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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Perspective

Addressing the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Hematopoietic Cell Transplantation: Learning Networks as a Means for Sharing Best Practices

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A B S T R A C T

The full impact of the coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), on the field of hematopoietic cell transplantation (HCT) is unknown. This perspective paper reviews the following: current COVID-19 epidemiology, diagnosis, and potential therapies; care considerations unique to HCT recipients; and the concept of a learning network to assimilate emerging guidelines and best practices and to optimize patient outcomes through facilitating shared learning and experience across transplantation centers.

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel single-strand RNA beta-coronavirus, has caused the current coronavirus disease 2019 (COVID-19) pandemic. As of April 13, 2020, the World Health Organization (WHO) had reported 1,773,084 laboratory-confirmed cases and 111,652 deaths globally [1]. The ultimate impact of COVID-19 on the field of hematopoietic cell transplantation (HCT) is currently unknown. This perspective paper anticipates the significant influence of COVID-19 on HCT recipients given their immunocompromised state, presence of other medical comorbidities, and concerns for higher infection-related severity and mortality, and also reviews the substantial impact of COVID-19 on the HCT-related healthcare system. To address these challenges, novel care approaches and ways to assimilate and share information in the background of rapid change are critically needed. Therefore, the concept of learning networks as interactive platforms for effectively assimilating

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and distributing evolving information to transplantation centers is introduced [2].

COVID-19: AN OVERVIEW

Epidemiology and Transmissibility

COVID-19 was first recognized in persons presenting with pneumonia of unknown etiology in Wuhan City, China in December 2019 [3,4]. The origin of the virus causing COVID-19, SARS-CoV-2, is currently unconfirmed, although emergence from an animal reservoir has been proposed [5,6]. Metagenomic next-generation sequencing of bronchoalveolar lavage (BAL) specimens from affected patients identified a previously unobserved coronavirus (CoV), initially referred to as novel coronavirus 2019 (2019-nCoV) [5]. The genome sequence of this 2019-nCoV was confirmed to be structurally related to other CoVs, including 89% identical to the bat severe acute respiratory syndrome (SARS-like CoV) and 82% identical to human SARS-CoV-1; thus, the virus was renamed SARS-CoV-2 [7-9]. SARS-CoV-2 is also similar to other zoonotic CoVs causing global outbreaks of severe respiratory illnesses, such as SARS-CoV-1 in 2002 and Middle East respiratory syndrome (MERS) in 2012, and has been confirmed to be transmitted from human to human [10].

In contrast to SARS-CoV-1 and MERS, the community spread of SARS-CoV-2 has been global, likely reflecting differences not only in how the virus may be transmitted [11], but also in its association with high viral loads in the upper respiratory tract [12] and significant asymptomatic carriage [13]. In this regard, the reported household transmission rate is estimated to be 15% [14]. The virus's basic reproduction number (R_0), an epidemiologic metric describing transmissibility in terms of the average number of cases that could be caused by 1 infected patient in a susceptible population [15], has been estimated as 1.4 to 3.0 [16], compared with ~1.2 to 3 for seasonal influenza R_0, ~12 to 17 for pertussis R_0, and ~12 to 18 for measles R_0 [15,17]. The COVID-19 case fatality risk (CFR) is estimated to be in the range of .25% to 4.7% [18,19], with the highest mortality reported in older adults with comorbidities and varying by geographic location [20]. Preliminary data from the United States suggest high fatality in persons age ≥85 years (CFR ~10% to 27%), lower CFR in persons age 65 to 84 years (~3% to 11%), and further declines in younger age groups (CFR ~1% to 3% in 55- to 64-year-olds, <1% in 20- to 54-year-olds) [21,22]. A striking finding in these data is the proportion of severe disease and hospitalization in younger adults (age 45 to 64 years), which contrasts with the Chinese experience [21].

Clinical Manifestations

After an estimated median incubation period of 5 days (range, 2 to 14 days), patients may present with fever (77% to 98%) and nonspecific symptoms similar to an influenza-like illness (eg, fever, cough, myalgia, fatigue) [4,23]. Although the spectrum of COVID-19 varies from asymptomatic infection to mild and severe disease, the most well-described clinical manifestation is lower respiratory tract disease (LRTD) that presents with shortness of breath and can progress to pneumonia and acute respiratory distress syndrome (ARDS) in 17% to 29% of patients [8,20,23,24]. Progression to LRTD generally occurs around 10 days after illness onset [4].

Although the risk factors for severe COVID-19 disease have not been fully elucidated, older age and medical comorbidities, including diabetes, cardiovascular disease, and pulmonary disease in adults, have been associated with severe disease [23,25-27], which often requires intensive care unit (ICU) care [24], with 47% to 71% of ICU patients requiring mechanical ventilation [24,28]. Additional complications include secondary infections (10%) and development of shock and multiorgan dysfunction [3].

Laboratory and Radiographic Findings

Lymphopenia is frequently reported with COVID-19, occurring in approximately 63% to 83% of patients [10,20,23,29]. Notably, decreases in $CD8^+$ T cells and B cells in adults have been associated with severe COVID-19 and poor response to therapy [30], whereas $CD8^+$ T cell and B cell recovery has been associated with moderate disease [31]. Finally, decreases in regulatory T cells also have been associated with a hyperinflammatory response in adults [32], necessitating the use of monoclonal blocking antibodies, such as tocilizumab [33].

Given these preliminary observations, lymphopenia and alloreactivity associated with HCT may portend a worse prognosis for COVID-19 in HCT recipients, similar to lymphopenia associating with LRTD progression and higher mortality from community respiratory viruses [34-36]. Interestingly, risk factors for endemic human CoV strains (eg, 229E, NL63, OC43, HKU1) vary based on age. Although endemic CoV was frequently detected in pediatric HCT recipients, low absolute lymphocyte count was not associated with progression to LRTD or severe LRTD, but level of immunosuppression was [37]. Among adult HCT recipients with endemic CoV, 34 of 112 (30%) progressed to LRTD, with graft-versus-host disease (GVHD), corticosteroids, hypoalbuminemia, and older age associated with disease progression [38].

