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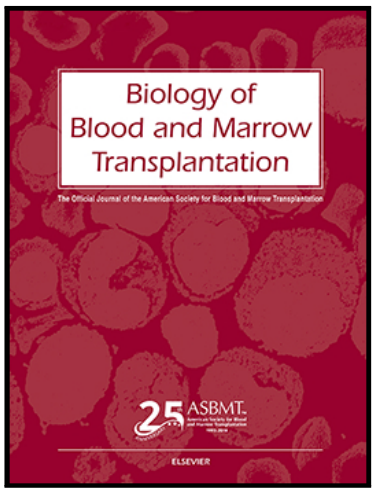

Addressing the impact of the Coronavirus Disease (COVID-19) pandemic on hematopoietic cell transplantation: Learning networks as means for sharing best practices

M.I. Ardura DO MSCS , D.M. Hartley PhD MPH , C. Dandoy MD , L. Lehmann MD , S. Jaglowski MD MPH , J.J. Auletta MD , for the Transplant-Associated Learning Network (TALNT)

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Addressing the impact of the Coronavirus Disease (COVID-19) pandemic on hematopoietic cell transplantation: Learning networks as means for sharing best practices

MI Ardura DO MSCS[1,2], DM Hartley PhD MPH[3,4], C Dandoy MD[4,5], L Lehmann MD[6];

S Jaglowski, MD MPH[7,8]; and JJ Auletta MD[1,2,8,9] for the Transplant-Associated Learning Network (TALNT)*

[1]Host Defense Program, Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, OH; [2]Department of Pediatrics, The Ohio University College of Medicine, Columbus, OH; [3]James M. Anderson Center for Health Systems Excellence, Cincinnati Children's Hospital, Cincinnati, OH; [4]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; [5]Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital, Cincinnati, OH; [6]Pediatric Stem Cell Transplant Center, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA; [7]Division of Hematology, The Ohio State University, Columbus, OH; [8]The Ohio State University Comprehensive Cancer Program; [9]Blood and Marrow Transplant Program, Division of Hematology/Oncology/BMT, Nationwide Children's Hospital, Columbus, OH

*Transplant-Associated Learning Network (TALNT) Collaborators:

- N Bhatt MD nbhatt@fredhutch.org Clinical Research Division, Fred Hutchinson Cancer Research Center; Department of Pediatrics, University of Washington, Seattle, WA
- J Huber PhD John.Huber@cchmc.org Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital, Cincinnati, OH
- MB Juckett MD mbj@medicine.wisc.edu Department of Bone Marrow Transplantation, University of Wisconsin School of Medicine and Public Health, Madison, WI
- M Mueller Mark.Mueller@cchmc.org Bone Marrow Transplantation and Immune Deficiency,

Cincinnati Children's Hospital, Cincinnati, OH

• S Rotz MD ROTZS@ccf.org Pediatric Hematology Oncology, Cleveland Clinic, Cleveland, OH

• R Phelan MD rphelan@mcw.edu Division of Pediatric Hematology/Oncology/BMT, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI

• S Tarquini PhD Sarah_Tarquini@DFCI.HARVARD.EDU Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

• C Rosati RN Christine_Rosati@DFCI.HARVARD.EDU Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Corresponding author: Jeffery J. Auletta, M.D.

Division of Hematology/Oncology/BMT

Nationwide Children's Hospital, Suite 5A.1, Columbus, OH 43205

Phone: 614-722-3582, Fax: 614-722-3369

Email: jeffery.auletta@nationwidechildrens.org

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Abstract

The full impact of the Coronavirus Disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2 virus, 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 patients; 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 transplant centers.

Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel single strand (ss) RNA beta-coronavirus, has caused the current Coronavirus Disease 2019 (COVID-19) pandemic. As of April 13, 2020, the World Health Organization (WHO) reported 1,773,084 laboratory confirmed cases and 111,652 deaths globally.[1] What ultimate impact COVID-19 will have on the field of hematopoietic cell transplantation (HCT) is currently unknown. This perspectives paper anticipates the significant influence of COVID-19 on HCT patients given their immune compromise, presence of other medical co-morbidities, 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 and distributing evolving information to transplant 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 though 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 CoV: 89% identical to the bat severe acute respiratory syndrome (SARS-like CoV) and 82% identical to human SARS-CoV-1, thus the virus was re-identified as SARS-CoV-2.[7-9] SARS-CoV-2 is also similar to other zoonotic CoV causing global outbreaks of severe respiratory illnesses like 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 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' basic reproduction number (R_0), an epidemiologic metric describing transmissibility in terms of the average number of cases that could be caused by one infected patient in a susceptible population,[15] has been estimated to be 1.4-3.0[16] versus seasonal influenza R_0 ~1.2-3, pertussis R_0 ~12-17, and measles R_0 ~12-18.[15,17] The COVID-19 case fatality risk (CFR) is estimated to be in the range 0.25-4.7%[18,19] with highest mortality reported in older adults with co-morbidities and varying by geographic location.[20] Preliminary data from the United States suggest high fatality in persons aged 85 years and older (CFR ~10%-27%), lower CFR in persons aged 65–84 years (~3%-11%), and further declines in younger age groups (CFR ~1%-3% in 55-64 year old persons, <1% in persons aged 20–54 years).[21,22] Striking in these data is the proportion of severe disease and hospitalization in younger adults (45-64 years of age), which contrasts with the Chinese experience.[21]

