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.

Biol Blood Marrow Transplant 26 (2020) 1983–1994

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Guideline

Guidelines for COVID-19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients

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Article history:
Received 22 July 2020
Accepted 22 July 2020

Key Words:
COVID-19
SARS-CoV-2
hematopoietic cell transplan
cellular therapy

A B S T R A C T

There are currently limited data on the epidemiology, clinical manifestations, and optimal management of Coronavirus Disease 2019 (COVID-19) in hematopoietic cell transplantation and cellular therapy recipients. Given the experience with other respiratory viruses, we anticipate that patients may develop severe clinical disease and thus provide the following general principles for cancer centers across the nation. These guidelines were developed by members of the American Society for Transplantation and Cellular Therapy Infectious Diseases Special Interest Group. Specific practices may vary depending on local epidemiology and testing capacity, and the guidance provided in this document may change as new information becomes available.

SCOPE

This document is intended as a guide for diagnosis and management of Coronavirus Disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, in adult and pediatric hematopoietic cell transplantation (HCT) and cellular therapy recipients. This document was prepared using available data and with expert opinion provided by members of the American Society for Transplantation and Cellular Therapy (ASTCT) Infectious Diseases Special Interest Group. The information provided herein may change as new information becomes available, including more data on epidemiology, clinical outcomes, and the efficacy of drug therapies, including clinical trial outcomes of novel therapeutics, especially data pertaining to transplant recipients or other immunocompromised patients. Updates may be available through the ASTCT website (www.astct.org). Additional guidance can be found in recent publications from the European Society for Blood and Marrow Transplantation [1] and the CAR T Cell Consortium [2].

DIAGNOSTIC CONSIDERATIONS IN HCT AND CELLULAR THERAPY RECIPIENTS

In the setting of known high community prevalence of COVID-19 or exposure to a known case of COVID-19, the following evaluations should be performed.

A. In any patient with upper or lower respiratory symptoms, perform PCR testing for SARS-CoV-2 in addition to multiplex PCR testing for other respiratory viruses from any respiratory sample obtained. Follow Centers for Disease Control and Prevention (CDC) recommendations for swab collection (https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html).
   1. Nasopharyngeal (NP) sampling should be performed preferentially over oropharyngeal sampling given preliminary data suggesting higher viral loads in nasal samples in early stages of illness [3]. In certain circumstances, other sample types, including anterior

Financial disclosure: See Acknowledgments on page e1991.
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https://doi.org/10.1016/j.bbmt.2020.07.027
1083-8791/

nasal, midturbinate nasal, oropharyngeal, or saliva, can be considered, and collection may be better tolerated.
2. Nasal washes are discouraged; however, in centers that use this method or if swabs are unavailable, washes can be done with appropriate personal protective equipment (PPE) in accordance with guidelines.

B. 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 to evaluate for LRTI should be considered.
1. Preliminary reports suggest the possibility of discrepancy between upper and lower respiratory tract specimen positivity [4], as has been reported with other respiratory viruses [5], and a longer time from symptom onset to clinical presentation.
2. A single negative test in the setting of high clinical suspicion should be interpreted with caution, and repeat testing of a lower respiratory sample, such as sputum, can be considered.

C. Routine bronchoalveolar lavage (BAL) is not recommended in patients testing positive for SARS-CoV-2 given the risk of transmission among health care workers (HCWs), 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), a lower respiratory tract endotracheal tube aspirate or BAL sample should be collected and tested for SARS-CoV-2. Copathogens should be evaluated and treated.

D. See testing recommendations below for HCT and cellular immunotherapy candidates and donors below.

E. Prolonged viral shedding: Patients with hematologic malignancies and HCT recipients may exhibit different viral dynamics and can remain positive for SARS-CoV-2 by PCR longer than the general population [6,7]. Prolonged RT-PCR positivity does not necessarily translate into ongoing active infection or presence of viable virus. Although prolonged PCR positivity has been reported in healthy individuals (30% positive at 4 weeks) [8], viable virus was recovered for only up to 9 days after symptom onset in mild to severe illness [9-11]. Among 108 individuals who tested positive by PCR after being negative, none had culturable virus present [12]. Data on how long immunosuppressed patients shed viable virus has not been evaluated but is expected to be prolonged compared with immunocompetent individuals. Information on SARS-CoV-2 viability in COVID-19–infected transplant recipients will be critical to develop recommendations for the duration of isolation precautions (see below).

F. COVID-19 serology: Several serologic assays are available to assess IgG/IgM responses to SARS-CoV-2 and identify current or past infection. Patients with hematologic malignancy and those undergoing HCT or chimeric antigen receptor (CAR) T cell therapy might not mount effective humoral immunity, and any serology results should be interpreted with caution. The US Food and Drug Administration (FDA) does not recommend serology as the sole basis of diagnosis of acute infection; however, serology can be used to supplement PCR testing in situations with high clinical suspicion. Cross-reactivity with other commonly circulating coronaviruses might occur with some commercial serologic tests. False-positive results also may occur from passive immunity transfer in patients receiving intravenous immunoglobulin (IVIG) therapy. Protective titers, waning of antibody response and durability of immunity remain unknown. The Infectious Diseases Society of America (IDSA) recently released a primer on COVID-19 serology addressing some of these concerns in general population [13]. Antibody testing should not be used for pretransplantation clearance or to guide isolation decisions, and routine serology testing is not recommended.

G. Routine serial PCR testing of asymptomatic inpatients and/or outpatients has been implemented at some centers and could be considered based on local epidemiology or in the evaluation of outbreaks. Recommendations may be updated as more data become available.