Other notable COVID-19 laboratory findings include leukopenia (9% to 25%) or leukocytosis (24% to 30%) and elevated transaminases (37%) [20,24]. The most common radiologic findings in patients with COVID-19 are unilateral or bilateral ground-glass opacities [39,40]. The most severe lung abnormalities occurred at approximately 10 days after symptom onset in patients who underwent sequential imaging [41,42].

Diagnosis

Viral Dynamics

The viral dynamics of SARS-CoV-2 are still being elucidated in real time [28,43]. SARS-CoV-2 has been detected in blood, urine, stool, upper and lower respiratory tract, and saliva using real-time polymerase chain reaction (RT-PCR) [20,23,44,45]. The performance characteristics of the SARS-CoV-2 PCR are unknown, and the diagnostic yield of the SARS-CoV-2 RT-PCR may be site-specific [43], may depend on clinical manifestations and disease severity [46,47], and may be influenced by variations in assay sensitivity and specificity [48]. As a result, the diagnostic capability of PCR may be suboptimal compared with other modalities such as chest imaging [49], and a negative PCR result does not conclusively exclude COVID-19.

Preliminary data suggest that SARS-CoV-2 viral loads are higher in BAL and sputum samples, followed by nasopharyngeal (NP) and throat specimens [12,28]. The median duration of viral detection from oropharyngeal specimens is 20 days (range, 8 to 37 days) [50]. In addition, SARS-CoV-2 viral loads from NP sites have been found to be similar in both asymptomatic and symptomatic patients [12]. Furthermore, SARS-CoV-2 transmission occurs from asymptomatic persons, who likely contribute to rapid viral dissemination [13]. The significance of ongoing viral detection by PCR in asymptomatic persons, including whether detection equates to viable/transmissible virus, remains an ongoing area of research. As serologic testing becomes more widely available, data will evolve regarding immunologic correlates of protection against SARS-CoV-2 infection [43,51,52].

Recommendations

Establishing the diagnosis of COVID-19 is important for understanding a disease in its evolution and instituting appropriate infection prevention precautions. Clinical judgment to guide testing is based on the presence of signs/symptoms compatible with COVID-19, disease severity, and local epidemiologic patterns of the disease. Clinicians should have a high index of suspicion to test patients who present with fever and/or lower respiratory tract (LRT) symptoms and have either recently traveled from an area of high community SARS-CoV-2 prevalence or have been exposed to a close contact with confirmed or suspected COVID-19 in the previous 14 days [53,54]. A close contact is defined as being within 6 feet (2 meters) of a COVID-19 case for a prolonged period or having direct contact with infectious secretions of a COVID-19 case [55]. In addition, patients with severe LRT disease of unclear etiology should be considered for testing. A coronavirus self-checker is now available to help guide patients through the process [56]. If a patient is considered a person under investigation (PUI) based on geographic [55] or healthcare [57] exposure, clinicians should immediately institute appropriate infection precautions (see details below) and notify their state and local health departments.

Current commercially available multiplex PCRs that detect endemic CoV do not detect SARS-CoV-2. Therefore, RT-PCR assays have been developed to improve the sensitivity of diagnostic testing; however, these also have limitations, as reviewed previously. For initial testing, the Centers for Disease Control and Prevention (CDC) recommends testing upper respiratory tract specimens (NP swabs) in all PUIs. In patients with a productive cough, sputum may be tested, but procedures that generate aerosols are discouraged. For example, BAL sampling is considered high-risk for aerosol dissemination and is not recommended in patients known to be positive for SARS-CoV-2 unless a co-infection is suspected. In patients receiving mechanical ventilation, LRT aspirate can be obtained. Chest imaging should be considered in patients positive for SARS-CoV-2 with LRT symptoms. Research is ongoing to improve diagnostic strategies, including more rapid, point-of-care PCR tests [58] and serologic assays to identify patients still at risk [59].

Treatment

Supportive care is the mainstay of COVID-19 treatment. Updated, interim clinical guidance for patients with confirmed COVID-19 is available from the CDC and WHO [60-62]. At this time, there are no proven effective therapies against SARS-CoV-2 [63]. The safety and efficacy of other treatment options for COVID-19 are currently being evaluated (Table 1) [64,65]. Recently, the WHO announced the "Solidarity Trial," a multicountry clinical research study to evaluate multiple potential treatment options against SARS-CoV-2—remdesivir, hydroxychloroquine, lopinavir/ritonavir, and lopinavir/ritonavir plus interferon-beta—compared with supportive care measures alone [66].

Remdesivir is an intravenous investigational novel nucleoside analog in development that has previously been used to treat Ebola and MERS infections [67,68] and has demonstrated

Table 1
Current investigational therapies being evaluated for COVID-19.

Agent	Data from Previous Studies	ClinicalTrials.gov Identifier, Other Sources
Remdesivir	Ebola, MERS	NCT04280705
		NCT04302766
		NCT04292899
		NCT04292730
		NCT04252664
		NCT04257656
Favipiravir	Ebola	NCT04310228 (In Japan)
		NCT04303299
Lopinavir/ritonavir [141-144]	SARS-CoV, MERS	NCT04261907
		NCT04276688
		NCT04307693
Chloroquine [145,146]	SARS-CoV	NCT04307693
		NCT04315896
Interferon-alpha 2B [147,148]	MERS	NCT04293887
Camostat mesylate	SARS-CoV	Approved in Japan, no previous human testing
Nitazoxanide [149]	Coronavirus	
Intravenous immunoglobulin (IGIV) from COVID-19 patients	N/A	NCT04264858
		NCT04261426
Mesenchymal stem cells	N/A	NCT04288102
		NCT04293692
		NCT04273646
Carrimycin	N/A	NCT04286503
Bevacizumab	Acute lung injury, ARDS	NCT04275414
		NCT04305106
Tocilizumab	N/A	NCT04317092
		NCT04310228
		Chinese National Health Commission guidelines [42]
Recombinant human angiotensin-converting enzyme 2	N/A	NCT04287686

N/A indicates not applicable.
A complete list of COVID-19 clinical trials is available at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=COVID-19).

in vitro activity against SARS-CoV-2 [69]. Remdesivir has been approved by the Food and Drug Administration (FDA) for a National Institutes of Health-sponsored randomized controlled clinical trial for hospitalized COVID-19 patients with advanced symptoms (ClinicalTrials.gov identifier NCT04280705). Remdesivir may be available for individuals via compassionate use requests (children or pregnant women) or under an expanded access program for severely ill patients (https://rdvcu.gilead.com/). Recent findings from a compassionate use trial using remdesivir in patients with severe COVID-19 demonstrated clinical improvement in 68% (36/53) of patients [70].

