH tested for COVID-19 compared with people without HIV (4.5% vs 3.5%; $P < .001$).[2] This discrepancy in the risk of infection was attributed to structural factors increasing exposure among PWH; the investigators noted a greater proportion of tested PWH were living in congregate housing or were homeless. Routine COVID-19 testing services in a federally qualified health center population in Chicago found the test positivity between March 2020 and July 2020 in PWH (10.6%) and HIV-negative patients (7.1%) was not significantly different in adjusted models.[3] Data from an insured Kaiser Permanente cohort in the United States found that PWH were twice as likely to be diagnosed with COVID-19, despite being younger and having fewer comorbidities than others in their network.[4] In the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) multisite cohort of PWH in the United States, the strongest predictors of having COVID-19 in 2020 were self-identifying as black or Hispanic, female sex, and having diabetes or hypertension. The only HIV-specific predictor of having COVID-19 in this cohort was having a history of having a $CD4^+$ cell count less than or equal to 350/mm^3 or a low current CD4/CD8 ratio; current $CD4^+$ cell count, being on antiretroviral therapy (ART), and viral suppression were not associated with COVID-19 incidence in this cohort.[5] Wider serosurveillance studies are necessary to determine absolute risk of infection conferred by HIV, with adequate controlling for structural factors that affect exposure as well as clinical risks that may affect symptom manifestation.

Descriptive epidemiology of the natural history of COVID-19 disease in people with human immunodeficiency virus

Infection with SARS-CoV-2 has differential consequences in PWH compared with persons without HIV. Several global registry data and cohorts have demonstrated a higher risk of severe disease and mortality from COVID-19 in PWH, with World Health Organization (WHO) global registry data estimating an adjusted mortality hazard ratio (HR) of 1.29 (95% CI, 1.23–1.35) in PWH, although most estimates did not adjust directly for $CD4^+$ cell count.[1,6,7] Some cohorts with a relatively higher proportion of PWH without immunosuppression have not observed increased mortality with HIV.[8] After infection with SARS-CoV-2, PWH can develop robust antibody and T-cell responses comparable to those seen in people without HIV; however, low $CD4^+$ cell count and low CD4:CD8 ratio, indicators of T-cell immunocompromise, are associated with impaired IgG antibody response, neutralization, and T-cell responses following infection.[9,10]

Time to clearance of SARS-CoV-2 may be prolonged in immunocompromised PWH compared with typical clearance time in immunocompetent persons. Cases have been documented of prolonged infectious viral shedding in immunosuppressed PWH with unsuppressed HIV viral loads, resulting in persistent illness and allowing accumulation of immune escape mutations in the viral genome.[11,12]

Many PWH experience an acute decrease in $CD4^+$ cell count at the time of SARS-CoV-2 infection, as a component of generalized lymphopenia that is a consequence of COVID-19. There is conflicting evidence about the effect of acute SARS-CoV-2 on HIV viral suppression in PWH. A small case series (n = 35) from Wuhan, China, found evidence of HIV viral blips (transiently detectable low-level viremia) during acute COVID-19 despite continuous ART.[13] Similarly, another study comparing PWH serum samples pre-COVID and serum samples in PWH with polymerase chain reaction (PCR)-proved COVID-19, using highly sensitive single-copy HIV viral assays, detected a trend toward increased detectable, low-level viremia in PWH with COVID-19.[14] The clinical significance of these viral blips in each setting likely is minimal but suggests an

immunomodulatory effect of SARS-CoV-2 on HIV immune control, which has unclear long-term implications.

No significant differences have emerged in non–HIV-specific inflammatory markers (eg, cytokines, C-reactive protein, D dimer, and other laboratory markers) or clinical presentation of COVID-19 in PWH compared with HIV-negative controls in larger cohorts.[15,16]

Predictors of severe disease and death in people with human immunodeficiency virus

Although studies conducted early in the COVID-19 pandemic did not detect a strong association between CD4 count and severity of COVID-19 outcomes,[17,18] subsequent well-characterized cohorts have established a strong and consistent association between HIV-associated immune suppression and increased risk of severe COVID-19 outcomes (hospitalization, intensive care, and mortality). In studies that better quantified the relationship of $CD4^+$ cell count to risk of COVID-19 hospitalization and death, however, $CD4^+$ cell count less than 200/mm^3 was consistently associated with increased risk of hospitalization[7,8,19] and death[7,19]; in the CNICS cohort of more than 15,000 PWH, $CD4^+$ cell count less than 350/mm^3 was significantly associated with an adjusted relative risk of 2.68 (95% CI, 1.93–3.71) for hospitalization.[20] The relationship between lack of ART or unsuppressed viral load and COVID-19 outcomes is less clearly defined, in part because the proportion of many PWH in US cohorts who are not on ART or virally unsuppressed is relatively small. In studies in which there is power to evaluate it, there seems to be a trend toward increased risk of hospitalization and mortality in PWH not on ART or virally unsuppressed.[7,21]

In PWH, non–HIV-specific comorbidities, including diabetes, obesity, liver disease, renal disease, and cardiovascular disease,[16,19,22,23] confer similar elevated risk of poor COVID-19 outcomes as in people without HIV.