Clinical manifestations

After an estimated median incubation period of 5 days (range 2-14 days), patients may present with fever (77-98%) and non-specific symptoms similar to an influenza-like illness (e.g., 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 17-29% of patients.[8,20,23,24] Progression to LRTD generally occurs around 10 days after illness onset.[4] Though 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 47-71% 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 63-83% of patients.[10,20,23,29] Notably, decreases in $CD8^+$ T-cells and B cells in adults have associated with severe COVID-19 and poor response to therapy[30] while $CD8^+$ T-cell and B cell recovery has associated with moderate disease.[31] Finally, decreases in regulatory T cells have also associated with a hyperinflammatory response in adults,[32] requiring the use of monoclonal blocking antibodies like tocilizumab.[33]

Given these preliminary observations, lymphopenia and alloreactivity associated with HCT may portend a worse prognosis from 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 (229E, NL63, OC43, HKU1) vary based upon age. Although endemic CoV were detected frequently among pediatric HCT recipients, low absolute lymphocyte count did not associate with progression to LRTD or severe LRTD, but level of immunosuppression did.[37] Among adult HCT recipients with endemic CoV, 34/112 (30%) patients progressed to LRTD with graft-versus-host disease (GvHD), corticosteroids, hypoalbuminemia, and older age associating with disease progression.[38]

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

Diagnosis

a. Viral dynamics

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], depend on clinical manifestations and disease severity,[46,47] and influenced by variation in assay sensitivity and specificity[48]. As a result, PCR diagnostic capability may be suboptimal in comparison to other modalities like chest imaging[49] and a negative PCR result does not conclusively exclude COVID-19.

Preliminary data suggest 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 8-37 days).[50] In addition, SARS-CoV-2 viral loads from NP sites have been found to be similar in both asymptomatic and symptomatic patients.[51] Furthermore, SARS-CoV-2 transmission occurs from asymptomatic persons, whom likely contribute to rapid viral dissemination[13]. The significance of ongoing viral detection by PCR in asymptomatic persons, including whether detection equates with 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.[43,52,53]

b. 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, the severity of disease, and local epidemiology patterns for the disease. Clinicians should have a high index of suspicion to test patients that 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.[54,55] A close contact is defined as being within

6 feet (2 meters) of a COVID-19 case for a prolonged period of time or having direct contact with infectious secretions of a COVID-19 case.[56] In addition, patients with severe LRT disease of unclear etiology should be considered for testing. A coronavirus self-checker is now available for patients to help guide them through the process.[57] If a patient is considered a person under investigation (PUI) by geographic[56] or healthcare[58] exposure, clinicians should immediately institute appropriate infection precautions (see details below) and notify their state and local health departments.

Current commercial 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 but have limitations as previously reviewed. For initial testing, the CDC recommends testing upper respiratory tract specimens (NP swaps) in all PUI. In patients with a productive cough, testing sputum may be performed, but procedures that generate aerosols are discouraged. For example, BAL sampling is considered high-risk for aerosol dissemination and is not recommended in a patient 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 and who have or develop LRT symptoms. Research is ongoing to improve diagnostic strategies, including more rapid, point of care PCR tests[59] and serologic assays to identify patients still at risk.[60]

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 World Health Organization (WHO).[61-63] At this time, there are no proven effective therapies against SARS-CoV-2.[64] Safety and efficacy of other treatment options for COVID-19 are currently being evaluated (**Table 1**).[65,66] Recently, the WHO has announced the "Solidarity Trial," a multi-country 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.[67]

Remdesivir is an intravenous investigational novel nucleoside analogue in development, that has previously been given for treatment of Ebola and MERS diseases[68,69] and demonstrated *in vitro* activity against SARS-CoV-2.[70] Remdesivir was approved by the Food and Drug Administration (FDA) for an NIH-sponsored randomized controlled clinical trial for hospitalized COVID-19 patients with advanced symptoms (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) patients.[71]