The use of convalescent plasma collected from patients who have recovered from COVID-19 is being evaluated as a treatment based on its use in other severe viral infections [71,72]. A recent limited intervention study noted that convalescent plasma therapy in adults with severe COVID-19 who were receiving multiple other investigational therapies was well tolerated (primary endpoint) and demonstrated potential clinical efficacy as measured by improvements in clinical symptoms, laboratory abnormalities, and radiographic imaging (secondary endpoints) [73]. Clinical trials are now available for adults to assess safety and efficacy of convalescent plasma based on virologic and clinical endpoints (https://clinicaltrials.gov).

Given the increasing data supporting a hyperinflammatory state in adults with severe COVID-19 [74], clinical research trials are ongoing to evaluate the effect of IL-6 blockade on COVID-19 outcomes [75,76]. Treatment with systemic corticosteroids is not routinely recommended, given a lack of survival benefit in SARS-CoV-1, possible adverse events, and concerns for prolonging viral replication and delaying viral clearance, unless clearly required for other indications (eg, ARDS, septic shock) [77].

Prevention

Three basic but effective strategies should be implemented by all inpatient bone marrow transplantation units and outpatient clinics (Table 2): (1) maintaining proper and frequent handwashing, including before and after patient encounters, as a primary tool to prevent the spread of respiratory illness; [78-80] (2) implementing standardized visitor screening that is limited to direct caregivers only [79,81]; and (3) mandating that sick employees stay home [78,79]. Transplantation centers should initiate these strategies immediately and identify mechanisms to reliably improve adherence to these best practices.

Given that nosocomial transmission of SARS-CoV-2 has been reported [28,82], best practices in hospital infection control must be implemented to prevent SARS-CoV-2 transmission to other patients and healthcare personnel [81]. Even after environmental contamination by SARS-CoV-2 [83], effective infection control practices and environmental cleaning can prevent nosocomial transmission of SARS-CoV-2 [84,85]. Infection prevention measures should be immediately instituted for any PUI, including masking the patient and moving him or her into a private room, optimally with airborne isolation. Hospital personnel should follow standard, contact, and airborne precautions, including the use of appropriate personal protective equipment (PPE) and eye protection [81] The COVID-19 pandemic has highlighted the continuing burden and challenges to healthcare resources that necessitate redirection of timely efforts to conserve, optimize, and restock equipment, including PPE [86].

In the ambulatory setting, preventative measures should be provided to HCT recipients and their household contacts (Table 3). Stable patients and PUI should contact their healthcare provider if they develop worsening symptoms and before presenting to medical facilities. In a medical emergency, they should inform emergency medical personnel of their immunocompromised status and possible COVID-19 exposure [78]. In addition, continued public health efforts should be maintained to mitigate community transmission of COVID-19 [87].

Multiple vaccine candidates have been identified [88], and clinical trials are underway [89], including an open-label phase 1 trial of differing doses of mRNA-1273 to assess their safety and efficacy against SARS-CoV-2 [90] and microneedle array-delivered SARS-CoV-2 subunit vaccines, which can be rapidly produced and generate potent antibody responses [91]. Together with rapid diagnostic and serologic testing, vaccines will serve as the foundation for current and future protection against SARS-CoV-2 [92].

Table 2
Process and Practice Interventions Associated with Improved Compliance

process	Potential Mechanisms for Process Measurement	Practice Interventions Associated with Improved Compliance
Handwashing [79,80]	Direct observation [150,151]	Patient, caregiver, and hospital staff handwashing education initiatives [153]
		Physician and staff financial incentives [153]
		Frequent reminders [152]
		Timely and frequent audits [154]
		Individual feedback to promote accountability [154]
	Amount of soap used [152]	
Screen patients and visitors for symptoms of acute respiratory illness [79]	Direct assessment for all persons entering the transplantation unit	Consider highly reliable interventions [155-158]
		Screening station at entry of unit
		Unit door locks for entry to limit entry onto unit without screening
Encourage sick or at-risk employees to stay home [78,79]	Number of employees self-reporting	Staff education of when self-reporting should be completed [159] Adoption of a just culture for self-reporting [160]; self-reporting is encouraged and rewarded and focuses not on individual blame, but on improving health

Table 3
Recommendations for Patients in the Ambulatory Setting to Prevent COVID-19

• Wash hands often with soap and water for 20 seconds (singing "Happy Birthday" to yourself twice while washing your hands = 20 seconds). If soap and water are not available and hands are not visibly dirty, use an alcohol-based hand sanitizer that contains ≥60% alcohol.
• Avoid touching your eyes, nose, or mouth.
• Avoid or at least maintain a distance of 6 feet (2 meters) away from anyone who has respiratory symptoms (cough or sneezing).
• Stay home if you feel sick or have cold-like or flu-like symptoms, including fever, cough, sore throat, headache, or body aches; contact your healthcare professional should your symptoms worsen before presenting for medical attention, if possible.
• Practice good cough hygiene, including covering your coughs and sneezes with a tissue and performing good hand hygiene.
• Avoid any unnecessary travel or travel to high-risk areas for COVID-19.
• Contact your healthcare professional if you think you may have come in contact with another person with suspected or confirmed SARS-CoV-2.
• Clean and disinfect any objects and surfaces that you touch frequently using a regular household cleaning spray or wipe.
• Refer to reputable information sources for additional details to prevent COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/community/index.html).

