Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Revised Guidelines for Coronavirus Disease 19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients (August 2022)

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A B S T R A C T

This document is intended as a guide for diagnosis and management of Coronavirus Disease 2019 (COVID-19), caused by the virus SARS-CoV-2, in adult and pediatric HCT and cellular therapy patients. This document was prepared using available data and with expert opinion provided by members of the (ASTCT) Infectious Diseases Special Interest Group (ID-SIG) and is an update of pervious publication. Since our original publication in 2020, the NIH and IDSA have published extensive guidelines for management of COVID-19 which are readily accessible (NIH Guidelines , IDSA Guidelines). This update focuses primarily on issues pertaining specifically to HCT/cellular therapy recipients. Information provided in this manuscript may change as new information becomes available.

PREFACE TO THE UPDATE

Since the declaration of the Coronavirus disease 2019 (COVID-19) pandemic more than 2 years ago, there have been significant therapeutic and preventative advances in the use of vaccines, antivirals, and monoclonal antibodies (mAbs) for prophylaxis and treatment. There has also been a dramatic decrease in COVID-19-related complications and mortality. COVID-19 testing has become widely available and incorporated in institutional guidelines. Prompt diagnosis of COVID-19 is instrumental for early treatment and isolation of patients to prevent spread in the community. Prevention of COVID-19 through vaccination is the most well-supported strategy to reduce COVID-19 incidence and/or severity, even in patients who may not be able to mount an adequate humoral response. For patients who are unlikely to have protective immunity or who cannot receive COVID-19 vaccines, a combination of mAbs (tixagevimab and cilgavimab [Evusheld]) is currently recommended, as long as it maintains neutralizing activity against circulating variants.

Treatment of COVID-19 has shifted from the inpatient to the outpatient setting with the availability of oral antiviral agents and mAbs. For hospitalized patients, detailed guidelines

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have been developed by the National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA). As acute mortality from COVID-19 has declined, persistent COVID-19, characterized by relapsing or progressing respiratory symptoms and persistent viral RNA positivity, has emerged as a challenge [1–4]. There has been a transformation in healthcare delivery with the incorporation of telehealth into our practice, and masking, handwashing, and social distancing have been woven into the social framework for the foreseeable future.

INTRODUCTION/SCOPE

This document is intended as a guide for diagnosis and management of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, in adult and pediatric hematopoietic cell transplant (HCT) and cellular therapy recipients. The document was prepared using available data and with expert opinion provided by members of the American Society of Transplantation and Cellular Therapy (ASTCT) Infectious Diseases Special Interest Group (ID-SIG) and is an update of a previous publication [5]. Specific practices may vary depending on local epidemiology and state and federal guidelines. Since our original publication in 2020, the NIH and IDSA have published extensive guidelines for management of COVID-19 that are readily accessible (NIH Guidelines, IDSA Guidelines). This update focuses primarily on issues pertaining specifically to HCT/cellular therapy recipients. The information provided in this article may change as new information becomes available.

COVID-19 PREVENTION

Vaccines

COVID-19 vaccines remain the cornerstone for prevention of severe illness, hospitalization, and death from SARS-CoV-2 infection. Our understanding of vaccine responses in immunocompromised patients has improved, leading to revised schedules and changes in the number of doses needed (Centers for Disease Control and Prevention [CDC] Vaccination in Immunocompromised). The ASTCT, National Marrow Donor Program (NMDP), and American Society of Hematology (ASH) have continued to engage with the CDC to better understand and communicate changes in vaccination schedules and types reflecting our better understanding of vaccine responses in immunocompromised patients (https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients).

Responses to COVID-19 vaccines are more likely to be blunted in HCT or cell therapy recipients compared with healthy individuals [6]. However, despite the scarcity of data, the high level of protection afforded to those vaccinated in the clinical trials, and the overall safety of the vaccine in clinical trials and post-emergency use authorization (EUA) experience, the ASTCT and ASH strongly support vaccination of this vulnerable patient population along with their caregivers, family members, and household contacts.

Passive Immunization

For patients who are unlikely to mount protective immunity or cannot receive COVID-19 vaccines, the combination of monoclonal antibodies (mAb) tixagevimab and cilgavimab (Evusheld) is presently recommended as long as it retains activity against circulating variants [7] (see Section IV, B.3) (FDA PrEP).

DIAGNOSTIC CONSIDERATIONS

Key Updates

- Timely diagnosis of COVID-19 is essential to ensure rapid treatment and limit transmission.
- Polymerase chain reaction (PCR) assays, either single-target or multiplex and with or without other respiratory viruses, are more sensitive than antigen-based testing and may be used on nasal, nasopharyngeal (NP), and lower respiratory specimens.
- Serologic tests are available for SARS-CoV-2 nucleoprotein (Np) and spike protein (Sp) IgG. HCT/cell therapy recipients may not mount IgG to natural infection or vaccination. The immunologic correlates of protective immunity to vaccination have not been established.

With ongoing community prevalence and transmission of COVID-19, any patient with exposure to a known case of COVID-19 or with symptoms compatible with COVID-19 should be tested for SARS-CoV-2. Patients with a known exposure who are asymptomatic at initial testing should be retested between 3 and 7 days after the exposure (CDC Postexposure Testing).