CONSIDERATIONS FOR EVALUATION BEFORE HCT OR CELLULAR THERAPY

Though data are limited regarding the impact of COVID-19 in HCT candidates, donors, and cellular therapy recipients, there is concern that COVID-19 could have a significant impact on post-transplantation or post-therapy outcomes. The following should be considered while weighing the risk of delaying or altering therapy against the risk of underlying disease progression. Figure 1 provides an overview of general principles to evaluate HCT and cellular therapy candidates.

HCT and Cellular Therapy Candidates

A. 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. If symptoms continue despite negative PCR results, consider repeat testing by multiplex respiratory viral PCR, including for SARS-CoV-2.

B. If SARS-CoV-2 is detected by PCR, HCT or cellular therapy procedures should be deferred. In patients with high-risk underlying malignancies, procedures including peripheral blood stem cell mobilization, bone marrow harvest, T cell collections, and conditioning/lymphodepletion should be deferred (14 days minimum) until the patient is asymptomatic and has at least 2 consecutive negative PCR tests $\geq$24 hours apart. RNA detection by PCR can outlast the presence of replication competent virus; therefore, the requirement for PCR clearance before treatment should be balanced against the urgency of proceeding with HCT in clinically recovered individuals.

C. In HCT and cellular therapy candidates with household SARS-CoV-2 exposure, procedures including peripheral blood stem cell mobilization, bone marrow harvest, T cell collections, and conditioning/lymphodepletion should be deferred for 14 days from the date of last contact. Exposed patients should be closely monitored for the development of symptoms, and if none, they should have 2 consecutive negative PCR tests $\geq$24 hours apart before proceeding with required procedures.

D. HCT and cellular therapy candidates should refrain from nonessential travel; practice good hygiene, social distancing, and mask-wearing in public; and avoid crowds and large group gatherings.

E. All HCT and cellular therapy candidates should undergo screening for SARS-CoV-2 infection by PCR in respiratory specimens before procedures and no more than 2 to 3 days before conditioning/lymphodepletion. Test turnaround time should be considered.

F. Interim treatment and/or longer deferral of definite therapy should be considered when feasible (eg, in multiple myeloma, germ cell tumors, consolidative transplants).

G. Consider pretransplantation evaluation by infectious disease, cardiology, and pulmonary consultants to assess

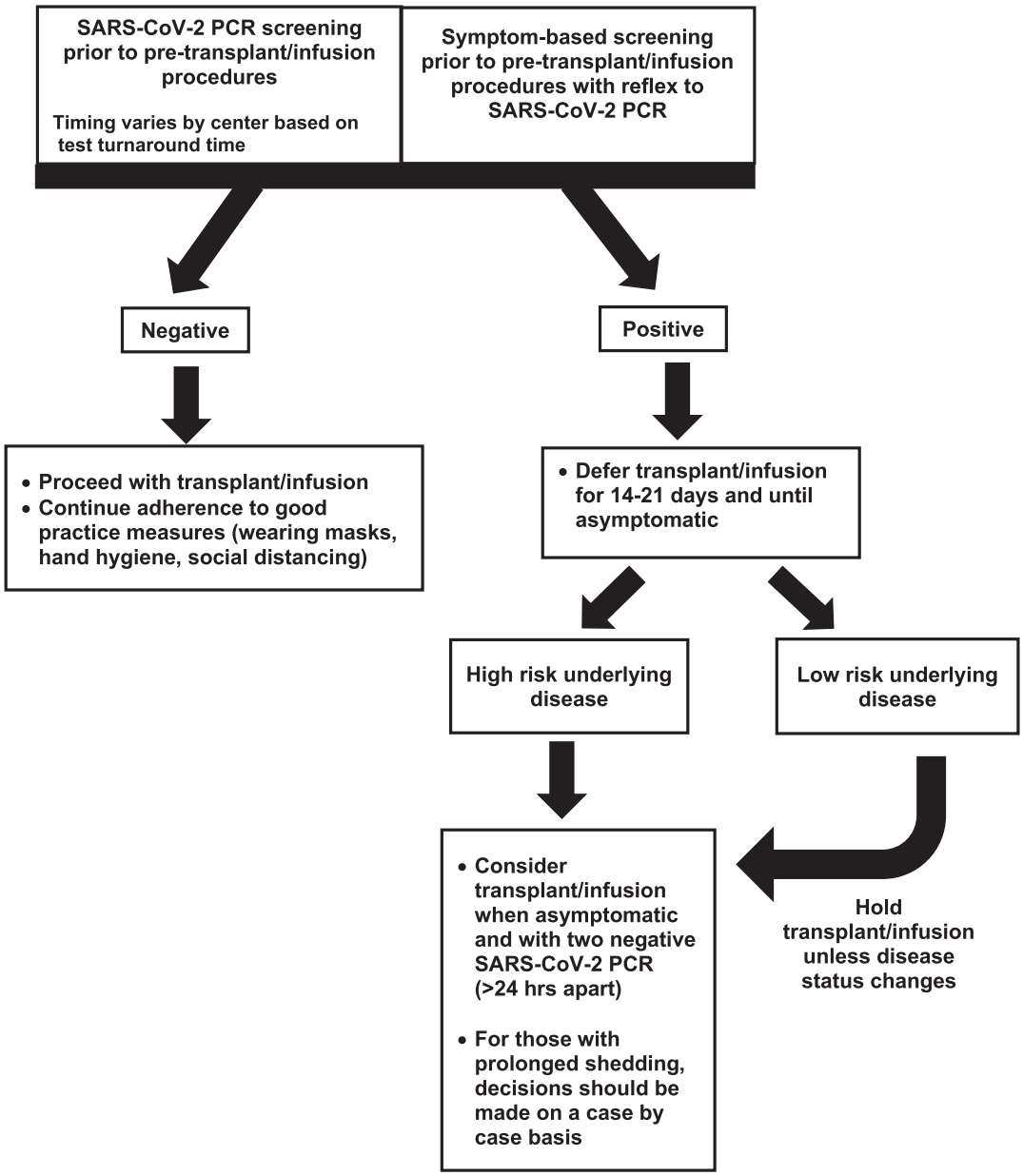

Figure 1. Evaluation of HCT and cellular therapy candidates.

cardiopulmonary status. Cardiac imaging, chest computed tomography scan and pulmonary function tests are recommended for patients recovered from COVID-19. Whether recovered patients are at increased risk for post-transplantation cardiopulmonary complications is unknown, and these patients should be carefully monitored.