COVID-19: CONSIDERATIONS IN UNIQUE PATIENT POPULATIONS

Children

Children with SARS-CoV-1 tend to have milder disease and more favorable outcomes compared with adults [93-95]. The epidemiology of SARS-CoV-2 in children is evolving, but early observations suggest that immunocompetent children experience milder COVID-19 than adults [28,45,96-98], even though they have high viral loads [99] and prolonged respiratory and fecal viral shedding after COVID-19 [45,100]. Children at higher risk for severe COVID-19, defined as necessitating hospitalization or intensive care, include those with cardiovascular and chronic lung disease, infants age <1 year, and immunocompromised patients receiving immunosuppressive therapy [101]. Radiographic changes in children are reportedly similar to those seen in adults, with ground-glass and patchy opacities the most common finding [102,103]. Given their milder disease but prolonged viral shedding, children may act as significant reservoirs for SARS-CoV-2 in the community.

Immunocompromised Patients

Unlike their immunocompetent counterparts, immunocompromised patients likely have different COVID-19 features, including but not limited to the following: viral incubation period and duration of shedding, onset and duration of clinical signs and symptoms, viral detection and associated laboratory features, risk factors for progression to severe disease, risk for concomitant and secondary infections, and response to supportive care or future antiviral therapies. Such additional data on viral dynamics and immune response are critical in defining the risk of SARS-CoV-2 transmission from potential HCT donors to recipients and the influence on transplantation outcomes.

Immunocompromised patient populations are at elevated risk for severe infection from SARS-CoV-2 (Figure 1). At the time of this report, the literature on COVID-19 in immunocompromised patients is very limited, consisting of 2 case reports of COVID-19 in adult renal transplantation recipients [104,105], 1 case report of COVID-19 in a renal transplantation and HCT recipient [106], and 2 case series on COVID-19 in adult cancer patients [107,108].

The single case report of COVID-19 in a HCT recipient describes a 51-year-old Chinese male who underwent allogeneic HCT for acute myelogenous leukemia in June 2019 and developed COVID-19 22 days after traveling to Wuhan in February 2020 [106]. The details of the patient's HCT are scanty, but he was receiving maintenance cyclosporine and was lymphopenic at the time of COVID-19 infection, which ultimately progressed within 10 days of symptom onset. He required mechanical ventilation and died 22 days after symptom onset, seemingly from nosocomial bacterial infection. As his SARS-CoV-2 RNA was negative after treatment with lopinavir/ritonavir and methylprednisolone and discontinuation of cyclosporine [106].

Liang et al [107] reported on 18 adult cancer patients out of 1590 patients with COVID-19, most of whom were cancer survivors (n = 12; 67%) not receiving cancer-directed therapy. After adjusting for risk factors (age, smoking, and other comorbidities), cancer was associated with an increased risk for severe events (odds ratio, 5.34; 95% confidence interval [CI], 1.80 to 16.18; $P = .0026$), including more rapid clinical deterioration requiring ICU admission (hazard ratio, 3.56; 95% CI, 1.65 to 7.69) [107]. Yu et al [108] reported on their institutional

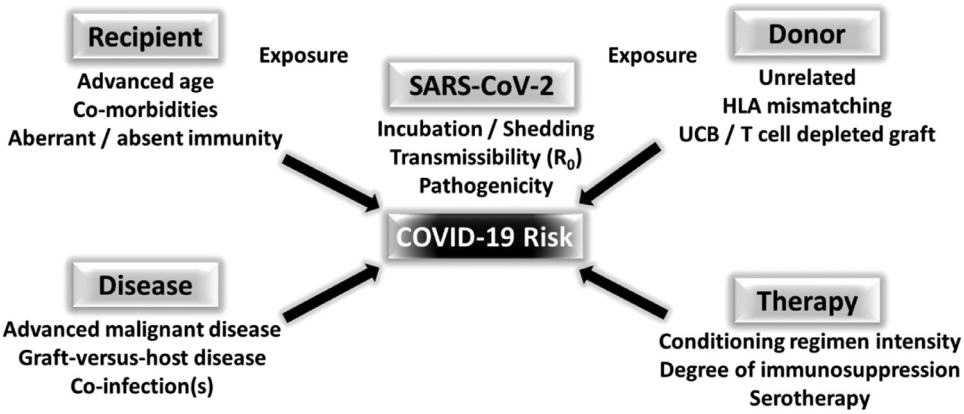


Figure 1. Presumed risk factors for COVID-19 in HCT recipients. The risk for developing COVID-19 is likely a composite of donor- and recipient-derived factors, underlying disease, and therapy received, in addition to exposure of both donor and recipient to SARS-CoV-2. In addition, factors inherent to the SARS-CoV-2 virus, including transmissibility (R_0), incubation period, and duration of shedding, also confer risk to the immunocompromised patient. UCB, umbilical cord blood.

experience with 12 of 1524 cancer patients who developed COVID-19 pneumonia during the COVID-19 outbreak in China. Similar to Liang et al [107], they found that cancer patients had a higher risk for developing SARS-CoV-2 infection (odds ratio, 2.31; 95% CI, 1.89 to 3.02) compared with the general community, and that older patients (>60 years) with non-small cell lung cancer (NSCLC) were at especially high risk [108]. Both groups concluded that cancer-directed therapies should be delayed and the frequency of hospital visits reduced, if possible, and that cancer patients with COVID-19 require more vigilant surveillance and likely more aggressive treatment.

In personal communications from the Italian experience in a pediatric hematology-oncology department in Lombardia, Italy on March 14, 2020, Balduzzi et al [109] reported that SARS-CoV-2 was not detected in any pediatric hematology-oncology or HCT patient, nor had any positive cases in these patients been reported elsewhere within Italy. The Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT) provided an update on their ongoing "prospective survey on impact of COVID-19 on stem cell transplant recipients" (https://www.ebmt.org/covid-19-and-bmt) at a webinar on March 20, 2020. Dr Per Ljungman reported that 15 patients (12 allogeneic HCT recipients and 3 autologous HCT recipients), with a median age of 59 years, developed COVID-19 post-HCT. Ten patients were diagnosed with an upper respiratory tract infection, and 5 patients were diagnosed with a lower respiratory tract infection. One of the 15 patients had died from COVID-19.

HCT Donors and Recipients

The COVID-19 pandemic poses unique challenges for the field of HCT related to donors, recipients, and cell products, all in the background of rapid change and stress to health care systems, suppliers, government agencies, and workforces. Reflecting such changes, guidelines for HCT from the American Society of Transplantation and Cellular Therapy (ASTCT) and the EBMT (summarized in Table 4) continue to evolve [110,111]. For the most up-to-date care guidelines and healthcare policies, the reader is directed to the Web-based resources listed in Table 5.