PCR tests are available with SARS-CoV2 as a single target or multiplexed with other respiratory pathogens. Antigen testing has overall lower sensitivity compared with PCR, especially with emerging variants, and the yield is highest at 4 days after symptom onset or on consecutive tests [8,9]. For patients with COVID-19-like illness, a PCR test on an upper respiratory sample should be sought even if an antigen test is negative [10,11]. The diagnostic yield for other sample types, including oropharyngeal, anterior nasal, mid-turbinate nasal, and saliva, may be comparable or lower [12,13].

A. In patients without SARS-CoV-2 detected in the upper respiratory tract but with clinical symptoms of lower respiratory tract infection (LRTI)—shortness of breath, hypoxia, tachypnea—chest imaging should be obtained to evaluate for LRTI. Workup for other etiologies (viral, bacteria, fungal) should be considered as clinically indicated.
   1. A single NP-negative test, especially an antigen test in the setting of high clinical suspicion, should be interpreted with caution, and short-interval repeat testing should be considered. Testing of a lower respiratory sample, such as bronchoalveolar lavage (BAL) fluid, should be considered [14].

B. Routine BAL is not recommended if a patient tests positive for SARS-CoV-2 on a NP swab unless a coinfection is suspected. If chest imaging is abnormal and in patients for whom it is clinically indicated (eg, those receiving invasive mechanical ventilation), an endotracheal aspirate or BAL sample should be collected and tested for SARS-CoV-2 and for possible other copathogens.

C. Prolonged viral shedding: Patients with hematologic malignancies and HCT/cellular therapy recipients may remain positive for SARS-CoV-2 by PCR longer compared with the general population [15,16]. Prolonged PCR positivity can reflect either nonviable viral RNA shedding or active infection with viable virus; the latter has been recovered up to 61 days after symptom onset in HCT recipients [17–20]. The use of cycle threshold (Ct) values as a proxy for viral load to guide transplantation-related decisions has been discouraged by the IDSA and the Association of Molecular

Table 1
Summary of Recommendations for Pre-Transplantation Evaluation of HCT and Cellular Therapy Recipients and Donors for SARS-CoV-2

SARS-CoV-2 Infection/Exposure Status		Recommendations
Recipient	Exposure to a confirmed COVID-19 case but asymptomatic*	Defer for 14 days.† If early infusion is desired, retest at 5-7 days and proceed if test is negative with absence of symptoms.
	Positive SARS-CoV-2 assay	If asymptomatic: defer infusion for at least 14 days. Consider early infusion if patient remains asymptomatic.‡ If symptomatic: defer infusion until clinical recovery and at least 14-20 days from a positive test. A negative SARS-CoV-2 PCR is not a prerequisite before transplantation given prolonged shedding.‡
Donor§	Exposure to a confirmed COVID-19 case but asymptomatic*	Symptom monitoring for 5-7 days; if patient remains asymptomatic, retest and if negative, proceed. Refer to local policy regarding the need for SARS-CoV-2 PCR testing.
	Positive SARS-CoV-2 assay	If asymptomatic: defer for 5-7 days, then proceed. If symptomatic: defer until clinical improvement (no fever for 24 hours) and at least 7 days from a positive test, whichever is longer.†

Local institutional polices vary in their screening procedures based on COVID-19 community levels and urgency of transplantation.
* Close contact to COVID-19 occurs when an individual is within 6 feet or less of someone with COVID-19 symptoms for at least 15 minutes regardless of mask wearing.
† Duration can be shortened for those who require immediate transplantation, weighing risks and benefits.
‡ For those with prolonged shedding and in need of immediate transplantation, can proceed with transplantation on a case-by-case basis.
§ Donors should adhere to good practice measures (masks wearing, hand hygiene, social distancing) during the 14 days period prior to donation

Pathology owing to a lack of standardization and discrepant results regarding its clinical utility [11]. The risk of transmission from extended shedding of viable virus remains unknown.

D. COVID-19 serology: Several serologic assays are available to assess different antibodies (IgG/IgM). Currently available tests are for Np IgG and Sp IgG. The presence of antibodies to Np reflects past infection. In contrast, antibodies to Sp may reflect past infection or (active or passive) immunization. The CDC has provided interim guidelines for COVID-19 antibody testing that can help clarify the interpretation of the different types of tests available [21]. Patients with a hematologic malignancy and those undergoing HCT or cellular therapy may not be able to mount effective humoral immunity in response to natural infection and/or SAR-CoV-2 vaccines [22–24]. Protective titers, waning of antibody response, and durability of immunity remain unknown. The IDSA and NIH do not recommend relying solely on serologic testing for diagnosis of SARS-CoV-2 infection [25,26].

Routine postvaccination serologic testing should not be used to guide decisions regarding primary and secondary preventive strategies (eg, mAb use). At present, the immunologic correlates of protection, such as antibody titer threshold, are not well defined.

PRETRANSPLANTATION HCT AND CELLULAR THERAPY CANDIDATES AND DONOR CONSIDERATIONS

Key *Points*

- Test-based or time-based approaches have been used for clearing COVID-19-recovered HCT and cellular therapy candidates and donors.
- The optimal approach must be individualized, taking into consideration the urgency of transplantation/cellular therapy as well as clinical and other considerations, such as severity of illness, therapeutics, and circulating variants.
- The long- term outcomes of COVID-19-recovered HCT recipients are yet to be determined.