Convalescent plasma collected from patients who have recovered from COVID-19 is being evaluated as treatment based upon its use in other severe viral infections.[72,73] A recent limited intervention study noted that convalescent plasma therapy in adults with severe COVID-19 whom were receiving multiple other investigational therapies was well tolerated (primary endpoint) and demonstrated potential clinical efficacy as measured by improvement in clinical symptoms, laboratory abnormalities, and radiographic imaging (secondary endpoints).[74] Clinical trials are now available for adults to assess safety and efficacy of convalescent plasma based upon virologic and clinical endpoints (https://clinicaltrials.gov).

Given the increasing data supporting a hyperinflammatory state in adults with severe COVID-19,[75] clinical research trials are ongoing to evaluate the effect of IL-6 blockade on COVID-19 outcomes.[76,77] Systemic corticosteroids are not routinely recommended for treatment, given 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 (e.g., ARDS, septic shock).[78]

Prevention

Three basic, but effective strategies should be implemented by all inpatient BMT units and outpatient clinics (**Table 2**): (1) Proper frequent handwashing, including before and after patient

encounters, is a primary tool to prevent spread of a respiratory illness;[79-81] (2) Standardized visitor screening that is limited to direct caregivers only[80,82]; and (3) Mandating that sick employees stay home.[79,80] Transplant centers should initiate these strategies immediately and identify mechanisms to reliably improve adherence to these best practices.

As nosocomial transmission of SARS-CoV-2 has been reported,[28,83] best practices in hospital infection control must be used to prevent SARS-CoV-2 transmission to other patients and healthcare personnel.[82] Despite environmental contamination by SARS-CoV-2,[84] effective infection control practices and environmental cleaning can prevent nosocomial transmission of SARS-CoV-2.[85,86] Infection prevention measures should be immediately instituted for any PUI, including masking the patient and moving him/her into a private room optimally with airborne isolation. Hospital personnel should follow standard, contact, and airborne precautions, including use of appropriate personal protective equipment (PPE) and eye protection.[82] However, the COVID-19 pandemic has highlighted the continued burden and challenges to healthcare resources that require redirection of timely efforts to conserve, optimize, and restock equipment, including PPE.[87]

In the ambulatory setting, preventative measures should be provided to HCT patients 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.[79] Additionally, continued public health efforts should be employed to mitigate community transmission of COVID-19.[88]

Multiple vaccine candidates have been identified[89] and clinical trials are underway,[90] including an open-label phase 1 trial of differing doses of mRNA-1273 to assess the safety and efficacy against SARS-CoV-2[91] and microneedle array delivered SARS-CoV-2 subunit vaccines, which can be rapidly

produced and generate potent antibody responses.[92] Together with rapid diagnostic and serologic testing, vaccines serve as the foundation for current and future protection against SARS-CoV-2.[93]

COVID-19: Considerations in unique patient populations

Children

Children with SARS-CoV-1 had milder disease and more favorable outcomes than adults.[94-96] The epidemiology of SARS-CoV-2 in children is evolving, but early observations suggest that immunocompetent children experience milder COVID-19 than adults,[45,97-100] even though they have high viral loads[101] and prolonged respiratory and fecal viral shedding after COVID-19.[45,102] Children at higher risk for severe COVID-19 defined as requiring hospitalization or intense care include those with cardiovascular and chronic lung disease, infants under one year of age, and immunocompromised patients receiving immunosuppression.[103] Radiographic changes in children are reported to be similar to adults with ground-glass and patchy opacities being the most common finding.[104,105] Given their having milder disease, but prolonged viral shedding, children may act as a significant reservoir 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 is critical in defining risk of SARS-CoV-2 transmission from potential HCT donor to recipient and the influence on transplant outcomes.

Immunocompromised patient populations are at higher risk for severe infection from SARS-CoV-2 (**Figure 1**). At the time of this manuscript, very limited has been published on COVID-19 in immunocompromised patients, namely two case reports of COVID-19 in adult renal transplant patients[106,107], one case report including a renal transplant and HCT recipient[108], and two case series on COVID-19 in adult cancer patients.[109,110]

The single HCT case report is 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.[108] HCT details are scant, but the patient was receiving maintenance cyclosporine (CSA) and was lymphopenic at the time of COVID-19 infection, which ultimately progressed within 10 days of symptom onset. The patient required mechanical ventilation and passed away 22 days after symptom onset, seemingly from nosocomial bacterial infection, as his SARS-CoV-2 RNA was negative after receiving lopinavir/ritonavir and methylprednisolone and discontinuing his CSA.[108]