Donor Considerations

In addition to standard infectious disease marker screening for donor clearance, screening of the donor for exposure to COVID-19 is essential to prevent potential transmission of SARS-CoV-2 to the HCT recipient as well as to avoid undo harm to the donor. Specifically, donor screening by symptoms

Table 4
Evolving ASTCT and EBMT Guidelines for Autologous and Allogeneic HCT Donors and Recipients During the COVID-19 Pandemic[1-5]

	Low-Risk Disease	High-Risk Disease	Information/Recommendations
Recipients			Avoid exposure to COVID-19
			Refrain from travel
			Practice good hygiene
Confirmed COVID-19	Defer HCT for 3 mo	Defer HCT until asymptomatic and at least 2 negative weekly PCRs	
Exposed COVID-19	Defer HCT for at least 14 d, preferably 21 d	Deferral based on clinical judgement	Follow SARS-CoV-2 testing per local guidelines
	SARS-CoV-2 PCR screen with symptoms	SARS-CoV-2 PCR screen with symptoms	ASTCT: Screen all recipients at initial evaluation and 2 d before conditioning
Respiratory symptoms	Multiplex respiratory PCR	Multiplex respiratory PCR	If SARS-CoV-2 detected, defer as feasible. Chest imaging recommended for lower respiratory tract symptoms.
	SARS-Cov-2 PCR if available (NP sampling)	SARS-Cov-2 PCR if available (NP sampling)	
Donors			Avoid exposure to COVID-19
			Refrain from travel
			Practice good hygiene
Confirmed COVID-19	Exclude from donation	Exclude from donation	Unclear when to donate in future
Exposed COVID-19	Defer donation for 28 d	SARS-CoV-2 PCR screen	Follow SARS-CoV-2 testing per local guidelines
	Monitor for COVID-19	Monitor for COVID-19	
Respiratory symptoms	Multiplex respiratory PCR	Multiplex respiratory PCR	Defer donation if SARS-CoV-2 positive
	SARS-Cov-2 PCR if consistent (NP sampling)	SARS-Cov-2 PCR if consistent (NP sampling)	
Product			
	Do not collect	Collect and freeze if possible	Acquire and freeze product before start of conditioning
			If unable to freeze product, arrange for alternative donor

1. Guidelines compiled from the ASTCT Interim Guidelines for COVID-19 Management in Hematopoietic Cell Transplant and Cellular Therapy Patients (version 1.2, March 18, 2020), the EBMT recommendations update (April 7, 2020), and National Marrow Donor Program's "New TC requirement for unrelated donor products" (March 23, 2020).
2. Exposure includes living in or traveling from high-risk areas (WHO level 2 and 3) or exposed to close contacts with COVID-19.
3. Repeat negative SARS-CoV-2 PCR screen if clinical suspicion for COVID-19 given variable screening test sensitivities (ie, false-negative rates).
4. Bronchoalveolar lavage (BAL) sampling is discouraged if the patient is known to be SARS-CoV-2-positive unless coinfection is suspected.
5. 5. Donor-to-recipient transmission of MERS- or SARS-CoV in blood/cell products has not been reported.

Table 5
Resources for the COVID-19 Pandemic Pertinent to HCT and Cell Therapy

Topic	Organization	Website
Blood product agencies: donation policies/ convalescent plasma	American Association of Blood Banks (AABB)	http://www.aabb.org/advocacy/regulatorygovernment/Pages/AABB-Coronavirus-Resources.aspx
	AABB COVIDPlasma.org	https://covidplasma.org
	American Red Cross (ARC)	https://www.redcross.org/get-help/how-to-prepare-for-emergencies/types-of-emergencies/coronavirus-safety.html
	ARC COVID-19 Convalescent Plasma Program	https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients.html
Health agencies: general epidemiology/guidelines	Centers for Disease Prevention and Control (CDC)	https://www.cdc.gov/coronavirus/2019-nCoV/index.html
	CDC Emerging Infectious Diseases (EID)	https://wwwnc.cdc.gov/eid/
	CDC *Morbidity and Mortality Weekly Report* (MMWR)	https://www.cdc.gov/mmwr/index.html
	Children's Hospital Association (CHA)	https://www.childrenshospitals.org/COVID19?utm_source=constant_contact&utm_medium=email&utm_campaign=covid19&utm_term=covid_webpage&utm_content=031220
	European Centre for Disease Prevention and Control (ECDC)	https://www.ecdc.europa.eu/en/novel-coronavirus-china
	World Health Organization (WHO)	https://www.who.int/emergencies/diseases/novel-coronavirus-2019
Government agencies: general policies/resources	Centers for Medicare & Medicaid Services (CMS)	https://www.cms.gov/outreach-education/partner-resources/coronavirus-covid-19-partner-toolkit
	European Medicines Agency (EMA)	https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19
	National Comprehensive Cancer Network (NCCN)	https://www.nccn.org/covid-19/
	National Institutes of Health (NIH)	https://www.nih.gov/health-information/coronavirus
	NIH US National Library of Medicine ClinicalTrials.gov	https://clinicaltrials.gov/ct2/results?cond=COVID-19
	National Institute of Allergy and Infectious Diseases (NIAID)	https://www.niaid.nih.gov/diseases-conditions/coronaviruses
	US Food and Drug Administration (FDA)	https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19
	US government (USA Gov)	https://www.usa.gov/coronavirus
Infectious disease organizations: general resources	European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	https://www.escmid.org/research_projects/emerging_infections_task_force/eitafoutbreak_news/
	Infectious Diseases Society of America (IDSA)	https://www.idsociety.org/covid19
	Pediatric Infectious Diseases Society (PIDS)	http://www.pids.org/resources/covid-19.html
	American Society for Transplantation and Cell Therapy (ASTCT)	https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5

(*continued*)

Table 5 (*Continued*)