HCT Donors

SARS-CoV and MERS-CoV have been detected in blood; however, there are no reported cases of transmission of these viruses through transfusion of blood products or cellular therapies [14]. SARS-CoV-2 has been detected in blood, but the duration of detection in the blood and clinical correlations are unclear [15]. A single case of a asymptomatic SARS-CoV-2–positive stem cell donor has been reported, with no adverse infection-related outcome in the recipient [16]. Current American Association of Blood Banks guidelines and FDA guidelines do not recommend screening for SARS-CoV-2 in blood products [17,18].

A. Donors with SARS-CoV-2 detected in a respiratory sample are considered ineligible to donate. However, an ineligible donor may be collected in certain situations. Refer to facility standard of practice for circumstances for use and documentation of urgent medical need and appropriate counseling on risks and benefits. Otherwise, consider donor eligibility if there is no history of severe respiratory disease and 28 days have elapsed since symptom resolution and since SARS-CoV-2 PCR in respiratory samples became negative. Specific circumstances for considering a donor eligible earlier than 28 days should be evaluated on a case-by-case basis.
B. Donors who had close contact with a person diagnosed with COVID-19 should be excluded from donation for at least 28 days. In individual circumstances, an asymptomatic donor may be considered eligible if respiratory samples are negative for SARS-CoV-2 by PCR. Donors should be closely monitored for COVID-19. Specific circumstances for

considering a donor eligible earlier than 28 days should be evaluated on a case-by-case basis.

C. Current recommendations for unrelated donors from the National Marrow Donor Program (NMDP) are available at https://network.bethematchclinical.org/news/nmdp/be-the-match-response-to-COVID-19/updates-for-transplant-centers-and-cooperative-registries/ Please refer to the NMDP guidelines for updated guidance.

D. If possible, ensure that an alternative stem cell source will be available. If multiple possible donors are available, choose a donor without risk.

E. During the 28 days before donation, donors should practice good hygiene, social distancing, and mask-wearing in public and avoid crowded places and large group gatherings.

INFECTION PREVENTION CONSIDERATIONS FOR HCT AND CELLULAR THERAPY RECIPIENTS

The IDSA has developed national guidelines for infection prevention of COVID-19 in healthcare systems [19]. HCT and cellular therapy recipients are unique populations that are at increased risk for complications from SARS-CoV-2 and for outbreaks within units and clinics in which cohorting of high-risk populations is common. Standard efforts to prevent transmission are key to prevention and include appropriate use of PPE among staff; symptom screening of patients, HCWs, and visitors and early isolation of symptomatic individuals; and high testing capacity. Efforts to prevent transmission should focus on all key domains, with recommendations that take into consideration the level of regional community spread and the risk of transmission from presymptomatic or asymptomatic individuals. The CDC recommends that when available, respirators (instead of facemasks) are preferred; they should be prioritized for situations where respiratory protection is most important and the care of patients with pathogens requiring Airborne Precautions. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.htm. World Health Organization and Canadian Health Department guidelines note that SARS-CoV-2 is transmitted primarily by respiratory droplets [20-22]. Regardless, PPE decisions are dependent on local supply, availability, and options for reprocessing. Figure 2 outlines general principles to consider.

Center Readiness

Centers should be ready to screen, evaluate, test, triage, isolate, and care for persons under investigation (PUI) or those with documented COVID-19 infection, with a focus on protecting clinical teams. Local planning to address outbreaks and hospital surge capacity are essential preparation efforts. Centers should use a hospital incident command structure to consolidate and communicate the work of individual groups, address shifts in local epidemiology, streamline organizational change, deal with workforce concerns, and communicate with patients, staff, and the community during the pandemic [23].

Administrative Controls

Transplantation and cellular therapy clinics and units should already have important administrative controls in place to protect against transmission of respiratory viruses. Owing to the unique characteristics of SARS-CoV-2, such as asymptomatic/presymptomatic transmission, prevention should be treated differently than other common community respiratory pathogens. The key recommendations are as follows:

Staff

Prevention Screening and Testing Recommendations for Staff.

A. All staff who enter clinics or units should undergo active screening for respiratory viral symptoms (for typical and atypical COVID-19 symptoms), and symptomatic staff should be sent home. If feasible, symptom screening should be performed at single entry points before entry in person or using web-based tools.

B. Limit entry points on the unit to facilitate screening.

C. Onsite SARS-CoV-2 testing for symptomatic staff should be available, with policies for return to work based on current CDC or local health department guidelines.

D. Asymptomatic testing of staff is not recommended unless an individual has a high-risk COVID-19 exposure or as part of an outbreak investigation. Routine testing of HCWs should be considered in the setting of widespread community transmission.