Liang and colleagues reported on 18 adult cancer patients out of 1590 COVID-19 patients, most of whom being cancer survivors (12, 67%) and not receiving cancer-directed therapy.[109] After adjusting for risk factors (age, smoking and other comorbidities), cancer associated with a higher risk for severe events (OR 5.34, 95% CI 1.80-16.18, p=0.0026), including more rapid clinical deterioration requiring ICU (HR 3.56, 95% CI 1.65-7.69).[109]

Yu and colleagues reported on their institutional experience with 12 of 1,524 cancer patients whom had COVID-19 pneumonia during the COVID-19 outbreak in China.[110] Similar to Liang and colleagues, Yu et al. found that cancer patients had a higher risk for developing SARS-CoV-2 infection (OR 2.31, 95% CI 1.89-3.02) versus the general community and that older patients (>60 y) with non-small cell lung cancer (NSCLC) were especially at risk.[110] Authors from both publications concluded that cancer-directed therapies should be delayed and reduce frequency of hospital visits, if possible, and that cancer patients with COVID-19 required 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 and colleagues reported that SARS-CoV-2 was not detected in any pediatric hematology-oncology or HCT patients nor had positive cases in these patients been reported elsewhere within Italy.[111] The Infectious Diseases Working Party of 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, 3 autologous) with a median age 59 years developed COVID-19 post-HCT. Ten and five patients were diagnosed with upper and lower respiratory tract infection, respectively. One of the 15 patients had died from COVID-19.

Hematopoietic cell transplant donors and recipients

The COVID-19 pandemic has caused unique challenges for the field of HCT relating to donors, recipients, and cell products, all in the background of rapid change and stress to health care systems, suppliers, government agencies, and workforces. As a reflection of such changes, HCT guidelines from the American Society of Transplantation and Cellular Therapy (ASTCT) and the EBMT summarized in **Table 4** continue to evolve.[112,113] For the most up-to-date care guidelines and healthcare policies, the reader is directed to the web-based resources listed in **Table 5.**

a. Donor considerations

In addition to standard infectious disease marker screening for donor clearance, screening the donor for exposure to COVID-19 is essential to prevent potential transmission of SARS-CoV-2 to the HCT candidate as well as not to cause undo harm to the donor. Specifically, donor screening by symptoms and exposure should occur at the time of donor clearance and prior to product collection. Donor exclusion is based upon the donor having COVID-19 at the time of screening or product collection. Given the notable overlap in symptoms among community respiratory viruses,[114] 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, donor back-up plans are needed, and frequent communication with the collection center is vital to ensure donor eligibility and plan for alternative donors as needed.[115] The use of alternative donors including umbilical cord transplants and haploidentical donors may be worth considering, particularly given their having similar outcomes with matched unrelated donor transplants.

b. Recipient considerations

HCT recipients should be screened for COVID-19 exposure during the pre-transplant work-up and up to and including the day prior to admission for transplant. If the HCT recipient is exposed to COVID-19 prior to transplant, patients with low-risk disease should have transplant deferred for at least 14 days (preferred 21 days) while being monitored for symptoms. If the transplant candidate has high-risk disease, HCT deferral is based upon clinical judgment.

Prior to transplant, patients who develop respiratory symptoms should have transplant postponed and undergo both community respiratory virus multiplex and SARS-CoV-2 PCR testing. Patients with COVID-19 should have autologous transplants deferred for at least three months, and allogeneic transplant until the recipient is asymptomatic and has at least two negative consecutive weekly PCR tests.

c. Transplant considerations

All elective HCT for non-malignant, non-urgent 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 start until the HCT donor and candidate have been cleared, and the donor product deemed acceptable for use and readily available. For unrelated donor grafts, the graft must be cryopreserved and on-site prior to the start of conditioning.

d. Blood and medication considerations

According to the U.S. FDA, no cases of transfusion-transmitted respiratory viruses, including MERS and SARS-CoV, have been reported to date.[116] In addition, no transfusion-transmitted infections of SARS-CoV-2 have been reported by the American Association of Blood Banks (AABB).[117]

Interruptions in the blood supply have occurred, and there will be a high likelihood that blood donors will either contract or be exposed to COVID-19. In this regard, SARS-CoV-2 RNA was detected via RT-PCR in 4 (3 whole blood, 1 platelet) of 2,430 total donor blood products (774 whole blood, 1,656 platelets) collected at the Wuhan Blood Center; but no definite viral transmission was noted.[118] The AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism is encouraging Americans to donate blood in order to maintain an adequate blood supply. The American Red Cross (ARC) is also encouraging blood donation and recommends 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.[119] Judicious use of blood products through the use of more stringent transfusion criteria should now be applied.