Topic	Organization	Website
Transplant organizations: donor/recipient screening and product guidelines		
	European Society for Blood and Marrow Transplantation (EBMT)	https://www.ebmt.org/covid-19-and-bmt
Donor registries: donor and product guidelines	National Marrow Donor Program (NMDP)	https://network.bethematchclinical.org/news/nmdp/be-the-match-response-to-covid-19/
	World Marrow Donor Association (WMDA)	https://share.wmda.info/display/DMSR/Coronavirus+-+COVID-19#/
Transplant registries: COVID-19 data collection	Center for International Blood & Marrow Transplant Research (CIBMTR)	https://www.cibmtr.org/Covid19/Pages/default.aspx
	EBMT Registry	https://www.ebmt.org/ebmt-patient-registry
	EBMT Infectious Diseases Working Party Prospective Survey	https://www.ebmt.org/ebmt/news/prospective-survey-impact-covid-19-stem-cell-transplant-recipients-and-patients-treated
Cell therapy regulatory agency	Federation for the Accreditation of Cellular Therapy (FACT)	http://www.factwebsite.org/News.aspx#news-id2014
	International Society Cell and Gene Therapy (ISCT)	https://isctglobal.org/news/
	Joint Accreditation Committee ISCTEurope & EBMT (JACIE)	https://www.ebmt.org/jacie-accreditation

and exposure should be done at the time of donor clearance and before product collection. Donor exclusion is based on the donor having COVID-19 at the time of screening or product collection. Given the notable overlap in symptoms among community respiratory viruses [112], respiratory multiplex PCR testing in addition to SARS-CoV-2 testing should be performed if the donor manifests respiratory symptoms. Additional considerations for donors include access to screening and collection centers, which may be impeded by travel restrictions and closures. Therefore, a donor backup plan is important, and frequent communication with the collection center is vital to ensure donor eligibility and to plan for alternative donors as needed [113]. The use of alternative donors, including umbilical cord blood and haploidentical donors, may be worth considering, particularly given the similar outcomes with these sources as with matched unrelated donor transplants.

Recipient Considerations

HCT recipients should be screened for COVID-19 exposure during the pretransplantation workup and up to and including the day before admission for transplantation. In the event of exposure to COVID-19 before transplantation, an HCT candidate with low-risk disease should have the procedure deferred for at least 14 days (preferably 21 days) while being monitored for symptoms. In an HCT candidate with high-risk disease, deferral of transplantation is based on clinical judgment.

Before transplantation, patients who develop respiratory symptoms should have the procedure postponed and undergo both community respiratory virus multiplex and SARS-CoV-2 PCR testing. In patients positive for COVID-19, autologous HCT should be deferred for at least 3 months, and allogeneic HCT should be deferred until the recipient is asymptomatic and has had at least 2 negative consecutive weekly PCR tests.

Transplantation Considerations

All elective HCTs for nonmalignant, nonurgent conditions should be delayed. However, more urgent HCT for high-risk malignant diseases may need to proceed despite donor and recipient exposure, as explained above. The conditioning regimen should not be initiated until the HCT donor and recipient have been cleared and the donor product has been deemed acceptable for use and is readily available. For unrelated donor grafts, the graft must be cryopreserved and on site before the start of conditioning.

Blood and Medication Considerations

According to the FDA, no cases of transfusion-transmitted respiratory viruses, including MERS and SARS-CoV, have been reported to date [114]. In addition, no transfusion-transmitted infections of SARS-CoV-2 have been reported by the AABB [115].

Interruptions in the blood supply have occurred, and there is a high likelihood that blood donors will either contract or be exposed to COVID-19. In this regard, SARS-CoV-2 RNA was detected by RT-PCR in 4 (3 whole blood, 1 platelets) out of 2430 total donor blood products (774 whole blood, 1656 platelets) collected at the Wuhan Blood Center, but no definite viral transmission was noted [116]. The AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism is encouraging to donating blood to maintain an adequate blood supply. The American Red Cross is also encouraging blood donation while recommending that individuals postpone donation if they have traveled to a pandemic area, been diagnosed with COVID-19, or been in contact with a person infected with COVID-19 [117]. Judicious use of blood products

through the use of more stringent transfusion criteria should now be applied.

With respect to the availability of pharmaceutical agents, including biological and immunosuppressive therapies, the American Society of Health-System Pharmacists has not posted any restrictions at this time [118]. However, interruptions in medication supplies are anticipated, given the significant amount of overseas drug manufacturing [119].

Research Considerations

Federal agencies and HCT-related research consortia have provided some guidance for patients enrolled in clinical trials with respect to anticipated deviations in sample acquisition, data reporting, and follow-up, as well as site visits by study moderators [120,121]. Such directions will need to anticipate disruptions caused by COVID-19 at the institutional level with respect to limitations on the clinical research office workforce. Most importantly, patient safety must be prioritized during the COVID-19 pandemic. To this end, central and institutional review boards will need to review protocol changes and offer suggestions [122].

ADDRESSING NEEDS OF PATIENTS AND HEALTHCARE PROVIDERS DURING COVID-19: A HOLISTIC CARE MODEL

The COVID-19 pandemic requires a multitiered approach to address boots-on-the-ground and system-level needs of HCT recipients and healthcare providers [123,124]. To this end, a holistic care model has been proposed with 4 interdependent focus areas: HCT patients and families, healthcare providers and institutions, government and regulatory agencies, and industry and the private sector (Figure 2). This care model functions by each focus area identifying and prioritizing goals that address basic to advanced needs within and across areas then working together to achieve those goals. Four vital components are needed to ensure that the model functions effectively: (1) agility to address and respond to rapid changes inherent to the COVID-19 pandemic; (2) consistent and accurate messaging at government, state or region, and local levels of care to provide unified recommendations for directing the public and industry; (3) reallocation and repurposing of available resources at the federal and local government and private sector levels to provide essential needs, including but not limited to diagnostics, therapeutics, finances, and essential goods; and (4) engaged and informed communities that understand their personal health needs, as well as the needs of the healthcare community at large.