As of January 2022, CDC guidelines recommend extending isolation to 20 or more days for immunocompromised patients and using a test-based strategy requiring 2 consecutive negative results. Given the known prolonged viral shedding in this population, we suggest an alternative approach for ending isolation that relies on significant clinical improvement and at least 14 to 20 days from a positive test. Decisions related to proceeding with HCT or cellular therapy should be individualized on a case-by-case basis while weighing the risks and benefits of delaying therapy and consequently risking underlying disease relapse and/or progression.

Based on our prior experience with other respiratory viruses, such transplantation-related characteristics as conditioning regimen type, donor and graft type, graft manipulation, and graft-versus-host disease (GVHD) prophylaxis can impact host immune responses and recovery from SARS-CoV-2 infection. There are no specific recommendations favoring one type of conditioning or GVHD prophylaxis strategy over the other. Multiple studies have shown that age and a shorter time from transplantation to COVID-19 infection are associated with poor outcomes [1,4,27]. For other respiratory viruses, the presence of LRTI and myeloablative conditioning are associated with an increased risk of post-HCT complications [28]. In a recent systematic review, a higher performance status was associated with decreased mortality in HCT recipients acquiring COVID-19 at all stages following transplantation (hazard ratio, .83; 95% confidence interval [CI], .74 to .93; P = .001) [29]. Based on our expert opinion and clinical experience in managing COVID-19 in this population, we provide a summary of recommendations on evaluating HCT and cellular therapy candidates in Table 1.

SARS–CoV–2 Screening of Asymptomatic HCT and Cellular Therapy Candidates

1. Given the negative consequences of COVID-19 on post-transplantation or post-cellular therapy outcomes and the unpredictable virulence of the circulating SARS-CoV-2 strains [4,27,30], it is currently encouraged to screen candidates for SARS-CoV-2 within 72 hours before receipt of conditioning or lymphodepleting regimens. The optimal test timing depends on the level of SARS-CoV-2 community transmission and testing turnaround time, which can vary by center.

2. HCT and cellular therapy candidates and their caregivers should practice good hygiene, social distancing, and protective masking in public and should avoid nonessential travel, crowds, and large group gatherings.
3. In HCT and cellular therapy candidates meeting the CDC's definition of SARS-CoV-2 exposure, procedures including peripheral blood stem cell mobilization, bone marrow (BM) harvest, T cell collection, and conditioning/lymphodepletion should be deferred for 14 days from the day of last contact. Exposed patients should be closely monitored for the development of symptoms and can be retested with SARS-CoV-2 PCR at 5 to 7 days. If the test is negative and the patient remains asymptomatic, transplantation can proceed. A shorter duration can be pursued on a case-by-case basis in patients needing immediate transplantation. No currently available antiviral or mAb is approved for postexposure prophylaxis; however, if authorized, mAb prophylaxis should be provided.
4. In those patients who remain asymptomatic but SARS-CoV-2 PCR-positive, the recommendation is to defer HCT or cellular therapy for 14 days. However, if early infusion is desired, retesting at 5 to 7 days and then proceeding if the test is negative is an option as long as the patient remains symptom-free.

HCT and Cellular Therapy Candidates with Active Respiratory Symptoms

1. HCT and cellular therapy candidates with symptoms of an acute respiratory tract infection should be tested for respiratory viruses, preferably by multiplex respiratory viral PCR, including SARS-CoV-2. Short-interval retesting is recommended for patients with initial negative PCR results.
2. If SARS-CoV-2 is detected, early treatment with antivirals or variant-specific mAb should be given in accordance with the latest Food and Drug Administration (FDA) recommendations. Deferral of HCT or cellular therapy is recommended for at least 14 days and until clinical improvement is evident (Table 1). Procedures including peripheral blood stem cell mobilization, BM harvest, T cell collection, and conditioning/lymphodepletion should be deferred for at least 14 days from a positive test and until the patient is clinically improved or asymptomatic.
3. Prolonged viral shedding is a known phenomenon of SARS-CoV-2 in both the general population and the immunocompromised population. RNA detection by PCR can outlast the presence of replication-competent virus, and thus the requirement for PCR clearance prior to treatment should be balanced with the urgency of proceeding with transplantation in clinically recovered individuals [20]. A negative SARS-CoV-2 PCR is not a pre-HCT/cellular therapy prerequisite in those who have fully recovered form COVID-19 unless clinically indicated. In a large multicenter study of both autologous and allogeneic HCT recipients, the median time to viral clearance was 24 days, and the longest was 210 days [3]. Transplantation candidates who are clinically recovered without evidence of lower airway involvement at the time of HCT or cellular therapy and are at least 14 to 20 days from diagnosis can pursue transplantation procedures at designated areas according to transplantation center practices/polices.
4. Persistent dry cough, fatigue, and loss of smell and taste may last for weeks or months after clinical recovery. Institutional isolation policies should be followed for clinically recovered patients with persistent SARS-CoV2 RNA positivity.
5. In patients recovering from COVID-19, consider pretransplantation evaluation by infectious diseases, cardiology, and pulmonary consultants to assess cardiopulmonary status with a cardiac workup, chest computed tomography scan, and pulmonary function tests as clinically appropriate.

Donor-Related Issues

Multiple studies have reported detection of SARS-CoV-2 in blood, associated primarily with symptomatic cases; however viremia is transient and low level, with no evidence of clinically significant viral transmission via blood products [31–40]. Current American Association of Blood Banks guidelines and FDA guidelines do not recommend screening for SARS-CoV-2 in blood products [41,42]. Within 14 days prior to donation, donors should practice good hygiene, social distancing, masking in public, and avoidance of crowded places and large group gatherings.