Treatment Considerations for people with Human Immunodeficiency Virus

Treatment of PWH hospitalized with COVID-19 is not different from treatment of non-immunosuppressed persons or persons without HIV. Treatment guidelines for the use of the antiviral remdesivir and corticosteroids, including dexamethasone, and consideration of immunomodulatory therapies, such as tocilizumab all are independent of HIV status or degree of immune compromise.[24] In contrast, for ambulatory PWH with COVID-19 and no supplemental oxygen requirement, given the demonstrated elevated risk of COVID-19 disease progression seen in PWH overall and most strongly among PWH with untreated HIV or with $CD4^+$ cell count less than 350/mm^3, these immunocompromised PWH meet National Institutes of Health (NIH) COVID-19 treatment guidelines recommendations criteria for consideration of early therapies, including approved neutralizing monoclonal antibodies (mAbs) with efficacy against the presumed infecting SARS-CoV-2 variant.[25] Oral antivirals (molnupiravir and nirmatrelvir/ritonavir) also may be appropriate early therapies for PWH, although the use of a ritonavir booster in the nirmatrelvir combination may have limiting interactions with certain antiretrovirals; the US Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for nirmatrelvir/ritonavir indicates that ritonavir- or cobicistat-containing ART regimens should be continued unmodified, with clinical monitoring for adverse effects.[26,27] PWH with immune compromise or uncontrolled viremia should be urgently prioritized for early therapeutics that have demonstrated efficacy in reducing the risk of severe outcomes, including hospitalization and death.

Prevention Considerations for People with Human Immunodeficiency Virus

PWH should be prioritized for receipt of preventive vaccines. PWH with $CD4^+$ cell counts less than 200/mm^3 were excluded from initial phase 3 vaccine efficacy trials,

but many trials included PWH without advanced HIV. Vaccine efficacy in PWH in trials was similar to people without HIV receiving the ChAdOx1 nCoV-19 vaccine (AstraZeneca, United Kingdom) and the BNT162b2 (Pfizer-BioNTech, United States) vaccine.[28–30] A study of 100 PWH and 100 matched HIV-uninfected controls found PWH had lower IgG antibody responses and viral neutralization assays responses after receipt of mRNA vaccines, with a stronger effect seen among PWH with lower $CD4^+$ cell counts or unsuppressed viral loads.[31] Given this observation of decreased vaccine-induced antibody responses in PWH with immunosuppression, PWH meeting these criteria are recommended to receive an additional vaccine dose as part of the initial series as well as a subsequent booster dose. A multicountry cohort of 6952 PWH showed COVID-19 vaccine uptake among PWH globally has broadly mirrored uptake in the general population for many countries, although this corresponds to wide variations in vaccination prevalence by country, with residence in a high-income country the most significant predictor of receipt of a vaccine.[32]

Health Care Access and Continuity of Care

Globally, the COVID-19 pandemic has had a devastating effect on continuity of care for PWH, including maintenance of ART and diagnosis and treatment of opportunistic infections.[33] Adapting care models during the pandemic to include telemedicine and telephone appointments has been successful in retaining some PWH in care[34] and limiting loss of viral suppression,[35] but these benefits were not experienced uniformly among PWH. Clinics patients with lower financial and technological resources were disproportionately less able to access care during shelter-in-place periods, with concomitant increased risk of loss of viral suppression seen in persons experiencing homelessness.[36] Increasing home postal delivery of ART enabled maintenance of viral load suppression in an Australian clinic cohort.[37]

Urgent Research Questions

Key research questions remain for addressing COVID-19 in PWH, in particular PWH with current or historic immunosuppression. Vaccines currently provide the best intervention for preventing severe disease in PWH, but vaccines might have lower efficacy in immunosuppressed PWH. Many questions remain regarding the relative immunogenicity of different vaccine types (mRNA, Ad5 vector, Ad26 vector, protein subunit, and whole-inactivated) for PWH, in particular PWH with $CD4^+$ cell count less than $350/mm^3$ or untreated HIV with persistent HIV viremia, the persistence of vaccine-induced immunity, and the optimal dosing and boosting interval for vaccines. Studies, such as the recently initiated COVID-19 Prevention Trials Network (CoVPN) 3008 protocol, evaluating the immunogenicity of the mRNA-1273 (Moderna, United States) vaccine in sub-Saharan Africa in countries with a high prevalence of HIV, are well poised to answer some of these questions, but additional global cohorts of vaccinated PWH should be engaged to assess immunologic markers while clinical and immunologic outcomes are awaited.[38]

Also critical to preventing COVID-19 and severe disease in PWH are additional research into use and indications for prophylactic therapies, including new oral antivirals and neutralizing mAbs, and identifying the PWH who would most benefit from these preventive therapeutics (eg, $CD4^+$ cell count thresholds, other historical immune indicators).

Finally, post-COVID sequelae (long COVID, or postacute sequelae of SARS-CoV-2 [PASC]), characterized by persistent neuropsychiatric, cardiovascular, pulmonary, and other symptoms after the acute phase of COVID-19 has resolved and replicating virus no longer can be demonstrated, is emerging as a significant source of morbidity

among people who have had COVID-19.[39] PASC is beginning to be studied in the general population; however, the incidence, prevalence, and predictors of PASC in PWH currently are unknown. One small study characterized PASC in an Indian cohort of 94 PWH, finding a PASC prevalence of 43.6% and increased risk among persons who had had moderate to severe COVID-19 compared with those who had had mild disease.[40] There is an urgent need to characterize risk and manifestations of PASC more broadly, including the relationship between immunosuppression and incidence of PASC, in PWH in larger, more diverse global cohorts. This information is critical to guide post-COVID HIV care, to understand potential interactions between HIV and COVID, and to inform interventional strategies to prevent and treat PASC in PWH.