With respect to availability of pharmaceutical agents including biologic and immunosuppressive therapies, the American Society of Health-System Pharmacists (ASHP) has not posted any restrictions at this time.[120] However, interruption in medication supply is anticipated given the significant amount of overseas drug manufacturing.[121]

e. 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.[122,123] Such directions will need to anticipate disruptions that COVID-19 has caused at the institutional level with respect to limitations on the clinical research office workforce. Most importantly, patient safety must be the prioritization during the COVID-

19 pandemic. To this end, central and institutional review boards will need to review protocol changes and offer suggestions[124].

Addressing needs of patients and healthcare providers during COVID-19: A holistic care model

The COVID-19 pandemic requires a multi-tiered approach to address boots-on-the-ground and system level needs of HCT patients and healthcare providers.[125,126] To this end a holistic care model is proposed with four interdependent focus areas including HCT patients and families, healthcare providers and institutions, government and regulatory agencies, and the industry and private sectors (**Figure 2**). The 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: (a) agility to address and respond to rapid changes inherent to the COVID-19 pandemic; (b) consistent and accurate messaging at government, state or region, and local levels of care to provide unified recommendations for directing the public and industry; (c) reallocation and re-purposing of available resources, at the federal and local government and private sectors levels to provide essential needs, including but not limited to diagnostics, therapeutics, finances and essential goods; and (d) engaged and informed communities that understand their personal health needs as well as the needs of the healthcare community at large.

To illustrate how the model might work, patients need access to faster point-of-care (POC) diagnostics and novel forms of therapy and prevention during COVID-19.[127] 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 of these products to patients but 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. Yet to ensure success, all proposed steps need 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, 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 less available. Therefore, developing a transplant-specific learning network could potentially enable goal-directed practice changes through information assimilation and sharing. The learning network could similarly function 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 which align scientific and cultural tools, which lead to knowledge generation to improve healthcare as a result of daily practice.[128] Specifically, learning health networks are multicenter collaborations consisting of healthcare providers, researchers, patients and families to drive healthcare innovation and improve outcomes.[2,129] 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 learnings efficiently in real time.[130-132] Recent evidence demonstrates that collaborative LHNs can achieve marked improvement in the quality of care.[129,133-136]

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 to enable collaboration.[137,138] They utilize a platform for sharing ideas and resources, which contains best practice materials and pertinent tools to

the mission of the network.[139] Members of the network receive regular reports on network functioning and key process and outcome measures that correlate to the mission of the network.

The Partnership of HIV-Free Survival (PHFS) is a learning health network consisting of six countries whose aim was to improve survival of infants born to mothers with HIV.[140] Through collaborative efforts, the PHFS has demonstrated mechanisms to use for prevention of mother-to-child transmission best-practices.[141] The primary purpose for the 112 pediatric hospitals participating in the Children's Hospitals' Solutions for Patient Safety (SPS) collaborative is to eliminate serious healthcare-associated harm. By using 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 every month (2013-2019).[142]

Transplant-Associated Learning Network Team (TALNT)

The Transplant-Associated Learning Network Team (TALNT), a learning network of the American Society for Transplant and Cellular Therapy (ASTCT), is a collaborative composed of transplant and cellular therapy academic practitioners. The purpose of TALNT is to improve the outcomes of adult and pediatric transplant and cellular therapy patients 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 in its infancy, 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, a message board consisting of 35 topics including timely recommendations and insight from our colleagues in China. Use has increased substantially with an average 20 posts per day, which are automatically summarized into daily "latest activity" by discussion category (e.g., PPE conservation) with

associated responses and documents posted. After responding to a survey defining initial focus areas (**Figure 4, panel A**), TALNT users are now providing substantive experiences, documents, and protocols relevant to focus areas and associated goals of the proposed holistic care model (**Figure 4, panel B**). 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. Additionally, TALNT has the capacity to collect and share de-identified patient and systems level data; so learning among participants improves outcomes in HCT recipients.

We believe learning networks can be transformative tools for the transplant 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 optimize our healthcare delivery, by enabling real-time collaboration and learning among practitioners and institutions.