Unrelated donors

There is no mandatory SARS-CoV-2 PCR testing requirement for all donors by the NMDP, especially for asymptomatic healthy donors. Transplantation/apheresis center screening policies vary by site and urgency of transplantation. For detailed guidelines and recommendations, we refer the reader to Updates for Donor, Apheresis/Collection and Recruitment Centers (bethematchclinical.org).

Related donors

a. Donors reporting close contact with a person diagnosed with COVID-19 should be monitored for 5 to 7 days and if remaining asymptomatic, may proceed with the donation.
b. Donors with SARS-CoV-2 detected in a respiratory sample should be managed based on their clinical status. If asymptomatic, isolate and defer the donation procedure for at least 5 days. If the donor becomes symptomatic, defer transplantation procedures until clinical improvement (no fever for 24 hours without antipyretics) and at least 7 days from a positive test, whichever is longer. Refer to local policy regarding the need for SARS-CoV-2 PCR testing. A shorter duration can be considered on a case-by-case basis and the urgency of transplantation.

TREATMENT CONSIDERATIONS

Key Points

- Treatment for symptomatic mild to moderate COVID-19 with antivirals or mAbs with activity against circulating variants should be started as early as possible after onset of symptoms.
- The optimal duration of therapy, sequential therapy, and combination therapy have not been studied in HCT/cellular therapy recipients. Treatment-related mutations are a concern in immunocompromised patients with persistent high-level viral replication.

Treatment recommendations have been published [43] (IDSA Guidelines; NIH Guidelines), and these guidelines are continually updated as additional data become available. Given the lack of data in HCT and cellular therapy recipients, treatment type and timing should be considered after a careful

review of drug interactions, drug toxicities, and overall level of immunosuppression. Additional information on drug toxicities and drug-drug interactions can be found in the ASTCT Pharmacy Special Interest Group guidance [44].

Antiviral Therapy

Remdesivir (Veklury)

The efficacy of remdesivir (RDV) against coronaviruses was first demonstrated in in-vitro and mouse studies of Middle East respiratory syndrome coronavirus and SARS-CoV [45,46] and in in-vitro models of SARS-CoV-2 [47]. On October 22, 2020, the FDA approved RDV for the treatment of COVID-19, with the most recent update recommending its use in hospitalized patients age ≥28 days weighing at least 3 kg or not hospitalized but at risk for progression to severe COVID-19 [48].

Data from the multinational, randomized, placebo-controlled ACTT-1 clinical trial of hospitalized patients (n =1062) with COVID-19 showed that those who received RDV had a significant reduction in time to clinical recovery compared with the placebo group (11 days versus 15 days) and a nonsignificant trend toward lower mortality (8% versus 11.6%) [49]. In contrast, data from the SOLIDARITY study [50] and the DisCoVeRy trial [51] failed to show any benefit, but both were open-label randomized controlled trials. Retrospective studies have shown mixed results [52,53]. More recently, Diaz et al. [54] showed a mortality benefit in patients receiving RDV versus patients receiving best supportive therapy.

The PINETREE study [55] of ambulatory patients within 7 days of diagnosis of COVID-19 who were randomized to 3 days of RDV versus placebo showed a RR reduction of 87% for hospitalization (.7% hospitalization on the RDV arm versus 5.3% on the placebo arm). These findings suggest that RDV might be beneficial in a subset of patients presenting early in the course of mild or moderate infection.

RDV is administered only via the i.v. route, which poses a challenge to centers without an outpatient biocontainment unit or infusion area. Main side effects reported in trials have included gastrointestinal symptoms, infusion reactions, abnormal liver enzymes, and possible nephrotoxicity, among others. Drug-drug interactions have not been fully elucidated; however, caution is advised against use with other strong CYP3A4 inducers, as they may reduce RDV levels.

The duration of treatment varies from 3-day courses in the outpatient setting (for mild to moderate COVID-19 illness), to 5 to 10 days for hospitalized patients. A randomized trial showed the same benefit regardless of duration of therapy, 5 days or 10 days [56]; however, some have suggested longer and repeated courses for immunocompromised patients, particularly in those with protracted courses and in conjunction with passive immunotherapy [57]. Reports have correlated the use of RDV with temporal improvement of symptoms and increased Ct values, suggesting a benefit [58–61]. There is a growing concern about the emergence of resistance in those with prolonged SARS-CoV2 infection and repeated remdesivir courses; resistance has been documented in immunocompromised patients [62,63].

Nirmatrelvir/ritonavir (Paxlovid)

This combination of antiviral agents was granted EUA by FDA in December 2021 for mild to moderate COVID-19 with symptom onset <5 days for outpatients or inpatients admitted for reasons other than COVID-19. The EPIC-HR randomized controlled trial showed a lower incidence of hospitalization or death by day 28 in the treatment group compared with the placebo group ($P < .001$; risk ratio [RR] reduction, 89.1%) with a treatment duration of 5 days; all 13 deaths occurred in the placebo group [64]. Drug-drug interactions are a major concern, particularly in those patients receiving calcineurin inhibitors for GVHD prophylaxis. Recent case reports document that some patients who were treated with nirmatrelvir/ritonavir experienced rebound respiratory symptoms ("rebound COVID-19") 2 to 8 days after completing a 5-day course of nirmatrelvir/ritonavir [65,66]. The CDC has recently issued a Health Alert Network Health Advisory to update the public on the potential for COVID-19 rebound after nirmatrelvir/ritonavir treatment. Nirmatrelvir/ritonavir has EUA approval for patients age ≥12 years.