Clinics Care Points

- PWH with $CD4^+$ T-cell counts less than 350/mm^3 or low $CD4^+$ T-cell count nadirs are at elevated risk for severe disease outcomes with COVID-19 and should be prioritized for vaccination (including additional doses), preventive therapeutic options, and early therapies (antiviral antibodies and mAbs) in the event of infection with SARS-CoV-2.
- To reduce all-cause and COVID-19–specific morbidity and mortality for PWH, it is essential to maintain access to routine HIV care during pandemic COVID-19, especially initiating and continuing ART to achieve and maintain virologic suppression of HIV. Approaches, including telemedicine, extended monthly dispensing, and home delivery of medications, should be explored to prioritize ART continuity.

COVID-19 IN SOLID ORGAN TRANSPLANTION

Epidemiology

Incidence of infection

SARS-CoV-2 infection has led to high mortality and morbidity in solid organ transplant (SOT) patients.[41–43] The incidence of COVID-19 SOT patients is higher than in immunocompetent patients.[44,45] In a large US cohort of 18,121 SOT patients, the incidence of clinically detected COVID was 10.2% from January 2020 to November 2020.[45] A large UK cohort study showed a positivity rate of 3.8% (197/5184) in waitlisted patients and 1.3% (597/46,789) of SOT recipients between February 2020 and May 2020.[42] A study (TANGO) from 12 transplant centers from March 2020 to May 2020, across the United States Italy, and Spain, showed 1.5% positivity rate (144/9845) in hospitalized kidney transplant patients.[46]

Effects of immunosuppression

SARS-CoV-2 infection induces both memory B-cell production and long-lasting functionally replete memory T-cell responses.[47,48] Community-acquired respiratory viral infections in SOT recipients usually are more severe in the early post-transplant period or after receiving lymphocyte-depleting therapies.[49] The pathogenesis of COVID-19 infection involves an early phase of highly replicating virus followed by a late phase of hyperactive or dysregulated immune system that leads to severe systemic effects. The immunosuppression in this population may impair development of T-cell immunity to SARS-CoV-2 virus.[50] Prolonged viral shedding has been observed beyond day 30 in transplant patients. The SARS-CoV-2 plasma viral load also has been associated with mortality in the kidney transplant population.[51] Immunosuppressive therapies may help with curbing severe immune responses in the late phases of COVID-19.[50,52] The effect of immunosuppressive therapies varies with the type and intensity and with phase of

illness. Most centers practice reduction or holding immunosuppression. Most retrospective cohort studies did not reveal any significant impact of immunosuppression on mortality,[41,46,53] except within a liver transplant cohort, in which mycophenolate-containing regimens were an independent risk predictor of severe disease (relative risk = 3.94), especially at doses of greater than 1000 mg/d.[44] These were retrospective studies, however, and must be interpreted with caution. The impact of type and degree of immunosuppression on the course of COVID-19 remains unclear. Further randomized controlled trials (RCTs) are needed to address this question.[54]

Predictors of severe disease and death

The mortality in the SOT population has ranged in studies from 6% to 27% (**Table 1**). The various risk factors associated with mortality in this population are increasing age (>60 years), chronic heart failure, chronic lung disease, obesity, lymphopenia, mycophenolate-containing regimens for immunosuppression, and lung transplantation.[41,42,44,53] In the lung transplant population, chronic lung allograft dysfunction was an independent predictor of mortality.[55] The rate of hospitalization for COVID-19 in SOT recipients also is high, ranging from 30% to 89%. Acute kidney injury has been reported in 24% to 52% of patients. A meta-analysis showed that age, male sex, diabetes mellitus, hypertension, chronic kidney disease, and cardiovascular disease are associated with acute kidney injury in transplant patients and also lead to increased mortality.[56] The reported rate of rejection associated with SARS-CoV-2 infection is low: 1.5% to 6%.

Treatment considerations

Antiviral

Remdesivir. Remdesivir is an inhibitor of viral RNA–based RNA polymerase, which is essential for viral replication of SARS-CoV-2. The Adaptive COVID-19 Treatment Trial (ACTT)-1) showed reduced time to clinical recovery in patients with severe COVID, especially on supplemental oxygen.[62] The WHO solidarity trial did not show any decrease in the in-hospital mortality in hospitalized patients compared with standard of care.[63] There was no significant difference in the outcomes between a 5-day versus 10-day course of remdesivir.[64] Treatment of SOT populations with remdesivir does not differ from that of the general population, although some consider the extended 10-day course for patients without improving clinical status, due to risk for increased duration of viral replication in this population.

Nirmatrelvir/ritonavir and molnupiravir. The FDA granted EUA for both the nirmatrelvir/ritonavir and molnupiravir antivirals in December 2021.