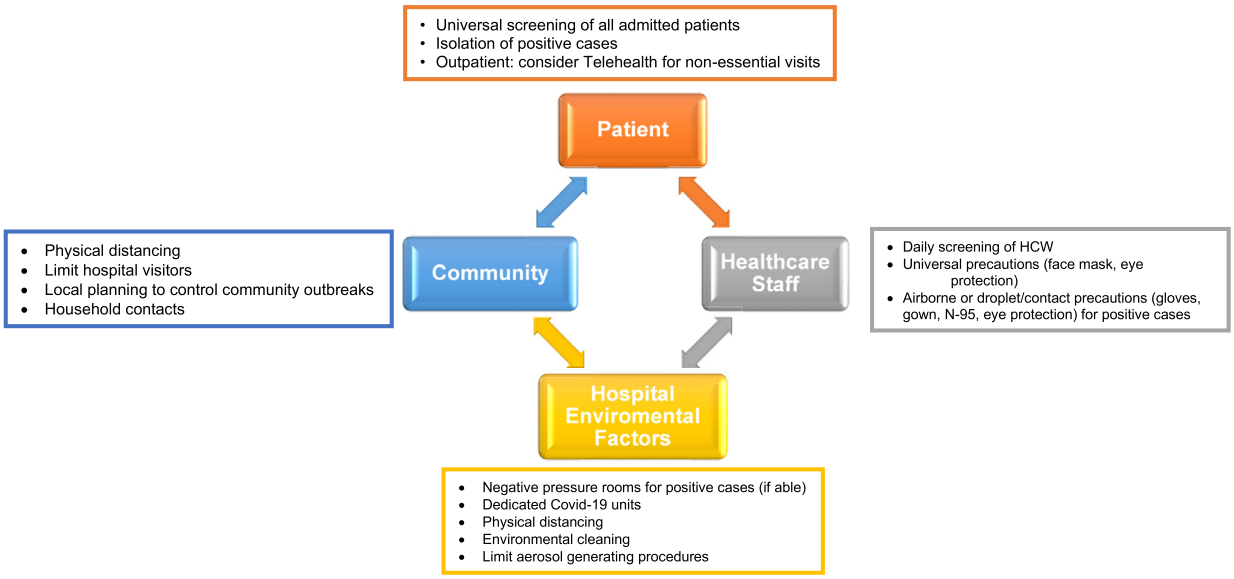

Figure 2. Suggested infection prevention practices for bone marrow transplant units.

E. Limit nonclinical staff (eg, research coordinators) who are not required to be in clinical areas.

PPE for Staff.

A. Universal Precautions: Extended-use masking (face mask) is recommended to prevent the risk of transmission from asymptomatic or presymptomatic individuals in both ambulatory and inpatient units. In addition, the CDC recommends eye protection (goggles, face shield, or mask with eye shield) for all patient care in regions with moderate to high community transmission.
   1. Education, training, and policies for all staff regarding safety and appropriate use of extended mask and/or eyewear are highly recommended to assist with:
      a) Prevention of self-contamination while wearing extended masks
      b) Disinfection of face shields or goggles between patients
      c) Ensuring safe and appropriate donning and doffing procedures
      d) Frequent hand hygiene when handling masks
      e) Identifying staff expected to participate in aerosol-generating procedures and fit-testing them for N95 respirators.
   2. Develop policies for non-patient care activities while using extended masks:
      a) Masking in all workspaces where social distancing is not possible
      b) Policies for removal and storage of masks/eyewear when on breaks, eating, and drinking
      c) Consider scheduling breaks and staggering shift start times to help avoid clustering in break rooms and allow physical distancing (particularly when not masked).

B. PUI or Person with Known COVID-19
   1. Non-aerosol-generating procedures: It is recommended that HCWs who care for PUI/COVID-19-positive patients should maintain droplet/contact precautions and wear gown, gloves, and either a face mask or an N-95 respirator (both with eye protection). Decisions regarding the type of mask are dependent on local policies and supply constraints. With universal masking policies for staff, face shields should be routinely used for PUI and COVID-19-positive patients for eye protection, to allow for prolonged mask use and limit mask contamination.
   2. Aerosol-generating procedures: All high-risk procedures should be avoided unless emergently required, and all HCWs should use an N-95 respirator (with eye protection, preferably a face shield). A powered air purifying respirator can be used if the HCW is not fit-tested, if facial hair precludes use, or if N95 supplies are limited; training before use is essential. Extended N95 respirator use or reuse during supply shortages should follow CDC recommendations. The FDA and CDC endorse sterilization methods for safe reuse of N95 respirators in these situations [24,25].
   3. 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

A. Universal screening of patients at single entry points for symptoms or contact with a known case of COVID-19. Prescreening on the day before an onsite appointment is also advised.

B. Isolation of all patients with active COVID-19 symptoms and testing for SARS-CoV-2 using an approved respiratory viral PCR. For ambulatory patients, testing should be done in designated spaces outside the transplant clinic.

C. Universal masking of patients in all clinical spaces and inpatient areas.

D. Develop policies to manage essential outpatient care for patients with known COVID-19 infection.

E. Develop policies for removing patients from droplet/contact (or airborne/contact) in conjunction with infection prevention teams. This remains an area of ongoing discussion both nationally and at individual centers. Options include:
   1. Viral clearance as documented by 2 negative SARS-CoV-2 respiratory PCR samples (eg, nasopharyngeal, anterior nasal, saliva) $\geq$24 hours apart from each other.
   2. As of July 17, 2020, CDC guidelines recommend a time-based strategy for severely immunocompromised patients in which discontinuation of precautions can be considered if at least 20 days have passed since symptom onset, at least 24 hours have passed since the last fever, and symptoms have improved [3]. There are insufficient data on the relationship among prolonged detection of virus by PCR, viable virus, and transmission potential in highly immunosuppressed patients, and thus the precise minimum duration of isolation is not known at this time.
   3. Decisions can be made based on a combination of symptoms and cycle time (if available), where patients must be asymptomatic [10,26]. This approach is reasonable for nonhospitalized patients.

F. Develop policies for preprocedure/surgery and preadmission testing in coordination with subspecialty services. Testing should be consolidated to avoid repeated swabbing in a short interval, and if multiple procedures and patient remains asymptomatic and without new exposure, a single test should remain valid for 1 week.