Molnupiravir (Lagevrio)

The FDA issued an EUA for molnupiravir in December 2021 based on the results from the MOVe-OUT trial, which randomized at-risk nonhospitalized patients with COVID-19 and at <5 days after symptom onset to 5 days of treatment versus placebo [67]. In the modified intention-to-treat analysis, 48 patients (6.8%) in the treatment group versus 68 (9.7%) in the placebo group met the primary end point of hospitalization or death (RR, 31%; 95% CI, .48 to 1.01); 1 death occurred in the treatment group, and 9 deaths occurred in the placebo group. Molnupiravir's mechanism of action has raised concerns about the emergence of resistant variants, and thus it is not currently used as first-line therapy. However, a phase 2a trial did not report the emergence of resistance despite nucleotide substitutions, and an infectious virus was not isolated from participants receiving 400 mg or 800 mg of molnupiravir, compared with 11.1% of placebo recipients [68]. Molnupiravir has EUA approval for patients age ≥18 years.

Antibody-Mediated Therapy

Monoclonal Antibodies

Therapeutic use. mAbs should be considered for recipients of HCT/cellular therapy who are age ≥12 years and meet all the eligibility criteria specified in the EUA. These agents should be administered as early as possible after confirmed infection and within the time limits specified in the EUA. When local availability of mAbs and resources for administration are limited, priority should be given to individuals deemed at highest risk for severe COVID-19, including patients with recent or planned receipt of autologous or allogeneic HCT or chimeric antigen receptor T cell (CAR-T) therapy.

Five monoclonal antibodies have been granted EUA from the FDA since November 2020 (Table 2). Bamlanivimab plus etesevimab, bebtelovimab, casirivimab plus imdevimab, and sotrovimab are indicated for the treatment of mild to moderate COVID-19 in nonhospitalized adult and pediatric patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progression to severe disease and/or hospitalization based on clinical trial data [69–71].

The recommendations for the use of mAbs have been fluid, owing to changes in the dominance of circulating SARS-CoV-2 variants. In late December 2021, as B.1.1.529 (Omicron) became the ascendant variant in the United States, the use of bamlanivimab plus etesevimab and casirivimab plus imdevimab was no longer recommended, considering their decreased efficacy against the Omicron variant [72]. Instead, sotrovimab was recommended for treatment of mild to moderate COVID-19 during the Omicron surge, but its use was halted by the FDA in favor of bebtelovimab in early April 2022 owing to increases in the proportion of cases caused by the Omicron BA.2 subvariants. Bebtelovimab, the newest agent to have received EUA by the FDA, is reported to have neutralizing

Table 2
EUA Applications of Monoclonal Antibodies

Generic Name	Indication(s)	Adults	Pediatrics	Dose and Route of Administration	Comments
Bamlanivimab + etesevimab	Outpatient treatment	Yes	Yes, including neonates	(≥40 kg) 700 mg bamlanivimab and 1400 mg etesevimab as a single i.v. infusion (21-39 kg) 350 mg bamlanivimab and 700 mg etesevimab as a single i.v. infusion (13-20 kg) 175 mg bamlanivimab and 350 mg etesevimab as a single i.v. infusion (1-12 kg) 12 mg/kg bamlanivimab and 24 mg/kg etesesimab as a single i.v. infusion	06/25/21: national pause due to Gamma and Beta variants 10/21/21: resumption of use 01/24/22: national pause due to Omicron variant (including all subvariants)
	Postxposure prophylaxis	Yes	Yes, including neonates	See dose for outpatient treatment.	
Bebtelovimab	Outpatient treatment	Yes	Yes (≥12 yr and ≥40 kg)	175 mg bebtelovimab as a single i.v. infusion	
Casirivimab + imdevimab	Outpatient treatment	Yes	Yes (≥12 yr and ≥40 kg)	600 mg casirivimab and 600 mg imdevimab as a single i.v. infusion or as 4 SC injections	01/24/22: national pause due to Omicron variant (including all subvariants)
	Postexposure prophylaxis	Yes	Yes (≥12 ys and ≥40 kg)	600 mg casirivimab and 600 mg imdevimab as a single i.v. infusion or as 4 s.c. injections For individuals with ongoing exposure to SARS-CoV-2 for longer than 4 weeks and are not expected to have an adequate immune response to complete SARS-CoV-2 vaccination: 300 mg casirivimab and 300 mg imdevimab as a single i.v. infusion or as 2 s.c. injections once every 4 weeks for the duration of ongoing exposure	
Sotrovimab	Outpatient treatment	Yes	Yes (≥12 yr and ≥40 kg)	500 mg sotrovimab as a single i.v. infusion	04/05/22: national pause due to Omicron BA.2 variant (including all subsequent subvariants, BA.4 and BA.5)
Tixagevimab + cilgavimab	Pre-exposure prophylaxis	Yes	Yes (≥12 yr and ≥40 kg)	300 mg tixagevimab and 300 mg cilgavimab administered as 2 consecutive i.m. injections.* For patients who received 150 mg tixagevimab and 150 mg cilgavimab ≤3 months earlier, a second dose of 150 mg tixagevimab and 150 mg cilgavimab should be administered as soon as possible. For patients who received 150 mg tixagevimab and 150 mg cilgavimab >3 months earlier, a second dose of 300 mg tixagevimab and 300 mg cilgavimab should be administered. Timing of repeat dosing cannot be determined owing to uncertainty regarding which variant(s) will become dominant.	