Nirmatrelvir is a SARS-CoV-2 protease inhibitor that inhibits viral replication. It is administered with ritonavir, which inhibits cytochrome P450 3A4, and raises nirmatrelvir levels to a therapeutic range. In the EPIC-HR(Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) trial, ritonavir-boosted nirmatrelvir (Paxlovid) reduced the risk of hospitalization or death by 88% compared with placebo in nonhospitalized high-risk adults with laboratory-confirmed SARS-CoV-2 infection and within 5 day of symptom onset.[65] This drug must be used with caution, however, in the transplant population, due to the drug interactions between ritonavir and calcineurin inhibitors (CNIs). In the MOVe-OUT (Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients)trial, molnupiravir reduced the rate of hospitalization or death by 30% compared with placebo in high-risk adults within 5 days of symptom onset, and the recommendations for its use in SOT recipients do not differ from those in the general population.[66]

Table 1
Studies of clinical outcomes of COVID-19 in solid organ transplantation

Study Name	Hospitalization Rates	Mortality (%)	Acute Kidney Injury (%)	Acute Rejection/ Graft Loss (%)	Predictors of Severe Disease or Death
Kates et al.[41] Total n = 482 Lung, liver, heart, kidney	78%	20.5	37.8	6	1. Age > 65 y 2. Chronic heart failure 3. Chronic lung disease 4. Obesity 5. Lymphopenia 6. Abnormal chest imaging
Vinson et al.[45] Total n = 1925 Lung, liver, kidney	42.9%		35.3	1.5	
Colmenero et al.[44] Total n = 111 Liver	86.5%	18			1. Mycophenolate-containing regimen (doses >1000 mg/d) 2. Male gender 3. Charlson comorbidity index 4. Dyspnea at diagnosis
Ravanan et al.[42] Total n = 597 All SOT		25.8%			Increased age
Coll et al.[53] Total n = 778 Kidney, liver, lungs, heart, pancreas	89%	27			1. Lung transplantation 2. Age >60 y 3. Hospital-acquired COVID-19
Cravedi et al.[46] Total n = 144 Kidney	All hospitalized patients	32	52		1. Older patients 2. High LDH, IL-6, and procalcitonin levels 3. High respiratory rate

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Table 1
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Study Name	Hospitalization Rates	Mortality (%)	Acute Kidney Injury (%)	Acute Rejection/ Graft Loss (%)	Predictors of Severe Disease or Death
Favà et al.[57] Total n = 104 Kidney	All hospitalized patients	27	47		1. Age 2. ARDS 3. Increased baseline LDH
Webb et al.[58] Total n = 151 Liver	82%	19	38		Age
Hadi et al.[59] Total n = 2307 Kidney, liver, heart, and lung	30.97%	6.45	24.73		
Fisher et al.[60] Total n = 128 Kidney, liver, heart, pancreas	All hospitalized patients	21.9	33.6		1. Male sex 2. Age 3. Diabetes mellitus 4. ANC and D-dimer on presentation 5. Level of respiratory support (WHO index 3 and 4) on presentation
Pereira et al.[61] Total n = 117 Kidney, liver, heart, kidney-pancreas	All hospitalized patients	23			

Abbreviations: ANC, absolute neutrophil count; ARDS, acute respiratory distress syndrome; LDH, lactate dehydrogenase.

Monoclonal antibodies

Various mAbs to the spike protein of SARS-CoV-2 have received EUA by the FDA for treatment of nonhospitalized patients with COVID-19, who are at a high risk of progression to severe disease. Real-world experience in SOT patients showed a decrease in hospitalization and respiratory failure compared with patients who did not receive mAbs (**Table 2**).with

Accumulating evidence indicates no role for neutralizing mAbs for treatment of COVID in nonimmunocompromised people with moderate to severe COVID-19 requiring hospital care and/or oxygen therapy; however, the role of mAbs for SARS-CoV-2 seronegative, highly immunosuppressed people with moderate to severe COVID-19 still is unclear and may have benefit.[67,68] MAbs generally are not authorized for use in hospitalized patients and, as such, require individual consideration for use in transplant populations.

Convalescent plasma

The FDA issued an EUA for treatment of hospitalized patients with COVID with convalescent plasma from donors who have recovered from COVID-19, which contains antibodies to SARS-CoV-2. In immunocompromised patients, there are only a few case series and retrospective studies that suggest some benefit, however, and RCTs are lacking.[73,74] In a double-blind, placebo-controlled RCT, administration of high-titer (>1:1000 anti–SARS-CoV-2 antibodies) convalescent plasma to older adults within 72 hours of onset of mild symptoms of COVID led to relative risk reduction of development of severe COVID by 48%.[75] In December 2021, the FDA extended the EUA for convalescent plasma to include immunocompromised nonhospitalized patients.

Table 2
Studies of monoclonal antibodies in solid organ transplant patients

Study	Population	Monoclonal Antibody	Outcomes
Yetmar et al.[69]	73 patients with lung, liver, kidney, and heart transplant	Bamlanivimab	1. 12.3% of patients required hospitalization for median of 4 d. 2. No deaths
Klein et al.[70]	20 of 95 kidney transplant patients	Balmanivimab	1. mAb administration led to 15% vs 76% emergency department/hospital visits ($P < .001$).
Del Bello et al.[71]	16/48 patients with kidney, kidney-liver, kidney-heart	5 bamlanivimab 9 bamlanivimab + etesevimab 2 casirivimab + imdevimab	1. 0 vs 46% patients developed severe respiratory failure in the non-mAb group ($P = .007$).
Jenks et al.[72]	175/617 high-risk patients	83% received bamlanivimab + etesevimab 16% bamlanivimab	1.7% vs 24% hospitalizations and 0 vs 2.7% deaths in mAb vs non-mAb groups, respectively

[a]Bamlanivimab or bamlanivimab + etesevimab research are presented for context, but these drugs no longer may be appropriate, depending on circulating variants of concern.

Immunomodulators

COVID-19–associated systemic inflammation results from cytokine release. Interleukin-6 (IL-6) is a proinflammatory cytokine that is released by various cells during systemic inflammation. It is hypothesized that modulating or inhibiting these levels may reduce the severity of COVID-19 infection.