To illustrate how this model might work, patients need access to faster point-of-care diagnostics and novel forms of therapy and prevention during COVID-19 [125]. To address this need, government and healthcare agencies must provide fast-tracking for these diagnostics and therapies by working with industry to facilitate product testing and production. One form of government support could be incentivizing industry with a fast-track approval process. Likewise, healthcare institutions need to provide access to these products for patients, but they can only do so by ensuring a safe work environment for care providers. In response, reallocation of resources and repurposing of manufacturing for PPE production would be supported by the government that could incentivize industry to create PPE garments and masks through grants or tax breaks. The effectiveness of this model hinges on a supportive community that receives consistent and reliable information to perform the needed tasks and to provide the needed resources by acting as an inclusive workforce (government, business, and healthcare industry).

Facilitating system learning is essential for the model's success, as health care providers need to apply successful best practices across institutions facing the COVID-19 pandemic, particularly as resources become increasingly scarce. Therefore, developing a transplantation-specific learning network

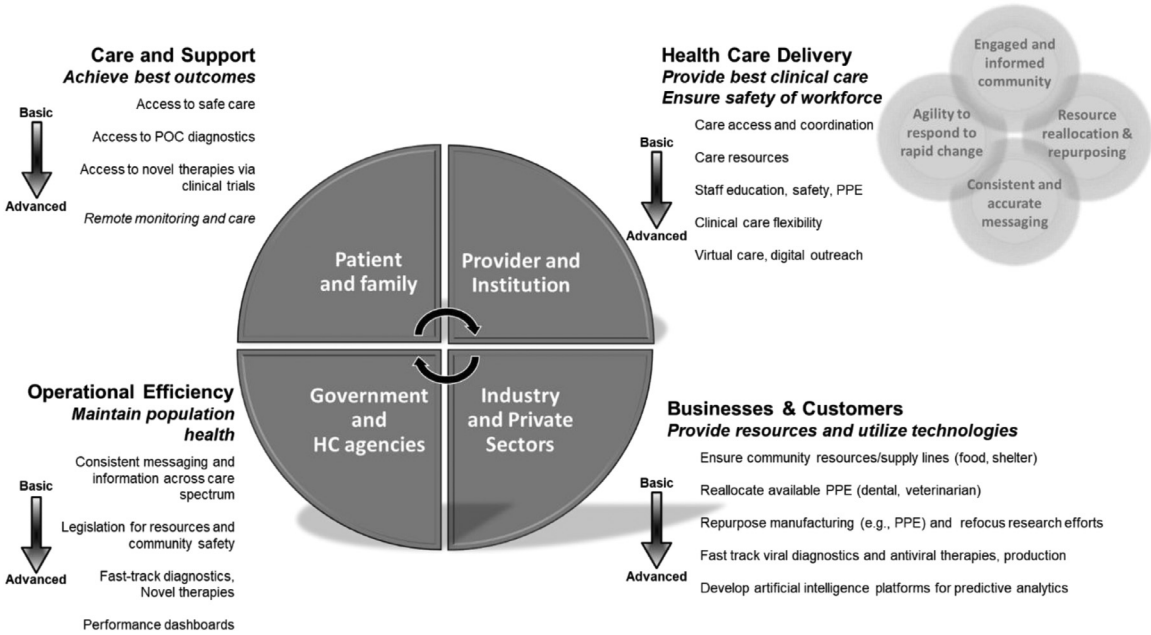


Figure 2. Proposed holistic care model for patients and healthcare providers during COVID-19. To address the COVID-19 pandemic, a holistic care model is needed that addresses 4 key areas—patients and families, healthcare providers and institutions, government and regulatory agencies, and the industrial and private sectors—through interdependent collaboration. Each focus area must identify and prioritize goals that address basic to advanced needs within and across areas. Finally, 4 key components are needed to ensure functionality of the model: agility to respond to changing needs, consistent and accurate messaging, resource reallocation and repurposing, and an engaged and informed community. HC, healthcare; POC, point of care.

potentially could enable goal-directed practice changes through information assimilation and sharing. The learning network could function similarly to address some of the goals in each focus area.

LEARNING NETWORKS: QUALITY IMPROVEMENT INITIATIVES TO DEFINE BEST PRACTICES

The Institute of Medicine defines learning health systems as networks that align scientific and cultural tools, leading to knowledge generation to improve healthcare as a result of daily practice [126]. Specifically, learning health networks are multicenter collaborations consisting of healthcare providers, researchers, patients, and families aimed at driving healthcare innovation and improving outcomes [2,127]. Institutions and individuals engaged in a learning health network work together to solve complex problems impacting patient care by sharing best practices, data, and new knowledge efficiently in real time [128-130]. Recent evidence demonstrates that collaborative learning health networks can achieve marked improvement in the quality of care [127,131-134].

Characteristics and Examples of Learning Networks

Learning network leaders facilitate alignment of the community around a common goal and have standards, processes, policies, and infrastructure in place to enable collaboration [135,136]. They use a platform for sharing ideas and resources that includes best practice materials and pertinent tools to address the mission of the network [137]. Members of the network receive regular reports on network functioning and key process and outcome measures that correlate with the mission of the network.

The Partnership of HIV-Free Survival is a learning health network comprising 6 countries with the goal of improving the survival of infants born to mothers with HIV [138]. Through collaborative efforts, this network has demonstrated effective best practices mechanisms for preventing mother-to-child transmission [139]. The primary purpose for the 112 pediatric hospitals participating in the Children's Hospitals' Solutions for Patient Safety collaborative is to eliminate serious healthcare-associated harm. From 2013 to 2019, by following best practices, approximately 14,000 children were protected from serious harm, with an estimated healthcare savings of $249.4 million and a consistent upward trend in harm prevented each month [140].

Transplant-Associated Learning Network Team

The Transplant-Associated Learning Network Team (TALNT), a learning network of the ASTCT, is a collaborative composed of transplantation and cellular therapy academic practitioners. The purpose of the TALNT is to improve the outcomes of adult and pediatric transplantation and cellular therapy recipients by building a sustainable collaborative network and operationalizing multi-institutional clinical, translational, and basic science research with quality improvement methodology to implement best practices.