G. Limit in-person appointments to essential visits and consider tele-health for others (eg, survivorship).

H. Provide education on COVID-19 and guidelines for community prevention for patients.

RECOMMENDED SYMPTOM SCREENING, TESTING, AND RESTRICTION POLICIES FOR CAREGIVERS, FAMILY, AND VISITORS

A. Universal screening of visitors at all entry points for symptoms or contact with a known case of COVID-19.
   1. Universal masking on entry to clinical spaces.
   2. Prohibition of primary caregivers on inpatient units should be considered during periods of high community incidence, but visitors should be highly regulated regardless of community risk. Limit number of visitors and hours on the unit and prohibit visitors age $<$12 years.
   3. Develop signs, posters and web-based portals to provide educate and disseminate information to caregivers and families.
   4. Testing for visitors may be considered in special circumstances such as caregivers for pediatric patients.
   5. Maintain visitor logs.

ENVIRONMENTAL CONTROLS

Transplant and cellular therapy units have additional measures in place to prevent transmission of respiratory pathogens, including invasive mold infections. National policies recommend single rooms for these high-risk patients, and positive

pressurization primarily to prevent fungal infections. High-efficiency particulate air systems are the standard for transplant and cellular therapy units. Some of these policies may conflict with efforts to limit transmission on units. Moreover, clinical spaces, workrooms, and hospital units are not ideally suited for social distancing.

Air Systems

Positive pressure on units is considered a potential but as-yet undefined risk for transmission. Centers must balance the risk of other major pathogens (eg, invasive mold) against 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 most have limited negative-pressure rooms in clinic and hospital environments. To limit transmission and conserve PPE, dedicated units are encouraged with widespread community spread. Available negative-pressure rooms should be used for COVID-19 positive patients whenever possible. 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 only with input from infection prevention and hospital engineering teams.

Physical Distancing

Staff work rooms should be reconfigured however possible to allow for more physical distancing (eg, removing chairs, creating mobile workstations). Where physical distancing is not possible, extended-use masks must be used appropriately and limited to only essential staff. Waiting areas should be modified to prevent close contact where possible. Strongly consider modification or closure of community spaces (eg, conference rooms) in ambulatory areas or repurpose them to increase waiting room space. Masking policies should target areas where physical distancing is not possible.

Environmental Cleaning

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

High-Risk Procedures

Efforts to limit aerosol-generating procedures should be considered for patients who have known COVID-19 or are PUI. Policies for nebulized medications, diagnostic bronchoscopy, and pulmonary function testing should be developed in conjunction with subspecialty services, intensive care units, and infection prevention teams to both limit potential exposures and ensure patient and staff safety.

TREATMENT CONSIDERATIONS FOR HCT AND CELLULAR THERAPY PATIENTS

Recently published guidelines are available from the IDSA (https://www.idsociety.org/Covid19guidelines) and the National Institutes of Health (NIH) (https://www.Covid19treatmentguidelines.nih.gov/). Given the lack of data on HCT and immunotherapy patients, treatment should be considered after careful consideration 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 [27]. Toxicity may be enhanced with combination therapy.

Treatment recommendations continue to change as additional data become available, and current guidelines should be consulted for up-to-date recommendations. HCT and cellular therapy recipients should be considered for COVID-19 treatment clinical trials if appropriate. Data from adult populations should be interpreted with caution given the overall lower incidence of severe disease in children. Drug availability is another important consideration. An overview of treatment recommendations at various disease stages is outlined in Table 2.

General Principles

A. Upper respiratory tract infection
   1. Consider chest imaging to evaluate for lower respiratory tract infection.
   2. With normal chest imaging and no symptoms (ie, testing done for surveillance), no therapy is recommended. Future clinical trials may enroll patients at the asymptomatic phase.
   3. With normal chest imaging and mild upper respiratory symptoms (eg, sore throat), patients should be considered for clinical trials, if available. Specific agents can be considered if symptoms progress. See below for additional considerations. Infectious diseases should be consulted.

B. LRTI
   1. Given challenges around obtaining imaging and BAL fluid, we propose the following definitions of LRTI:
   2. Proven LRTI: detection of SARS-CoV-2 by PCR from BAL with consistent radiographic changes
   3. Possible LRTI: consistent radiographic changes or the presence of LRTI symptoms (cough, shortness of breath, hypoxemia) with a positive upper respiratory tract SARS-CoV-2 PCR test.
   4. LRTI may be complicated by severe lung inflammation and the development of acute respiratory distress syndrome (ARDS).
   5. LRTI from SARS-CoV-2 may be complicated by subsequent bacterial or fungal coinfection. Viral coinfection also should be considered and treated if agents are available.
   6. Therapy should be considered in patients with LRTI; agents may be added as combination therapy as severity increases.
   7. Infectious diseases consultation is recommended.

C. Extrapulmonary manifestations: COVID-19 primarily causes respiratory tract disease; however, patients may also experience cardiac, central nervous system, hepatic, and renal disease (reviewed in Table 1). The frequency of these manifestations in recipients of HCT or cellular therapy is unknown.

Rationale for Use of Selected Agents

Antiviral Agents

Remdesivir

The efficacy of remdesivir against coronaviruses was first demonstrated in in vitro and mouse studies of MERS-CoV and SARS-CoV [28,29] and in in vitro models of SARS-CoV-2 [30].

