MultipleMyelomaHub

General MM

COVID-19 and EBMT recommendations for patients with hematological malignancies

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The Lymphoma Hub, Multiple Myeloma (MM) Hub, Acute Myeloid Leukemia (AML) Hub, and Graft-*versus*-Host Disease (GvHD) Hub present an article on the latest guidelines and recommendations for the management of Coronavirus Disease 2019 (COVID-19) in patients with hematological malignancies.

Introduction[1]

The novel coronavirus, SARS-CoV-2, is an RNA virus of zoonotic origin that causes Coronavirus Disease 2019 (COVID-19). SARS-CoV-2 is the third coronavirus of animal origin to pass into humans in the last 15 years, following SARS-CoV-1 and MERS-CoV.

The virus has been found in respiratory tract specimens, feces, whole blood, serum, saliva, urine, and conjunctival secretion. It is transmitted between humans via droplets spread by infected persons coughing, sneezing or exhaling, or by touching droplets on contaminated surfaces and touching the eyes, nose, or mouth. A recent study by van Doremalen *et al*. found the virus can be found on surfaces up to 72 hours after contamination, dependent on humidity and temperature conditions.[2]

The main unanswered question is how long an infectious person is asymptomatic in the early phase of infection, during which time they are transmitting the disease to others. The incubation period is reported to be, on average, 5 days but varies between 2 –14 days, with some shorter and longer incubation periods reported. There is also some evidence of molecular development of the virus, though it is unclear if this may lead to more or less severe disease.

Following its discovery in Wuhan, Hubei province, China, it has rapidly spread across the globe, with the World Health Organization (WHO) declaring the outbreak a pandemic. Most countries, particularly those with high case and mortality rates, such as Italy and Spain, have imposed restrictions to slow the spread of the virus and allow the healthcare systems to operate within capacity.

It is recommended to follow national, local, and institutional guidelines and to avoid exposure. The WHO recommendations for preventing spread of disease are available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public.

More indication-specific expert opinions to provide guidance for healthcare providers of patients with hematological diseases have been published on Lymphoma Hub and MM Hub. To access COVID-19 resources compiled by the American Society of Hematology, click here.

The disease | COVID-19

- Symptoms vary greatly between patients: some have no symptoms, while others experience acute respiratory distress syndrome (ARDS)
- Risk factors for severe disease include
  - higher age
  - co-morbidities, such as heart and lung disease and cancer
- Children appear to have milder disease
- The most common symptoms include
  - fever: 88%
  - dry cough: 68%
  - fatigue: 38%
  - sputum production: 33%
  - dyspnoea: 19%
  - sore throat: 14%
  - headache: 14%
  - myalgia or arthralgia: 15%
- Some patients report experiencing diarrhea (4%) and vomiting (5%)
- Data reported from China indicates 80% of infections are mild, 14% are severe, and 6% are critical
- The fatality rate varies between countries, with China reporting a 2.3% mortality rate. The exact rate is currently difficult to assess due varying use of testing between countries.

European Society for Blood and Marrow Transplantation (EBMT) recommendations for transplant units[1,3]

In March 2020, the EBMT published a set of guidelines, based on the opinion of a panel of experts, for the management of COVID-19 for transplant units. The document was prepared by Per Ljungman, Jan Styczynski, Malgorzata Mikulska, and approved by Nicolaus Kröger, Rafael Duarte, Harry Dolstra, and Andreu Gusi. Additionally, on March 20, 2020, Per Ljungman presented a Webinar on behalf of the EBMT entitled 'COVID-19 in stem cell transplant patients. What do we know?' This article summarizes the treatments under investigation and the recommendations for transplant centers, recipients, and donors.

Advice for transplant centers

- Restrict visitors on transplant floors
- Ask staff with respiratory symptoms to stay home
- Test staff according to national and local guidelines
- In areas with high community transmission, defer non-critical clinic visits or substitute for telemedicine visits if appropriate and feasible
- Train staff in proper procedures

Scheduling transplant procedures

- Defer non-urgent transplants
- Remember that access to stem cell donors may be restricted if
    - the donor becomes infected between clearance and harvest
    - the harvest center staff become infected and are not be able to perform the harvest (logistical issues)
    - it is not possible to move stem cells over closed borders and transport options are be limited or cancelled
- Before starting conditioning, it is strongly recommended to have secured the stem cell product by cryopreservation. Where it is not possible to delay conditioning therapy, having an alternative back-up donor is recommended

Advice for stem cell donors

- Whilst the virus can be detected in the blood, there have not been reports of transmission from donor to recipient, however the following guidelines have been issued by World Marrow Donor Association (WMDA) and are endorsed by the EBMT:
    - Donors who are diagnosed with COVID-19 should not donate
        - It is not known when they may be subsequently cleared to donate, but a 3-month deferral should be considered except where the need is urgent; in such cases, individual consideration should be made
    - Donors who have close contact with someone diagnosed with SARS-CoV-2 should not donate for at least 28 days
        - Monitor donor for COVID-19
    - If the patient's need is urgent, the donor is well, and the test for SARS-CoV-2 is negative, where no alternative donor is available, earlier collection may be considered if a risk assessment has been considered and local quarantine rules permit
    - Donors who travel to, or have been in close contact with someone from, a high-risk area should not donate for at least 28 days
    - Donors should practice good hygiene measures and avoid crowded places and large social gatherings for 28 days prior to donation

Advice for patients awaiting hematopoietic stem cell transplant (HSCT) or chimeric antigen receptor (CAR) T-cell (CAR-T) therapy