A large, multicenter RCT (RECOVERY, Randomised Evaluation of COVID-19 Therapy) showed decreased 28-day mortality in hospitalized patients with COVID-19 on supplemental oxygen or invasive mechanical ventilation, who received 10 days of dexamethasone (an anti-inflammatory agent).[76]

Tocilizumab and sarilumab, mAbs to IL-6 receptor, are used in management of certain rheumatological disorders and cytokine release syndrome related to chimeric antigen receptor T-cell (CAR-T) therapy. In the RECOVERY and REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) trials, tocilizumab was reported to have mortality benefit in COVID patients with respiratory decompensation, requiring oxygen or noninvasive ventilation.[76,77] These trials, however, did not include SOT patients. These drugs must be used with caution in the SOT population due to an increased risk of secondary infections.

Janus kinase (JAK) inhibitors prevent phosphorylation of proteins that lead to immune activation and inflammation. The COV-BARRIER (Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19) trial showed a decrease in the 28-day mortality, and the ACTT-2 trial showed improved time to recovery in patients who received baricitinib with remdesivir.[78,79] At this time, there is insufficient evidence to recommend for or against the use of these immunomodulators in immunocompromised patients.

Proposed treatment algorithm for solid organ transplant patients with COVID-19 as outlined below.

Prevention

Vaccine safety in solid organ transplant patients

A study of 741 SOT patients undergoing mRNA vaccination showed that the reactogenicity of this vaccine was similar to that seen in immunocompetent adults. There were no cases of anaphylaxis or new SARS-CoV-2 diagnosis. Only 1 patient developed acute rejection after the second dose.[80]

Immunogenicity of vaccines in solid organ transplantation

A significant proportion of organ transplant patients do not develop humoral response despite 2 doses of mRNA vaccine. In 658 transplant patients undergoing vaccination, 46% patients did not have an antispike protein antibody response after 2 doses of vaccine. Poor humoral response was associated with use of antimetabolite immunosuppression.[81] In another study of 127 SOT patients receiving mRNA-1273 (Moderna), anti–receptor binding domain of the antispike protein (RBD) antibody response was seen in 34%, neutralizing antibody in 29%. $CD4^+$ T-cell responses were observed in 48% of patients,[82] and these responses were present in a significant proportion of patients who also were antibody negative.

Vaccine effectiveness

Various studies showed that vaccine effectiveness in immunocompromised patients was lower compared with immunocompetent patients (**Table 3**). The immunogenicity of vaccines is low in transplant patients, and although there lack sufficient vaccine efficacy data in this population, there is observation of reduced clinical effectiveness. The breakthrough infection rate ranged from 0.4% to 0.8%. A UK registry study of

Disease Severity	Recommendations
Nonhospitalized setting	1. Sotrovimab (for Omicron variant B.1.1.529) Other authorized mAbs, if activity against circulating variants of concern 2. Remdesivir 3. Paxlovid (nirmatrelvir/ritonavir)—monitor for drug-drug interactions 4. Molnupiravir (only if above options are not available)
Hospitalized, not requiring supplemental oxygen (not admitted for COVID-19)	1. Sotrovimab (for Omicron variant B.1.1.529) Other approved mAB with activity against circulating variants of concern 2. Remdesivir 3. Consider adjustment of immunosuppression based on severity of disease, risk of rejection, type of transplant, etc.
Hospitalized, requiring supplemental oxygen	1. Consider mAb use via expanded access protocol. 2. Start remdesivir and dexamethasone. 3. Consider adjustment of immunosuppression based on severity of disease, risk of rejection, type of transplant, etc.
Hospitalized, requiring oxygen via high-flow nasal cannula or noninvasive mechanical ventilation	1. Consider mAb use via expanded access protocol. 2. Start remdesivir and dexamethasone. 3. Consider adjustment of immunosuppression based on severity of disease, risk of rejection, type of transplant, etc. 4. There is insufficient evidence at this time about the risks and benefits of use of tocilizumab or baricitinib with dexamethasone in this population. Careful monitoring due to increased risk of secondary opportunistic infections
Hospitalized, requiring oxygen via invasive mechanical ventilation	1. Start dexamethasone 2. Consider adjustment of immunosuppression based on severity of disease, risk of rejection, type of transplant, etc.

SOT patients showed a lower mortality rate in vaccinated versus unvaccinated individuals.

Vaccine schedule and third vaccine dose

In transplant candidates, it is recommended that patients receive 3 dose series of mRNA vaccine at least 2 weeks prior to transplantation, or, if infeasible, 1 month post-transplant. In patients who receive B-cell– or T-cell–depleting therapies, postponing to 3 months post-transplantation should be considered. The American Society of Transplantation and Centers for Disease Control and Prevention (CDC) both strongly recommend 3 dose series of the mRNA vaccine (Pfizer and Moderna) followed by a booster dose and an additional second dose of the Johnson and Johnson vaccine for all transplant recipients and the eligible household and close contacts of all transplant recipients.

A third dose of an mRNA vaccine is recommended 28 days after the most recent mRNA vaccine. An additional booster dose is recommended to be given 5 months after the last primary dose of the mRNA vaccine. Several small studies showed an improvement in humoral response after the third dose of the vaccine in transplant patients who did not develop adequate response after 2 doses (**Table 4**).