Table 1
Extrapulmonary Manifestations of COVID-19 Described in Mostly Nonimmunocompromised Hosts

Category	Manifestations
Cardiac disease	Underlying cardiovascular disease (coronary artery disease, heart failure, cardiac arrhythmias) is associated with an increased risk of in-hospital death among patients with COVID-19 [69]. Cardiac dysfunction, including myocarditis, pericarditis, acute cardiac injury, and arrhythmias, have been described. Myocardial injury is reported in >25% of critical cases and may present as acute myocardial injury and dysfunction on initial presentation, or myocardial injury that develops as COVID-19 disease intensifies [70].
Central nervous system manifestations	Encephalitis, acute polyradiculitis, stroke, and central venous sinus thrombosis have been described. The postulated mechanisms for the neurologic complications are thought to be from direct viral invasion, inflammation-induced coagulopathy, or postinfectious autoimmune reactions.
Renal and hepatic dysfunction	Renal and hepatic dysfunction have been described in severe COVID-19 disease, with the need for continuous renal replacement therapy described in >15% of cases in 1 series [71,72].
Thromboembolic events	Severe COVID-19–associated infection is associated with coagulopathy that is prognostic of poor outcomes [73]. Although some laboratory findings resemble sepsis-associated disseminated intravascular coagulopathy, COVID-19 associated coagulopathy appears to be more thrombotic rather than hemorrhagic. The most common coagulopathy presentations are characterized by thrombocytopenia and elevated serum D-dimer levels [74,75]. There are reports of both venous and arterial thromboembolic events in these critically ill patients [76], but it remains unclear whether they are unique to COVID-19 disease or simply part of the sepsis, cytokine storm, and impending multiorgan failure.
Multisystem inflammatory syndrome in children	Several case series have described a severe systemic inflammatory syndrome associated with SARS-CoV-2 PCR or serology positivity in children and adolescents. Clinical manifestations include fever, shock, severe abdominal pain, and myocardial dysfunction with marked elevation in cardiac damage markers. The syndrome has not been described in HCT or immunotherapy patients.

Data from 2 randomized placebo-controlled trials have been published. In 237 hospitalized adults with SARS-CoV-2, there was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between the remdesivir and placebo groups [31]. Limitations of the study included early termination, resulting in inadequate power, and coadministration of multiple agents that may have affected the outcomes.

Data from a multinational randomized, placebo-controlled trial (Adaptive COVID-19 Treatment Trial [ACTT]) of hospitalized patients (n =1063) with COVID-19 showed that patients who received remdesivir had a significant reduction in time to clinical recovery (11 days versus 15 days for placebo) and a nonsignificant decrease in mortality (8% for remdesivir versus 11.6% for placebo) [32]. Based on these data, recently published NIH guidelines [33] recommend the use of remdesivir for the management of severe COVID-19 disease in hospitalized patients. Currently, remdesivir has not been approved by the FDA, but it is available through emergency use authorization for treatment of hospitalized patients with COVID-19 [34]. Remdesivir is not recommended for mild or moderate COVID-19 outside the setting of a clinical trial. In mostly immunocompetent adults with severe COVID-19, 5 days of therapy was equivalent to 10 days of therapy for clinical improvement by day 14 [35]. Compassionate use is available only for pregnant women and children aged ≤18 years with severe disease. The optimal duration of therapy in HCT and immunotherapy recipients is not known.

Table 2
Treatment Considerations

Disease Stage	Treatment Recommendations
Asymptomatic positive (if surveillance testing done)	Clinical trial if available
Upper respiratory tract infection only	Clinical trial if available
LRTI without oxygen requirement	Clinical trial if available
	See text for additional considerations
	See discussion about antibiotics in text
LRTI with oxygen requirement or mechanical ventilation	Clinical trial if available
	Consider remdesivir and/or dexamethasone (see text for additional considerations)
	See discussion about antibiotics and IVIG in text

Adverse events most often reported in available clinical data include transient elevations in transaminases, anemia or decreased hemoglobin, acute kidney injury, pyrexia, and hyperglycemia. In the ACTT trial, these adverse events were not significantly different between the remdesivir and placebo groups [32]. There are no known major drug-drug interactions with remdesivir [27]. Recent reports showed that agents that inhibit P-glycoprotein substrate, such as amiodarone and chloroquine, can confer drug interactions [36]. Physicians should be vigilant for any emerging toxicities from unanticipated drug interactions.

Chloroquine/hydroxychloroquine

Large observational studies among hospitalized patients with COVID-19 have not demonstrated any benefit with hydroxychloroquine alone [37] or in combination with azithromycin [38]. In a randomized controlled trial of hydroxychloroquine for mild to moderate COVID-19, there was no effect on viral clearance by day 28 [39]. Moreover, in a randomized controlled trial of hydroxychloroquine for postexposure prophylaxis, there was no effect on development of illness compatible with COVID-19 [40].

Adverse reactions include nausea and diarrhea, hypoglycemia, agranulocytosis, liver function test abnormalities, and QTc prolongation. High dose hydroxychloroquine (600 mg twice daily for 10 days), in combination with azithromycin, was associated with higher rates of mortality and QTc prolongation [41]. Concomitant medications that cause QTc prolongation should be avoided. Given the data suggesting limited efficacy and potential for toxicity, hydroxychloroquine is not recommended outside of a clinical trial. Combination therapy with azithromycin is not recommended.

Antibody Therapy

Convalescent Plasma

Passive antibody transfer with convalescent plasma has been used in the treatment of or prophylaxis against other viral pathogens, including respiratory viruses. The experience with COVID-19 is limited to small case series comprising patients on concomitant antiviral therapies and corticosteroids, with suggestion of faster viral clearance and clinical recovery with early treatment, but no clear mortality benefit [42-45]. Limited experience from the SARS-CoV-1 epidemic also indicated potential benefit with convalescent plasma when used in the first 2 weeks of illness rather than in the late hyperimmune phase [46]. The FDA recently provided guidance for the use of COVID-19 convalescent plasma under an emergency Investigational New Drug request [47]. In the United States, more than 20,000 patients with COVID-19 have received convalescent plasma through an expanded access protocol (https://ccpp19.org/; https://www.usCovidplasma.org/; https://clinicaltrials.gov/ct2/show/NCT04338360). In an open-label randomized study of patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant decrease in the time to clinical improvement within 28 days. Interpretation was limited by early termination of the trial, which might have been underpowered to detect a clinically important difference [48]. Additional randomized clinical trials are ongoing. At present, the type and concentration of antibodies against SARS-CoV-2 in the convalescent plasma used for treatment is not standardized. Furthermore, the optimal timing and dosing schedule are not established. If COVID-19 convalescent plasma is pursued, it should be in the context of a clinical trial. No recommendation can be made for or against the use of convalescent plasma at this time.