* The recommended dose of tixagevimab plus cilgavimab was increased due to reduced neutralizing activity against the Omicron subvariants.

activity against a broad range of SARS-CoV-2 variants, including Omicron and its most recent subvariants BA.4 and BA.5. Newer agents are currently in development.

Pre-exposure prophylaxis. The combination of tixagevimab plus cilgavimab is authorized under EUA for pre-exposure prophylaxis in moderately to severely immunocompromised patients who may have an inadequate immune response to COVID-19 vaccination or those who are not able to be fully vaccinated with any available COVID-19 vaccines owing to a documented history of severe adverse reaction to a COVID-19 vaccine or its components [7]. However, tixagevimab plus cilgavimab should not be prioritized over COVID-19 vaccination in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response. Although it is recommended to wait 2 weeks after COVID-19 vaccination to give tixagevimab plus cilgavimab, there are no timing restrictions for COVID-19 vaccine administration after receipt of tixagevimab plus cilgavimab.

The FDA has issued revisions in the dosing of tixagevimab plus cilgavimab in response to data indicating that a higher dose may be more protective against the Omicron subvariants BA.1 and BA.1.1 than the originally authorized dose and also may retain activity against BA.2, BA.2.12.1, BA.4, and BA.5 subvariants (Table 2) [73]. Redosing is recommended every 6 months in patients who need ongoing protection. In addition, there is a need for ongoing rapid surveillance, given data suggesting that selective pressure can lead to antibody-resistant viral variants in patients previously treated with mAbs [74,75].

Convalescent plasma (CP)

Although the REMAP-CAP investigators did not find meaningful improvement in organ support-free days in critically ill adults with COVID-19, many of whom were immunocompetent, a subgroup analysis of 126 patients with immunodeficiencies suggested a possible benefit (odds ratio, 1.51; 95% CI, .80 to 2.92), although this was not statistically significant [70]. However, this result was generated prior to the Omicron surge, and the current supply of CP was not generated from donors who recovered from Omicron infection. Thus, the role of CP is limited at this time.

Given the conflicting data on the benefit of CP in immunocompromised patients, the NIH COVID-19 Panel does not recommend either for or against the use of high titer COVID-19 CP for the treatment of COVID-19 in patients with impaired humoral immunity (NIH COVID-19 Convalescent Plasma).

Intravenous immunoglobulin (IVIG)

Currently available IVIG products may contain variable quantities of antibodies against circulating variants at the time of collection; however, routine IgG products should not be used as COVID-19 therapeutic agents. The national COVID-19 Treatment Guidelines Panel recommends against the use of non-SARS-CoV-2-specific IVIG for the treatment of acute COVID-19, except in clinical trials [69]. HCT and cellular therapy recipients who require use of IVIG for other purposes should continue to receive it as clinically indicated.

Immunomodulatory and Anti-Inflammatory Agents

A subset of patients with severe COVID-19 display a unique pattern of inflammatory response with multiorgan dysfunction. Variable presentations, such as hyperinflammatory response, immune dysregulation, macrophage activation syndrome, hemophagocytic lymphohistiocytosis, and cytokine release syndrome, have been described [76,77]. Other aspects of innate, adaptive immune response signaling cascade and complement pathway activation also might be implicated in the pathogenesis of COVID-19 [78].

Corticosteroids

Results from a large randomized open-label controlled trial, RECOVERY, of dexamethasone 6 mg daily for up to 10 days (n = 2104) demonstrated a reduction in 28-day mortality compared to standard of care (n = 4321) of 22.9% in patients on dexamethasone and 25.7% in patients allocated to usual care (adjusted RR, .83; 95% CI, .75 to .93) [79]. Although the benefit was across the board, the effect was more pronounced in patients on mechanical ventilation at the time of randomization (n = 1007). The use of corticosteroids in patients with severe disease (requiring oxygen support or mechanical ventilation) is recommended. In contrast, routine use of corticosteroids is not recommended in patients with mild or moderate disease who do not require supplemental oxygen.

Other immunomodulatory therapies

Multiple anti-inflammatory/immunomodulatory drugs, including anti-interleukin (IL)-6 (tocilizumab and sarilimab), anti-IL-1 (anakinra), and Janus kinase inhibitors (baricitinib, tofacitinib, and ruxolitinib), have been investigated. Hospitalized patients receiving dexamethasone who exhibit worsening inflammation and rapid progression in their oxygen requirement may benefit from adjunct therapy with one of several agents, including oral baricitinib [80,81] or i.v. tocilizumab [82,83]. If either of these is not available, tofacitinib can be used instead of baricitinib and i.v. sarilimab can be substituted for i.v. tocilizumab [83,84]. The combination of baricitinib and i.v. tocilizumab is not recommended, as it may result in unnecessary deleterious immunosuppressive effects, leading to additional infectious complications [69]. Caution should be practiced when extrapolating the effects of these agents in HCT and cellular therapy recipients, owing to their underrepresentation in these clinical trials, the potential enhancement of immunosuppression, and unanticipated infectious and noninfectious adverse events. A list of immunomodulatory agents and their characteristics can be found at Immunomodulators: COVID-19 Treatment Guidelines (nih.gov).