Table 3
Studies of vaccine effectiveness in solid organ transplant patients

Study	Results
Embi et al.[83] Multistate analysis across 7 health care systems	VE against COVID-19 associated hospitalization was lower (VE 77%) in immunocompromised patients compared with immunocompetent patients (VE 90%). VE was much lower (59%) in SOT and stem cell transplant patients.
Aslam et al.[84] 2151 SOT (912 vaccinated and 1239 controls)	Infections occurred in 61 of unvaccinated vs 4 of fully vaccinated patients. Vaccination led to 80% reduction in the incidence of symptomatic COVID-19.
Ravanan et al.[85] UK transplant registry Unvaccinated, n = 6748 Vaccinated, n = 39,727	The 28-d mortality rate was 12% in unvaccinated vs 7% in vaccinated individuals.
Malinis et al.[86] Fully vaccinated SOT individuals, n = 459	Breakthrough infection occurred in 3/459 (0.65%) fully vaccinated individuals.
Anjan et al.[87] Vaccinated SOT individuals (n = 2957)	Breakthrough infections occurred in 26 patients (0.87%). 5 (19.2%) had severe COVID-19 and 2 (7.6%) patients died.
Qin et al.[88] Fully vaccinated SOT individuals (n = 18,215)	Breakthrough infections occurred in 151 patients (0.83%). Of those, 87 (0.48%) were hospitalized. Of those, 14 (0.077%) died.
Mehta et al.[89] Fully vaccinated kidney transplant individuals (n = 1680)	Breakthrough infections in 8 patients and 3 were hospitalized

Abbreviation: VE, vaccine effectiveness.

Monoclonal antibodies for postexposure prophylaxis

Vaccines are effective in preventing severe COVID-19 infection in immunocompetent persons, but transplant patients do not always mount an adequate immune response and still may be at a risk of breakthrough infections, as discussed previously.

Two large RCTs showed that administration of mABs for postexposure prophylaxis was effective in prevention of COVID-19 in certain high-risk patients. Bamlanivimab monotherapy significantly reduced the incidence of COVID-19 (8%, vs 15% in placebo group) in 966 nursing and assisted living home residents with a confirmed index case.[94] In another RCT, administration of casirivimab and imdevimab to high-risk patients (household contacts) within 96 hours of exposure led to a reduction of acquiring symptomatic COVID-19 infection by 81% compared with placebo. This trial included immunosuppressed patients as well.[95] Based on these 2 trials, the FDA expanded the EUA indication to use certain mABs for postexposure prophylaxis in high-risk individuals, preferably within 7 days of exposure, assuming the mAb has activity against locally circulating variants.[96]

Pre-exposure prophylaxis

One important strategy for prevention of COVID-19 in persons with significant immunosuppression, who are not expected to mount a response to vaccines, is providing

Table 4
Studies showing immunogenicity of third vaccine dose in solid organ transplant patients

Study	Results
Hall et al.[90] An RCT of 120 patients, third dose of vaccine vs placebo	1. Increased anti-RBD antibody level in 55%, vs 18% in placebo group 2. After third dose, median percent virus neutralization was 71%, vs 13% in placebo group. 3. SARS-CoV-2–specific $CD4^+$ T-cell counts 432 vs 67 cells per 10^6
Kamar et al.[91] 101 SOT patients who received third dose of Pfizer vaccine	1. 26 of 59 (44%) patients who were seronegative prior to the third dose became seropositive. 2. Patients who were older, on higher immunosuppression, and had lower estimated glomerular filtration rate did not have an antibody response.
Benotmane et al.[92] Study of 159 kidney transplant patients who received a third dose of Moderna vaccine	1. Serologic response was observed after a third dose in patients who had a weak response after the second dose. 2. Patients who were on tacrolimus, mycophenolate, or steroids were less likely to develop an antibody response.
Stumpf et al.[93] 71 kidney transplant patients who received third dose of Pfizer vaccine	1. Increase in cumulative humoral response from 6% to 55% after first and third doses, respectively 2. Cellular response was present in 26% (9/35) patients.

mAb for pre-exposure prophylaxis. In November 2021, the FDA authorized (EUA) the AstraZeneca Evusheld (tixagevimab with cilgavimab) for pre-exposure prophylaxis for immunocompromised individuals. In a randomized placebo-controlled trial, administration of Evusield for pre-exposure prophylaxis led to 77% decrease in development of symptomatic COVID-19 compared with placebo.[97]

Impact of COVID-19 on Transplantation

There was a decline in transplantation all over the world during the first several months of pandemic, for various reasons.[50] Early in the pandemic, there was a national decline in the number of transplants by 35% from January 2020 to April 2020. There also was an increase in the waitlist deaths by 26%. These changes were more significant in regions with high COVID-19 burden. The largest reductions were seen in kidney (42%) and lung (40%) transplant patients.[98]

A survey was conducted to understand the impact of COVID-19 on transplant activity on organ transplants in 111 centers across the United States. Complete suspension of live kidney and liver transplantation was reported by 71% and 67% centers, respectively. Many centers were limiting their transplants to higher-acuity patients. Some transplants were limited by supplies, personnel, and capacity. In-person outpatient visits were limited by 98% of respondents, laboratory draws were stopped/limited by 20%, and 96% reported using telemedicine.[99] There also was a decline in the availability of ICU beds, because they were occupied by the critically ill COVID patients. Pretransplant COVID screening measures for donors and recipients were

implemented by most centers. There was an 11% decline in donor organ authorization by families from March 2020 to May 2020. Donor cause of death due to substance abuse increased by 35% and trauma decreased by 5% in that time period.[100]

The transplantation societies have issued guidance for safe donation and transplantation practices, and there is an increased use of telemedicine for outpatient care to minimize hospital exposure.