Conclusions

COVID-19 has caused significant impact to immunocompromised hosts, particularly HCT recipients, as well as HCT donors and medical caregivers. This work extrapolates from past CoV data and experience and summarizes current SARS-CoV-2 data, offering both care considerations and recommendations based on currently published data. Ongoing modifications will be required as more data becomes available about COVID-19 in immunocompromised patients that will better inform individual and system-level care. Clinical personnel and transplant 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 transplant centers, and local and state

health departments will be vital in providing optimal care to all patients, especially those at highest risk for severe COVID-19.

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

Agent	Data from prior studies	Clinical trials number, other sources
Remdesivir	Ebola, MERS	NCT04280705 NCT04302766 NCT04292899 NCT04292730 NCT04252664 NCT04257656
Favipiravir	Ebola	NCT04310228 (In Japan) NCT04303299
Lopinavir/ritonavir[143-146]	SARS-CoV, MERS	NCT04261907 NCT04276688 NCT04307693
Chloroquine[147,148]	SARS-CoV	NCT04307693 NCT04315896
Interferon-alpha 2B[149,150]	MERS	NCT04293887
Camostat mesylate	SARS-CoV	approved in Japan, no prior human testing
Nitazoxanide[151]	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

ARDS, acute respiratory distress syndrome; CoV, coronavirus; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; COVID-19, coronavirus disease 2019; N/A not applicable
Complete list of COVID-19 clinical trials available at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=COVID-19)

Table 2. Process and practice interventions associated with improved compliance

Process	Potential mechanisms for process measurement	Practice interventions associated with improved compliance
Handwashing[80,81]	Direct observation[152,153] Amount of soap used[154]	• Patient, caregiver and hospital staff handwashing education initiatives[155] • Physician and staff financial incentives[155] • Frequent reminders[154] • Timely and frequent audits[156] • Individual feedback to promote accountability[156]
Screen patients and visitors for symptoms of acute respiratory illness[80]	Direct assessment for all persons entering the BMT unit	Consider highly reliable interventions[157-160] • 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[79,80]	Number of employees self-reporting	• Staff education of when self-reporting should be completed[161] • Adoption of a *just culture* for self-reporting[162] ○ Self-reporting is encouraged and rewarded and avoids focusing on individual blame but on improving the 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 a fever, cough, sore throat, headache or body aches; contact your healthcare professional should your symptoms worsen before presenting to 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]

Table 4. Evolving ASTCT and EBMT transplant guidelines for autologous and allogeneic hematopoietic cell transplant donors and recipients during the COVID-19 pandemic

	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 months	Defer HCT until asymptomatic and negative weekly PCR at least x 2	
Exposed COVID-19	Defer HCT at least 14 days, prefer 21 days SARS-CoV-2 PCR screen with symptoms	Deferral based upon clinical judgement SARS-CoV-2 PCR screen with symptoms	Follow SARS-CoV-2 testing per local guidelines ASTCT: Screen all recipients at initial evaluation and 2 days before conditioning
Respiratory symptoms	Multiplex respiratory PCR SARS-Cov-2 PCR if available (NP sampling)	Multiplex respiratory PCR SARS-Cov-2 PCR if available (NP sampling)	If SARS-CoV-2 detected, defer as feasible. Chest imaging recommended for LRT symptoms.
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 days Monitor for COVID-19	SARS-CoV-2 PCR screen Monitor for COVID-19	Follow SARS-CoV-2 testing per local guidelines
Respiratory symptoms	Multiplex respiratory PCR SARS-Cov-2 PCR if consistent (NP sampling)	Multiplex respiratory PCR SARS-Cov-2 PCR if consistent (NP sampling)	Defer donation if SARS-CoV-2 positive.
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

Notes:

1. Guidelines compiled from American Society for Transplantation and Cell Therapy (ASTCT) Interim Guidelines for COVID-19 Management in Hematopoietic Cell Transplant and Cellular Therapy Patients (Version 1.2, March 18, 2020), European Society for Blood and Marrow Transplantation (EBMT) Recommendations Update April 7, 2020, and National Marrow Donor Program "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 (i.e. false negative rates).
4. Bronchoalveolar lavage (BAL) sampling is discouraged if the patient is known to SARS-CoV-2 positive unless co-infection is suspected.
5. Donor to recipient transmission of MERS- or SARS-CoV in blood/cell product has not been recorded.