There are no current recommendations regarding specific antimicrobial prophylaxis when immunomodulatory agents are used in HCT and cellular therapy recipients specifically for COVID19. Infection-specific screening strategies and antimicrobial prophylactic measures should be individualized based on epidemiologic and underlying disease risk factors, as well as serologic status. The use of immunomodulators for COVID19 in patients with uncontrolled bacterial, fungal, or viral infections is not recommended. Given the lack of supporting data, the use of any combination immunomodulatory therapy for COVID-19 treatment, such as baricitinib plus tocilizumab, other Janus kinase inhibitors (eg, ruxolitinib), siltuximab, fluvoxamine, and inhaled corticosteroids outside the setting of a clinical trial is not recommended.

Combination Therapy

Inhibiting several steps in viral replication for other RNA viruses, such as human immunodeficiency virus and hepatitis C virus, has proven to be an effective approach. Although no antiviral drug combination against SARS-CoV-2 has been tested clinically, various antiviral combinations have been studied in vitro. Molnupiravir-based combinations have shown increased antiviral activity against SARS-CoV-2 in vitro; additive effects were noted when combining nirmatrelvir/

ritonavir with remdesivir and molnupiravir [85,86]. Other novel agents, such as brequinar and pyrazofurin, also have shown synergy when combined with molnupiravir and remdesivir [86]. Although not yet studied, the additive effects of combined antiviral therapy may prove particularly beneficial in immunocompromised patients at high risk of prolonged shedding/viral replication and at risk for emergence of resistance. Routine antiviral combination is not recommended at present, however, given the lack of solid data in this setting.

SURVEILLANCE AND PREVENTION OF OPPORTUNISTIC INFECTIONS

There have been many reports of opportunistic infections after COVID-19, particularly in patients with underlying immunocompromising conditions.

Fungal Infections

COVID-19-associated pulmonary aspergillosis (CAPA) was described early in the pandemic, particularly in patients treated with steroids and those receiving mechanical ventilation [87,88]. Rates of CAPA as high as 33.3% have been reported, with up to 80% mortality in case series [89,90]. Recently published diagnostic criteria for CAPA may help define the true incidence [91]. Antifungal prophylaxis could be considered for high-risk patients.

Other fungal infections post-COVID-19 have been reported, including invasive candidiasis [92,93], cryptococcosis [94,95], *Pneumocystis jirovecii* [96,97], and, even more concerning, mucormycosis [98].

Viral Infections

Immunocompromised HCT/cellular therapy recipients may have coinfections with several respiratory viruses; thus screening for other respiratory viruses is recommended during the initial assessment (Section II.A), especially with the ending of mask mandates in the general community and resultant resurgence of the usual community respiratory viral pathogens.

Infection Prevention Considerations

The IDSA and CDC have developed national guidelines for infection prevention of COVID-19 in healthcare systems [99,100]. HCT and cellular therapy recipients are vulnerable patients at increased risk for complications from SARS-CoV-2 and for healthcare-associated COVID-19 within units and clinics in which cohorting of high-risk populations is common. The institution of preventive measures to reduce transmission is of utmost importance; such measures include:

1. Appropriate use of personal protective equipment (PPE) by healthcare workers (HCWs) and patients
2. Symptom screening of patients, HCWs, and visitors and early isolation of symptomatic individuals
3. Early testing
4. Effective HCW vaccination programs.

Efforts to prevent transmission should focus on all key measures, with recommendations that take into consideration the level of community spread and the risk of transmission from mildly symptomatic or asymptomatic individuals. SARS-CoV-2 is transmitted primarily through small and large respiratory droplets [101–103]. Long-range transmission by small-particle aerosols can occur, which has informed the current CDC guidance for transmission-based precautions.

Center Readiness

For future surges, HCT centers should be ready to rapidly implement COVID-19 protocols during community surges. The CDC's most recent community risk levels should be used by healthcare facilities to implement a tier-based approach that can be used to guide:

- Universal PPE practices
- Rapid scaling of COVID-19 testing availability and protocols for asymptomatic testing (eg, before procedures)
- Symptom screening and triage
- Visitor restriction policies
- Environmental controls and care models for hospitalized patients
- Resources for outpatient COVID-19 management (infusion centers)
- Preparation for measures to maintain workforce integrity during surges: testing, return to work policies, special considerations for HCWs in HCT units
- Remote care
- Vaccination program for HCWs.

Owing to the unique characteristics of SARS-CoV-2, including asymptomatic transmission, prevention of SARS CoV-2 in recipients of HCT or cellular therapies should be more stringent than prevention of other common community respiratory pathogens. The key recommendations are as follows:

1. Universal precautions: A face mask is recommended in all clinical areas regardless of community COVID-19 levels. In addition, during periods of COVID-19 surges, universal eye protection should be implemented. For aerosol-generating procedures, universal N-95 respirator use is recommended.
2. Confirmed or suspected COVID-19: The patient should be placed in a negative-pressure room if available, with airborne precautions. HCWs should wear a gown, gloves, an N-95 respirator, and eye protection.
3. Suspected COVID-19: The patients should be placed on droplet precautions, and eye protection should be worn. Aerosol generating procedures should be minimized, but when necessary, N-95 respirators should be worn by HCWs.
4. Staff-staff interaction on campus: Limit staff congregating during breaks and handoffs. Consider policies around safe carpooling and use of public transportation.