Organ Transplantation from COVID-positive Donors

Little is known about the transmissibility of SARS-CoV-2 virus during organ transplantation. All deceased organ donors are tested for SARS-CoV-2 PCR by nasopharyngeal swab within 72 hours prior to transplantation, as per the Organ Procurement and Transplantation Network (OPTN) policy. Lower respiratory tract (LRT) testing of COVID by bronchoalveolar lavage is recommended in all potential lung donors, because there is a likelihood of missing an active infection with an upper respiratory tract (URT) sample alone. Between May 27, 2021, and July 31, 2021, OPTN identified 12 donors who had negative URT but positive LRT SARS-CoV-2 tests.[101] There were 3 reported cases of transmission of COVID via lung transplantation, where the URT sample was negative but the LRT sample returned positive from the donor after transplantation. One of the recipients died.[102,103] Hence, it is recommended that all lung donors must be tested for SARS-CoV-2 by LRT samples prior to transplantation. There was no transmission reported in the nonlung organ transplantation from these donors. A recent report of 10 patients who received kidneys from SARS-CoV-2–positive donors reported good outcomes in all patients, without the development of active COVID infection.[104] Long-term data in large samples, however, still are lacking. Based on these data, accepting lungs from SARS-CoV-2–positive donors must be deferred. Nonlung organs from COVID-positive donors may be considered in recipients, depending on the risk of mortality or complications from delaying transplantation.

COVID-19 IN HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

Epidemiology

Risk of infection and natural history of disease

Much of the data regarding natural history of disease in hematopoietic cell transplant (HCT) patients were gathered early in the pandemic. Incidence of COVID-19 infection in HCT patients around the world varied by local rates of infection and infection prevention practices. A group of HCT patients in New York City were followed weekly for 2 months, in the spring of 2020, with access to testing and early treatment. Of the 254 patients tracked, 24 reported symptoms that prompted testing, and 6 of the 254 were diagnosed with COVID-19, all of whom received prompt care with good outcomes.[105]

A report from the Center for International Blood and Marrow Transplant Research (CIBMTR) of 318 HCT patients with COVID-19, from March 2020 to August 2020, found moderate to severe disease in greater than 50% of patients, with 14% requiring mechanical ventilation overall.[106] Those with allogeneic HCT had a 30-day survival rate of 68%, and those with autologous HCT had a 67% 30-day survival rate after COVID-19 diagnosis.[107] A similar survey from Europe, which included 382 HCT recipients diagnosed with COVID-19 prior to July 31, 2020, found 6-week survival rates of 78% in allogeneic HCT recipients and 72% in autologous recipients; in this group, 83% developed LRT disease, and 22.5% required ICU care.[107] The reported median time to viral resolution was 24 days, with the longest time to resolution 210 days, consistent with long-term viral replication in immunosuppressed hosts.[107]

In a smaller series, a group from Turkey found a mortality rate of 15.6% in patients who were hospitalized for COVID-19 with HCT and 11.8% in those with cancer without HCT, compared with 5.6% in those without cancer.[108] In Spain, mortality of 20% was reported in allogeneic HCT recipients and 24% in autologous HCT. Shah and colleagues[109] found an overall survival rate of 78% in a series of 77 allogeneic HCT, autologous HCT, and CAR-T recipients with a diagnosis of COVID-19. Overall, 48%, 26%, and 22% had mild, moderate, and severe disease, respectively.[109]

Predictors of severe disease and death

In the CIBMTR study, age greater than 50 years of age (HR 2.53, $P = .02$), male sex (HR 3.53, $P = .006$), and development of COVID-19 within 12 months of transplantation (HR 2.67, $P = .005$) were associated with a higher risk of mortality among allogeneic HCT recipients. In those with autologous transplantation, those with lymphoma had a higher risk of mortality that those with plasma cell disorder or myeloma (HR 2.41, $P = .033$).[106] In the European survey by Ljungman and colleagues,[107] age and level of immunodeficiency as calculated by a scoring index were found to be associated with an overall increased risk of death, and ongoing immunosuppression was the only risk factor in the allogeneic HCT recipients associated with need for ICU care. Not surprisingly, better performance status was associated with an overall decreased risk of death.[106]

In the series from Turkey, HCT recipients on immunosuppressive agents had a higher mortality rate than those who were not receiving exogenous immunosuppression (33% vs 11.5%,).[108] As was seen in the study by Shah and colleagues,[109] active malignancy was associated with worse outcomes in hospitalized HCT patients with COVID-19. In those without active malignancy, however, survival rates were similar to the general population hospitalized in the same area. Clinical variables associated with either need for ventilatory support or death included the number of comorbidities (HR for $\geq$2 vs 0 comorbidities 5.41, $P = .004$), presence of infiltrates on chest imaging (HR 3.08, $P = .032$), and neutropenia (HR 1.15, $P = .04$).[109]

Treatment Considerations

For HCT and cellular immunotherapy candidates, current guidelines recommend deferring transplantation or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T-cell collection, and conditioning or lymphodepletion in patients who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease, including the ability to give anti–SARS-Cov-2 mAb, which can be given as early treatment of infection or postexposure prophylaxis prior to lymphodepletion.