Abbreviations: CoV= Coronavirus; COVID-19, Coronavirus Disease 2019; HCT, hematopoietic cell transplantation; LRT, lower respiratory tract; MERS, Middle East respiratory syndrome; NP, nasopharyngeal; PCR, polymerase chain reaction; SARS-CoV-2, severe acquired respiratory syndrome coronavirus 2

Table 5. Resources for the COVID-19 pandemic pertinent to hematopoietic cell transplantation 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 U.S. 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
	U.S. Food & Drug Administration (FDA)	https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19
	U.S. 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
Transplant Organizations: Donor / Recipient Screening and Product Guidelines	American Society for Transplantation and Cell Therapy (ASTCT)	https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5
	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

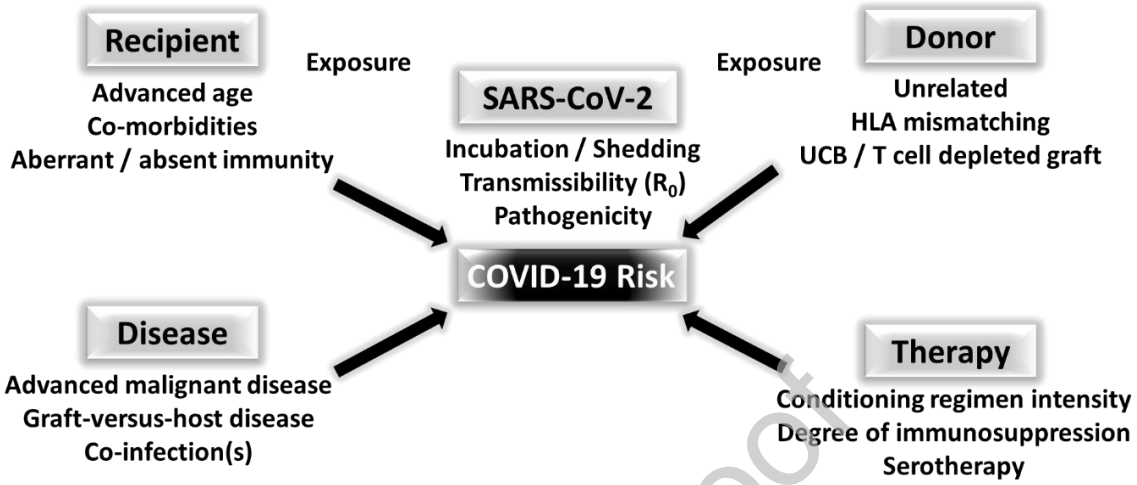


Figure Legends

Figure 1. **Presumed risk factors for COVID-19 in hematopoietic cell transplant patients.** 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 like transmissibility (R_0), incubation period, and duration of shedding also confer risk to the immunocompromised patient. COVID, Coronavirus Disease 2019; HLA, human leukocyte antigen; R_0, basic reproduction number; SARS-CoV-2, Severe Acute Respiratory Syndrome-coronavirus 2; UCB, umbilical cord blood.