Potential adverse reactions associated with convalescent plasma infusion include transfusion-related acute lung injury, transfusion-associated circulatory overload, and other allergic transfusion reactions. Early safety indicators from 5000 treated patients in the United States suggest that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19 [49]. Another theoretical concern is the risk of antibody-dependent enhancement that may occur in in patients with preexisting non-neutralizing SARS-CoV-2 antibodies [50,51]. Whether these observations translate to clinical settings is unclear.

Monoclonal Antibodies

Monoclonal antibodies directed against the receptor-binding domain (RBD) and other epitopes of the viral spike protein have the potential to provide a standardized and scalable option for the treatment and prevention of COVID-19. As of June 26, 2020, 2 anti-SARS-CoV-2 monoclonal antibodies are in early-phase clinical trials: JS S016 (Junshi Biosciences) and combination therapy with REGN10933 + REGN1087 (Regeneron Pharmaceuticals).

Adjunctive Therapies

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 [52]. Other aspects of innate, adaptive immunity response signaling cascade and complement pathway activation also might be implicated in the pathogenesis of COVID-19 disease [53]. The role of anti-inflammatory drugs, such as tocilizumab (anti-IL-6), sarilumab (anti-IL-6), anakinra (anti-IL1), baricitinib (anti-JAK), and ruxolitinib (JAK inhibitor) are being explored (Table 3). Given the absence of concrete data showing clinical efficacy, no recommendation either for or against the use of these agents can be made at this time. Given their broad immunosuppressive effect, these agents should be used only in the context of a clinical trial. Patients with uncontrolled infection bacterial or fungal infections should not receive these agents.

Corticosteroids

In SARS-CoV-1, steroid therapy was associated with an increased need for ICU admission and mortality [54], although lower mortality and shorter hospitalization was seen among critical cases [55], and the use of pulsed steroids resulted in lower oxygen requirements and better radiographic outcomes compared with nonpulsed steroids [56]. In MERS-CoV-2, however, steroid therapy was evaluated by both dose and duration, and no effect was seen on mortality; however, increased time to RNA clearance was observed [57]. One study of SARS-CoV-2 suggested that delayed use of steroids may increase the risk of death in the ICU [58]. In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death [59]; short courses of low- to moderate-dose steroids has also been recommended in critically ill patients [60].

Preliminary results from a large randomized controlled trial of dexamethasone (n = 2104) compared with usual care (n = 4321) demonstrated reduced 28-day mortality in the dexamethasone group (22.9% versus 25.7.%; adjusted rate ratio, .83; 95% confidence interval, .75 to .93) [61]. The effect was most pronounced in patients on mechanical ventilation at the time of randomization (n = 1007), although an effect was also seen in patients on supplemental oxygen alone.

The use of steroids in patients with severe disease (requiring oxygen support or mechanical ventilation) should be considered, although there are currently no data on key questions, including whether there is antagonistic effect of dexamethasone given concomitantly with antiviral agents, what steroid equivalents can be equally effective, and outcomes and/or adverse events associated with dexamethasone in immunocompromised patients. The routine use of steroids is not recommended in patients with mild disease.

IVIG

Currently available IVIG products are unlikely to contain specific antibodies to SARS-CoV-2 and thus are unlikely to improve clinical disease via a direct neutralizing antibody effect. IVIG has been suggested to have anti-inflammatory or immunomodulatory effects; however, given the lack of conclusive clinical data for treatment of coronaviruses and national shortage of IVIG products, the routine use of IVIG is not recommended at this time. There are no data on the use of hyperimmune immunoglobulin for SARS-CoV-2.

Antimicrobials

Data on coinfection with bacterial and fungal pathogens in patients with COVID-19 are scant [62-64]. We do not recommend routine antibiotic use in patients with SAR-CoV-2 limited to the upper respiratory tract, unless indicated for other reasons according to local protocols (ie, management of febrile neutropenia). Physicians should be vigilant for emerging

Table 3
Immunomodulatory and Anti-Inflammatory Agents Under Investigation for COVID-19

Drug/Mechanism	Proposed Concept	Published Reports/Clinical Observations
Tocilizumab: A recombinant humanized monoclonal antibody against both soluble and membrane-bound IL-6 receptor	Inhibits IL-6–mediated proinflammatory responses. No established IL-6 cutoff values to predict disease severity or clinical outcomes.	Multiple reports showed improved oxygen requirement, normalization in CRP, and resolution of fever, and increased the lymphocyte count to normal [77-80].
	The optimal timing and dosing schedule of tocilizumab are not established.	Others showed tocilizumab failed to prevent ICU admission or impact disease progression and mortality [81-83].
	Monitor for hepatic function abnormalities, local injection site reactions, and possible inducible effects on drugs metabolized by CYP450 given the drug's long half-life. FDA black box warnings for the risk of severe infections that can lead to hospitalization and death [84].	IL-6 levels normally increase after tocilizumab administration from inhibited cytokine/receptor catabolism. Post-tocilizumab IL-6 levels should not be used as a surrogate marker for clinical response [85,86].
Baricitinib: Janus kinas inhibitor, approved for rheumatoid arthritis [88]	Interference with viral endocytosis.Concerns for impairment of IFN-mediated antiviral response	In a pilot study of 12 patients with moderate COVID-19 disease, the baricitinib group showed improved respiratory function parameters and CRP values compared with the standard of care. No adverse events were noted. and no cancer patients were included [87].
Anakinra A recombinant human IL-1 receptor antagonist. Approved for rheumatoid arthritis. Off label use for familial Mediterranean fever and hemophagocytic lymphohistiocytosis syndrome [92,93]	Counteract SARS-CoV-2–induced severe inflammatory response with macrophage activation syndrome–like picture or cytokine release syndrome [89].	Clinical trials are currently conducted outside the United States.
		A small Italian retrospective study of 29 patients showed a better mortality rates in patients with acute respiratory distress syndrome who received high-dose i.v. anakinra. Patient also received hydroxychloroquine and lopinavir/ritonavir [90].
		A French study compared outcomes of 52 patients with COVID-19 with 44 historical patients. The anakinra group had lower rates of mechanical ventilation or death (25% versus 73%; $P < .0001$) with similar results for death only ($P = .0063$) [91].