SARS-CoV-2 VACCINATION IN HEMATOPOIETIC CELL TRANSPLANT

A few studies of antibody response to 2 doses of mRNA vaccines after HCT helped inform the decision to offer third doses to immunocompromised people, including HCT patients. A study from France found that after a second dose of the Pfizer BNT162b2 vaccine, 83% of 117 HCT patients had detectable antispike IgG antibodies, but only 62% had antibodies at the level detected in immunocompetent control participants. Factors associated with nonresponse to vaccine were being a haploidentical transplant recipient, vaccination within 1 year after HCT, lymphopenia (<1000 cells/mL), and receipt of immunosuppression or chemotherapy at the time of vaccination.[110] Another study of 63 HCT recipients in Switzerland who received either of the SARS-CoV-2 mRNA vaccines found that 76% had some humoral response after 2 doses. Age greater than 60 years, vaccination within 6 months of HCT, or use of

antithymocyte globulin during conditioning all were associated with lack of response to vaccination in this group.[111] As in other populations not expected to mount adequate vaccine responses, use of authorized anti–SARS-CoV-2 mAbs for pre-exposure prophylaxis may be warranted.

Timing of vaccination after hematopoietic cell transplant

Vaccination should be delayed for 3 months following HCT or CAR-T therapy to maximize vaccine efficacy, according to National Comprehensive Cancer Network (NCCN) guidelines. The European Society for Blood and Marrow Transplantation (EBMT) guidelines recommend waiting for at least 3 months in high transmission areas, preferably for 6 months if the transmission is low. It also is recommended to repeat the vaccine series if vaccinated prior to HCT.

Currently, the CDC and international societies, including the NCCN, CIBMTR, and EBMT, all recommend a third dose of mRNA vaccine for those who received 2 doses of an mRNA SARS-CoV-2 vaccine after transplant, after a minimum 4-week interval from the prior dose.[112,113] Boosters continue to be recommended following completion of the initial series, as in nonimmunocompromised persons.

QUALITY OF LIFE DURING THE PANDEMIC

A survey study of 101 patients post-HCT was done to assess their supportive care needs. Largely, there were unmet physical and psychological needs of the patients. Compliance with exercise programs was low. Women had more unmet psychological needs compared with men, and measures of their quality of life were low.[114] A cross-sectional analysis of 205 patients undergoing HCT enrolled in a supportive care trial found that enrollment during COVID-19 was not associated with pre-HCT symptoms of depression, anxiety, posttraumatic stress disorder, fatigue, or quality of life impairment. During the COVID-19 era, patients reported negative implications, such as increased isolation and increased family and caregiver distress, and positive implications, such as engagement in meaningful activities and increased support from caregivers.[115] Telehealth services can be helpful to provide increased support and interventions to meet patient needs and reduce distress.

COVID-19 IN OTHER IMMUNOCOMPROMISED POPULATIONS

In a large registry (COVID-19 and Cancer Consortium) of 928 cancer patients with confirmed SARS-CoV-2 infection, the factors that were associated with increased 30-day mortality were increased age, male sex, comorbidities, smoking, and having active cancer. Type of cancer or chemotherapy was not associated with mortality.[116] Another prospective observational study of COVID patients with active cancer and symptomatic COVID-19 reported mortality of 28%. Risk of death was associated with advancing age, male sex, and presence of comorbidities, such as hypertension and cardiovascular disease. There was no significant effect of chemotherapy, immunotherapy, or radiation therapy on mortality.[117]

In a recent report from COVID-19 Global Rheumatology Alliance physician registry, of 2869 people with COVID-19 on disease-modifying antirheumatic drugs, 21% required hospitalization and 5.5% died. Patients on rituximab or JAK inhibitors had higher rates of hospitalization and deaths compared with tumor necrosis factor (TNF)-α inhibitors.[118] An international registry (SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion - Inflammatory Bowel Disease) to record outcomes of COVID-19 in patients with inflammatory bowel disease of 525 patients, 31% were hospitalized and 3% died. Risk factors for severe COVID-19

were increased age, greater than 2 comorbidities, and use of systemic steroids. Use of TNF-α inhibitors was not associated with severe disease.[119] Another study from the same registry, with 1400 patients, showed that thiopurine monotherapy and combination of TNF-α antagonists with thiopurine monotherapy had higher risk of severe COVID-19 compared with TNF-α monotherapy.[120]

A case series of 7 immunocompromised patients (5 with common variable immunodeficiency [CVID] and 2 with agammaglobulinemia) described mild symptoms in agammaglobulinemia compared with severe disease in CVID patients; 1 patient died and 3 required ICU admission.[121] In another report of 10 patients with CVID from New York City, only 1 patient was hospitalized and none died. All these patients were on regular immunoglobulin replacement.[122] Pre-exposure and postexposure prophylaxis should be prioritized for any of these groups at risk of poor vaccine response and higher risk of disease progression as well as prioritized for early treatment of infection with mAbs and/or antivirals.

SUMMARY

COVID-19 has had a major impact on the SOT population. Although developed policies and practices have been developed for better management during this pandemic, there still is a need for better preventive measures due to the depressed immune response in this vulnerable population. There also is a need for better therapeutic agents for management of this infection. There still are some uncertainties about some practices, such as management of immunosuppression, vaccine responses, and role of immunomodulators, which need to be studied.

CLINICS CARE POINTS

- Three-dose primary series of vaccination and a booster, along with masking, social distancing, and avoiding large indoor crowds, are recommended for all immunocompromised patients to prevent severe COVID-19 infection.
- Anti–SARS-CoV-2 mAbs use can be considered for pre-exposure and postexposure prophylaxis and for early treatment in high-risk patients who are not expected to have developed an antibody response despite having received appropriate vaccine series.
- The use of nonlung organs from SARS-CoV-2–positive donors may be considered; however, more robust data are needed to evaluate the safety and transmission.

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