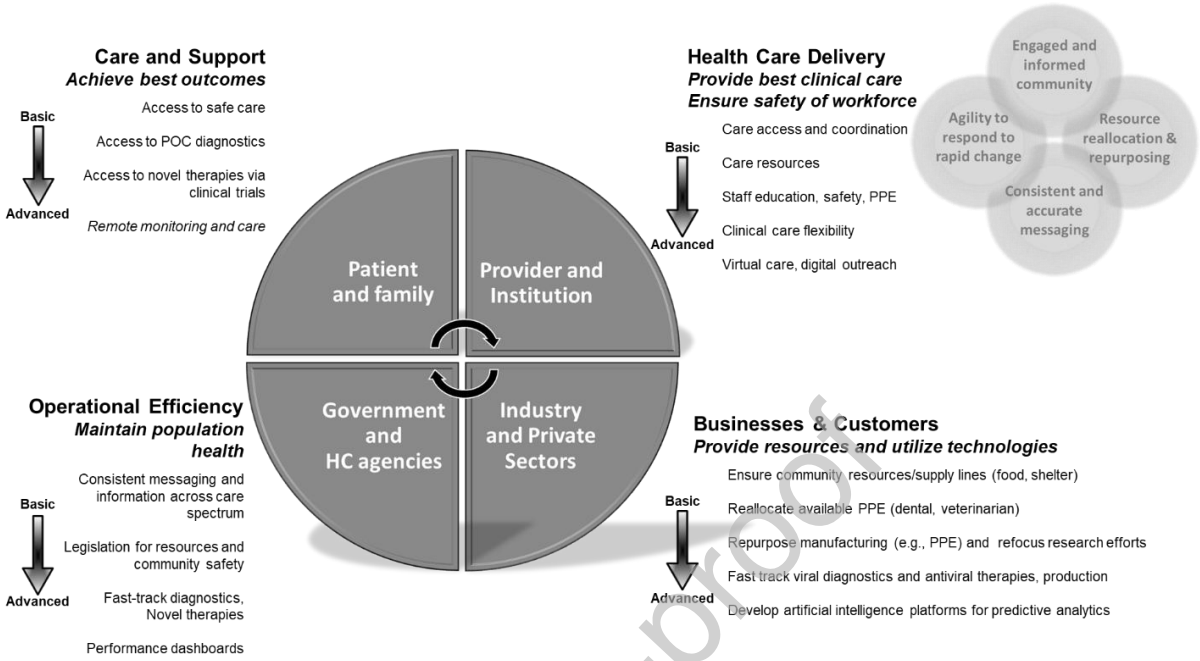


Figure 2. **Proposed holistic care model for patients and healthcare providers during COVID-19.** In order to address the COVID-19 pandemic, a holistic care model is needed that addresses four key areas (patients and families, healthcare providers and institutions, government and regulatory agencies, and the industry and private sectors) through interdependent collaboration). Each focus area must identify and prioritize goals that address basic to advanced needs within and across areas. Lastly, four 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). POC, point of care; PPE, personal protective equipment.

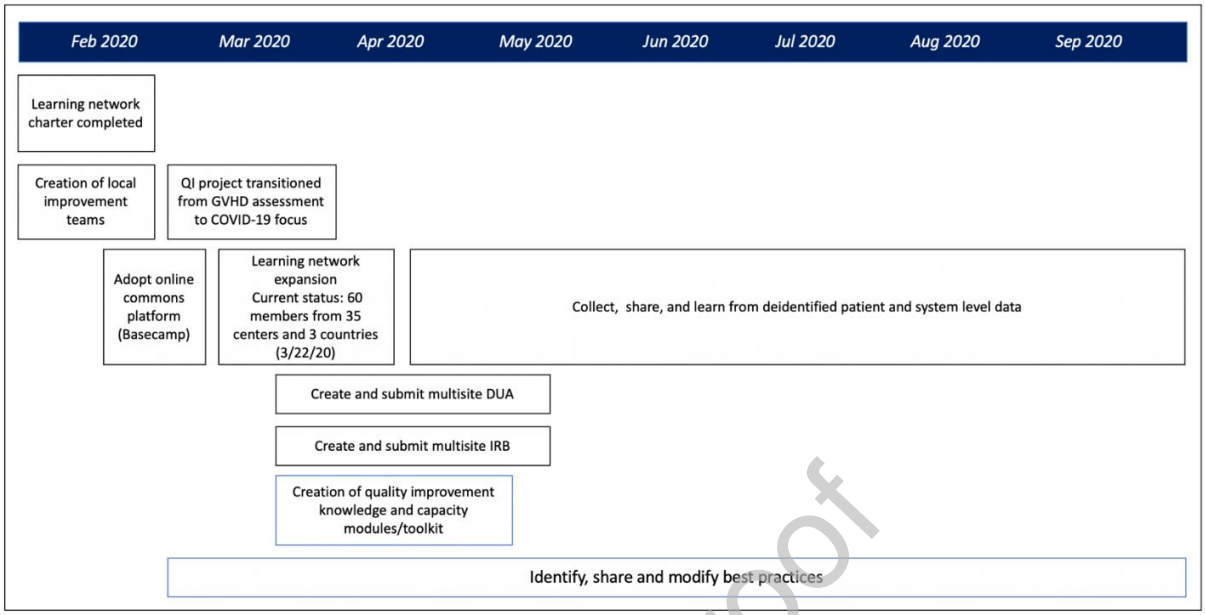
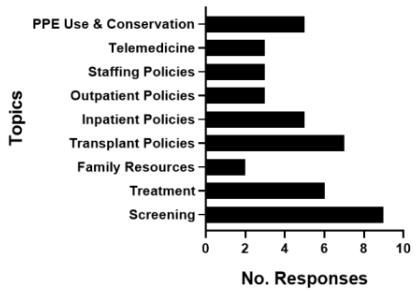


Figure 3. Timeline for Transplant-Associated Learning Network Team (TALNT). Timeline showing relevant activities of TALNT, including membership profile and short-term and long-term goals. COVID-19, Coronavirus Disease 2019; DUA, data use agreement; GVHD, graft-versus-host disease; IRB, institutional 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 on-line platform relevant to care model focus areas and goals. Panel A. TALNT membership survey results. Members were asked to rank what topics would be most helpful for addressing COVID-19. The top three topics became the focus for future interaction among the membership. **Panel B. Topic three 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. ASTCT, American Society for Transplantation and Cellular Therapy; COVID-19, Coronavirus Disease 2019; EBMT, European Society for Blood and Marrow Transplantation; PPE, personal protective equipment.