Although still in its infancy, the TALNT has expanded dramatically, coinciding with the impact of the COVID-19 pandemic (Figure 3). The network started with 16 members and now includes 102 individuals from 35 hospitals from Belgium, Brazil, China, Lithuania, Spain, and the United States. An online platform with rules for participation, posting, and participation contains nearly 100 COVID-19-related documents, along with a message board covering 35 topics, which includes timely recommendations and insight from our colleagues in China. Use has increased substantially, with an average of 20 posts per day, which are automatically summarized into daily "latest activity" by discussion category (eg, PPE conservation), with associated responses and documents posted. After responding to a survey defining initial focus areas (Figure 4A), TALNT users are now providing substantive experiences, documents, and protocols relevant to focus areas and associated goals of the proposed holistic care model (Figure 4B). The network will continue its initial efforts on COVID-19, while longer-term goals include continued expansion, creation of best practices, and production of a quality improvement toolkit that includes online learning modules. In addition, the TALNT has the capacity to collect and share deidentified patient and systems-level

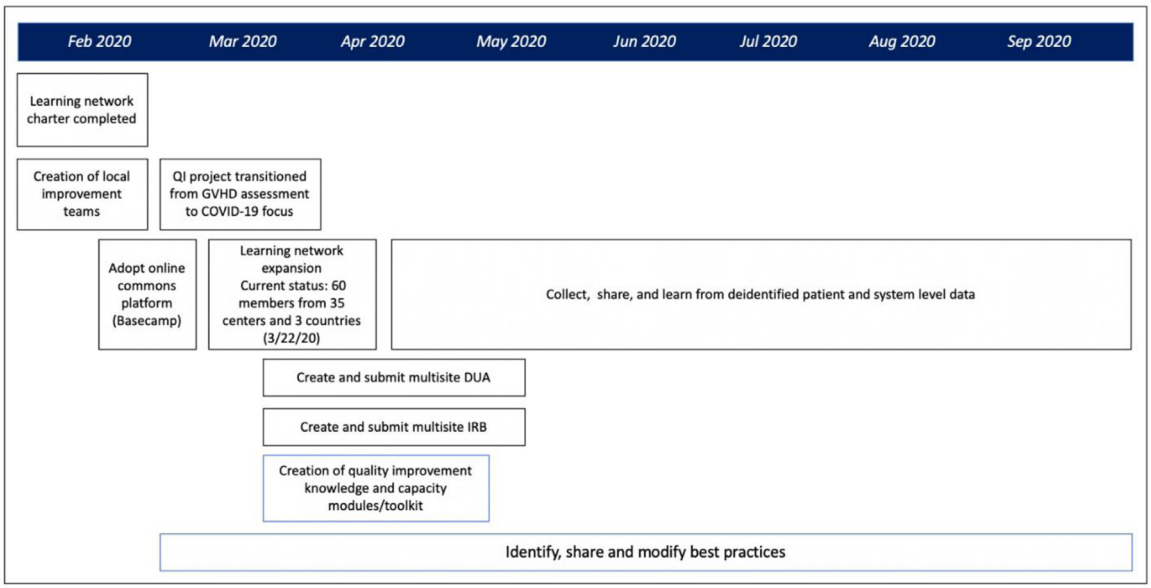
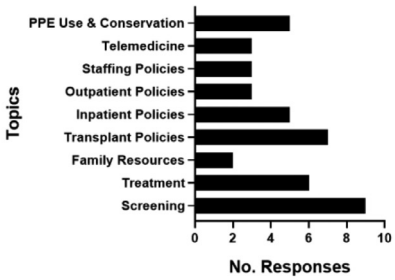


Figure 3. Timeline showing relevant activities of the TALNT, including membership profile and short-term and long-term goals. DUA, data use agreement; GVHD, graft-versus-host disease; IRB, institutional review board; QI, quality improvement.

A



B

Top 3 topics	Focus Areas	Goals	Examples of relevant content posted (questions or information listed)
Screening	Patient and Family	Access to diagnostics	What are your hospital policies on screening staff and patients?
	Provider and Institution	Care resources	Is your institution providing pre-transplant COVID-19 screening?
		Care coordination	I'm curious what changes centers have made to daily rounding? Is everyone still rounding live? Anyone doing table or virtual rounds incorporating Skype/Zoom for support staff etc? How are these working?
Transplant policies	Patient and Family	Access to safe care	ASTCT and EMBT Donor and Recipient Guidelines, EBMT COVID-19 Conference Call notes
	Provider and Institution	Staff safety, education	What is the mask policy at your center? Are asymptomatic care team members wearing masks when they are in contact with BMT patients?
		PPE	What policies are in place at your institution for conserving PPE?
Treatment	Patient and Family	Access to therapies	Does your institution have COVID-19 treatment guidelines?
	Provider and Institution	Care resources	For centers currently treating patients with COVID-19, what recommendations would you give hospitals and providers that have not yet been impacted by the pandemic?

Figure 4. TALNT survey results and subsequent content shared through an online platform relevant to care model focus areas and goals. (A) TALNT membership survey results. Members were asked to rank which topics would be most helpful for addressing COVID-19. The top 3 topics became the focus for future interaction among the membership. (B) The top 3 topics and their relevance to focus areas and goals of the proposed holistic care model needed to confront the COVID-19 pandemic. Examples of content posted on the online platform are provided, including questions as well as publications.

data, and so learning among participants can translate into improved outcomes in HCT recipients.

We believe that learning networks can be transformative tools for the transplantation community given the COVID-19 pandemic. Our TALNT learning health network is aligned to decrease morbidity and mortality from COVID-19 in the HCT population and to optimize our healthcare delivery by enabling real-time collaboration and learning among practitioners and institutions.

CONCLUSIONS

COVID-19 has a significant impact in immunocompromised hosts, particularly HCT recipients, as well as HCT donors and medical caregivers. The present report extrapolates from previously published CoV data and experiences, summarizes current SARS-CoV-2 data, and offers both care considerations and recommendations based on current data. Ongoing modifications will be necessary with the increasing availability of data about COVID-19 in immunocompromised patients that will better inform individual and system-level care. Clinical personnel and transplantation centers must keep abreast of changing dynamics, evolving SARS-CoV-2 data, and governmental policies and recommendations within the context of their local epidemiology. Open collaboration and communication among institutional infectious disease, infection control, and prevention teams within transplantation centers and local and state health departments will be vital in providing optimal care to all patients, especially those at greatest risk for severe COVID-19.

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