Prevention, Symptom Screening, and Testing Recommendations for Patients

1. Universal screening of patients at single entry points for respiratory symptoms or close contact with COVID-19 is imperative.
2. Follow PPE and testing protocols as outlined above.
3. Patients and caregivers should be masked at all times in the healthcare environment.
4. Policies and protocols for removing patients from droplet/contact (or airborne/contact) isolation should be developed with Infection Prevention experts. This remains an area of ongoing discussion both nationally and at individual centers. Options include:
   a. Viral clearance, as documented by 2 negative SARS-CoV-2 respiratory PCR samples (eg, NP, anterior nasal, saliva) obtained ≥24 hours apart.

b. As of January 14, 2022, CDC guidelines recommend a time-based strategy for severely immunocompromised patients in which discontinuation of isolation precautions can be considered if at least 20 days have passed since the first day of symptoms or a positive viral test (in asymptomatic patients) [104]. There are insufficient data on the relationship between prolonged detection of virus by PCR and viable virus and transmission potential in highly immunosuppressed patients, and thus the precise minimum duration of isolation is unknown at this time.
c. There are insufficient data to guide clinical decisions about ending isolation based on Ct values (when/if available) in patients with prolonged SARS-CoV-2 positivity. Consultation with an Infectious Diseases specialist is recommended.

5. Policies and protocols for preprocedure, presurgery, preradiation therapy, and preadmission testing should be developed in coordination with subspecialty services and other stakeholders.
6. Telehealth visits should be considered when appropriate to limit in-person appointments.
7. Patients should be educated on COVID-19 and strategies for community prevention.
8. Criteria are needed for retesting previously positive patients when reinfection is suspected.

Symptom Screening, Testing, and Restriction Policies for Caregivers, Family, and Visitors

1. Universal screening of visitors at all entry points for symptoms or contact with a known case of COVID-19 is important.
2. Universal masking is required on entry to the healthcare environment.
3. Restricting primary caregivers on the inpatient units should be considered during periods of high community transmission, along with limiting the number of visitors and the time spent in the healthcare environment and restricting children age $<$12 years.
4. Signs, posters, and web-based portals are significant methods of educating and disseminating information to caregivers, visitors, and family members.
5. A visitor database should be maintained to facilitate contact investigations.

Environmental Controls

Recipients of HCT and cellular therapy should be housed in single rooms under positive pressure to primarily prevent fungal and respiratory viral infections. High-efficiency particulate air systems are standard in these single rooms.

Air systems

Positive pressure on HCT units is considered a potential but as-yet undefined risk for transmission. Centers must balance the risk of other major pathogens (eg, invasive mold) versus the risk of COVID-19 when deciding whether unit air flows should be modified. Most centers do not have the capacity to modify unit air systems, and there are limited numbers of negative-pressure rooms in clinic and hospital environments. Guidelines recommend using negative-pressure rooms for COVID-19 patients whenever available and to consider cohorting positive patients and staff providing care to COVID-19-positive patients within the unit to limit exposures if a dedicated unit is not available or feasible. Options to modify individual rooms with portable negative-pressure systems, mobile HEPA filtration equipment, and external ventilation can be considered but should be implemented with input from Infection Prevention experts and hospital engineering teams.

Physical distancing

Staff work rooms should be reconfigured however possible to allow for more physical distancing during periods of high community spread. Modifying waiting areas and community spaces (eg, conference rooms) to prevent close contact when possible in ambulatory areas or repurposing them to increase waiting room space should be considered. Well-ventilated spaces should be made available to staff for meal consumption.

Environmental cleaning

Policies to ensure appropriate room cleaning and agents used for cleaning rooms are considered sufficient to disinfect high-touch areas. Additional efforts to disinfect frequently touched surfaces, especially in high traffic areas such as waiting rooms, cafeterias, elevators, and other common spaces with EPA-registered hospital-grade disinfectants, should be considered. Supplementary decontamination with UV-C light devices, if available, may be considered, particularly for inpatient locations, procedure suites, and designated COVID-19 units.

Mandatory COVID-19 Vaccination

Institutions should strongly consider mandating COVID-19 vaccination for HCWs, or at least for HCWs who work on BM transplantation units.

FUTURE DIRECTIONS

Since the start of the COVID-19 pandemic, transplantation centers have had to adapt to a rapidly changing landscape. Masking, social distancing, and various forms of telehealth seem to be operative for the foreseeable future. The pandemic provided an impetus for discovery, innovation, and collaboration. Advances in mAb design and manufacturing capacity brought to the bedside several products, which were quickly superseded by emerging variants. Lessons learned from COVID-19 potentially can be applied to other respiratory viruses. Advances in adoptive T cell therapy were applied to generate COVID-19-specific T cells, with ongoing clinical trials for treatment of persistent COVID-19. Administration schedules for COVID-19 vaccines and mAbs are being optimized as our understanding of immunologic correlates of protection expands.

A number of questions remain pertaining to the use of antivirals in HCT/CAR-T recipients who were not included in large clinical trials of COVID-19 therapeutics. There is a lack of data pertaining to optimal doses, duration of treatment, combination or sequential treatment, and risk of antiviral resistance in this patient group. Long COVID-19 is a challenge, particularly in patients with dysregulated immunity, such as HCT/CAR-T recipients. The optimal management of long COVID-19 remains unclear, and the impact of early therapy in preventing long COVID-19 is yet to be determined. Answers to these and more questions will continue to be shaped by the evolution of the virus, our collective immunity, and current and future therapeutics.

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