nosocomial and opportunistic infections, because typical signs of infection might be masked secondary to iatrogenic and inherent immunosuppression. Antimicrobial prophylaxis should be continued in patients who are currently receiving it. It may be reasonable to restart antimicrobial prophylaxis for those in whom it was recently discontinued if they are started on an immunomodulatory agent.

Anticoagulation Therapy

No official guidelines addressing the optimal management of COVID-19-associated coagulopathy (CIC) have been published to date. A recent expert opinion review suggests using venous thromboembolism prophylaxis for these patients during hospitalization [65]. The American Society of Hematology and NIH have also published general guidance on management of CIC on their respective websites [33,66].

Other Agents Not Currently Recommended

Several other agents have been used in the treatment of SARS-CoV-2, including lopinavir/ritonavir, ribavirin, and interferons. These agents are not currently recommended for HCT and cellular therapy recipients. A full discussion of the rationale against this recommendation are outlined in the Supplementary Material.

SURVIVORSHIP

The estimated current number of HCT survivors in the United States is ~250,000, and it will continue to increase [67]. The Center of International Blood and Marrow Transplant Research is currently gathering data on HCT recipients with SARS-CoV-2 infection. There is no guidance available specifically addressing the needs of HCT survivors as the country plans to reopen. Patients in this group are diverse and may vary in their net state of immunosuppression. Our panel suggests that they continue to practice caution during social interactions, encourage the use of face masks, and practicing hand hygiene. Because community spread will differ among geographic areas, it is important to follow local trends and guidance provided by local departments and the CDC. HCT survivors should discuss returning to work with their treating physicians and should take necessary precautions at their workplace. Acknowledging the physical and psychological needs for HCT survivors and seeking help for their physical and mental health needs, especially during the pandemic phase, is of utmost importance [68].

ACKNOWLEDGMENTS

The author thank the following colleagues for their valuable input: Ella Ariza-Heredia (University of Texas MD Anderson Cancer Center), Paul Carpenter (Fred Hutchinson Cancer Research Center), Guang-Shing Cheng (Fred Hutchinson Cancer Research Center), Janet Englund (Seattle Children's Hospital), Stephen J. Forman (City of Hope National Medical Center), Rebecca Gardner (Seattle Children's Hospital), Terry Gernsheimer (Fred Hutchinson Cancer Research Center), Joshua Hill (Fred Hutchinson Cancer Research Center), Michael Linenberger (Fred Hutchinson Cancer Research Center), Catherine Liu (Fred Hutchinson Cancer Research Center), Zahra Mahmoudjafari (University of Kansas Health System), Monzr Al Malki (City of Hope National Medical Center), Ryotaro Nakamura (City of Hope National Medical Center), Chikara Ogimi (Seattle

Children's Hospital), Miguel Ángel Perales (Memorial Sloan Kettering Cancer Center), Bipin Savani (Vanderbilt University Medical Center), Eileen Smith (City of Hope National Medical Center), Cameron Turtle (Fred Hutchinson Cancer Research Center), and Masumi Ueda (Fred Hutchinson Cancer Research Center).

Financial disclosure statement: A.W. receives research support from Ansun, VB Tech, Amazon and Allovir, and is a consultant for Kyorin. M.B. receives research support from Gilead, Janssen, Ansun, Vir Bio, VB Tech, and Amazon and is a consultant for Kyorin, Gilead, ReViral, Janssen, Ansun, Moderna, Vir Bio, GSK, Pulmocide, Pulmotect, Bavarian Nordic, ADMA, and Allovir. S.A.P. receives research support from Global Life Technologies and participates in research trials with Chimerix and Merck & Co. He also currently participates in a clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (U01-AI132004); vaccines for this trial are provided by Sanofi-Aventis. R.F.C. receives research grants from Merck, Karius, Chimerix, Viracor, Takeda/Shire, AiCuris, Janssen, Ansun Pharmaceuticals, Oxford Immunotec, and Gilead Sciences. He is a consultant for Merck, Ansun, Oxford Immunotec, Shire, Janssen, Partner Therapeutics, ADMA Biologics, and Oxford Immunotec. S.D. receives research support from Merck, Gilead, Ansun, Shire/Takeda, and Karius and serves on advisory boards for Merck and Janssen. He is a consultant and part of a speaker's bureau for Merck. G.A.P. has received research support from Merck, Shire/Takeda, Chimerix, and Astellas and consulting and other fees from Merck, Astellas, Chimerix, Octapharma, Partner Therapeutics, ADMA Biologics, Shionogi, Cidara, Ampynx, and Siemens.

Authorship statement: M.Z.A., M.B., R.F.C., S.D., Z.E.B., M.K., G. A.P., S.A.P., and Z.S. contributed equally to this work.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.07.027.

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