- Self-isolate at home for 14-days prior to the start of conditioning with non-crucial clinic visits avoided
- Receive testing for SARS-CoV-2
    - Test results must be negative prior to the start of conditioning therapy, regardless of upper respiratory symptoms
- Have treatment plans reconsidered if testing positive for SARS-CoV-2:
    - For patients with low-risk disease: postpone transplant/CAR-T for 3 months
    - For patients with high-risk disease, due to the risk of the underlying disease, transplant should be deferred until the patient is asymptomatic and has two repeated virus polymerase chain reaction (PCR) negativity, at least 1 week apart
- Have transplant procedures, such as peripheral blood stem cell mobilization, bone marrow harvest, and conditioning therapy, postponed for 14, preferably 21 days, after close contact with a person diagnosed with COVID-19

- Patients should be monitored for COVID-19 with confirmed PCR negativity before procedures are undertaken

Advice for patients who have recently received a HSCT or CAR-T

The aim of prevention in the HSCT recipient population is to avoid infection, since the most vulnerable are believed to be those early after HSCT, patients with GvHD, and patients with chronic pulmonary complications. However, this is an assumption and not supported by data.

- Restrict the risk of exposure to infected individuals with preventative measures, such as good hand hygiene, cough etiquette, social isolation, personal protective equipment, cleaning of surfaces, and avoid sharing objects
- Travel only if absolutely necessary, and travel by private car instead of trains, buses, or planes where possible
- Diagnostic procedures should follow local guidelines. Testing is recommended for patients in a high-risk area of transmission or who have been in close contact with someone infected
    - SARS-CoV-2 tests can read false negative results. These should be repeated if there is a suspicion of COVID-19, for example with pneumonia or severe illness
    - Testing for influenza and respiratory syncytial virus (RSV) by multiplex PCR is recommended
- Patients positive for SARS-CoV-2 should undergo chest imaging by computerized tomography (CT) and have their oxygenation impairment evaluated
- Routine bronchoalveolar lavage (BAL) is not recommended for patients who test positive due to the risk of infection to healthcare workers, unless co-infection is suspected
- If chest imaging is abnormal, and for patients where it is clinically indicated, a lower respiratory tract aspirate or BAL sample should be collected and tested for SARS-CoV-2. Co-pathogens should also be evaluated and treated

Current treatment options for patients with COVID-19[1,3]

- Patients with mild upper respiratory infection
    - Unknown if therapy provides a benefit
    - Consider chest imaging to evaluate lower respiratory tract infection (LRTI)
        - If chest imaging is normal and there are no symptoms, no therapy is recommended
        - If chest imaging is normal and there are mild upper respiratory symptoms, patients should be considered for clinical trials
    - Patients with progressing symptoms or LRTI
        - There are challenges around obtaining imaging and BAL fluid, so two definitions are proposed:
            - Proven LRTI: detection of SARS-CoV-2 by PCR in BAL fluid consistent with radiographic changes
            - Possible LRTI: consistent radiographic changes or presence of LRTI symptoms with a positive upper tract SARS-CoV-2 PCR test
        - LRTIs may be complicated by severe lung inflammation, the development of ARDS, or bacterial or viral co-infection, which should be treated if agents are available
        - Therapy should be considered for LRTI, with additional agents added as combination therapy with increasing severity

- Participation in a clinical trial should be considered
- Best evidence so far is for chloroquine/hydroxychloroquine
  - Compassionate use of remdesivir has been granted in severe cases
- In more severe cases, anti-inflammatory therapy may be considered

- Treatment for co-pathogens should be optimized

There are currently no approved treatments in Europe or the United States for COVID-19, with no vaccine available. **Table 1** summarizes some of the agents under investigation for the management of COVID-19. The WHO has announced a large trial, SOLIDARITY, in which four different drugs or combinations will be tested: remdesivir; chloroquine; a combination of two drugs, lopinavir and ritonavir; and the two drugs plus interferon beta.[4]

Table 1. Investigational agents for the treatment of COVID-19[1]

Agent and class	Mechanism of action	Evidence and ongoing trials	Adverse events
Chloroquine and hydroxy-chloroquine — heme polymerase inhibitor	Increases endosomal pH required for virus/cell fusion and interferes with glycosylation of cellular receptors of SARS-CoV, leading to a reduction of viral load	Inhibits SARS-CoV-2 *in vitro*. Reported success in 100 patients in China with COVID-19 — it inhibited exacerbation of pneumonia, improved lung imaging findings, promoted virus negative conversion, and shortened disease course. Included in the SOLIDARITY WHO trial	Nausea and diarrhea (mild), bone marrow suppression, renal and liver dysfunction, and retinopathy with prolonged use
Remdesivir — a nucleotide analogue	Inhibits RNA-dependent RNA polymerase. Activity *in vitro* and in an *in vivo* mouse model of MERS-CoV and in *in vitro* models of SARS-CoV-2	Compassionate use program for patients who are hospitalized with confirmed SARS-CoV-2 by PCR who have invasive mechanical ventilation. Clinical trials underway, including the SOLIDARITY WHO trial	Transient elevations of transaminases & hypotension during infusion. Should not be used with paracetamol or acetaminophen
Lopinavir/ ritonavir — protease inhibitors	Currently used to treat HIV. In SARS-CoV-1, treatment was associated with increased survival, lower need for pulse steroids, ARDS/death as outcome reduced, a progressive decrease in viral load, early rise in lymphocyte count, and fewer nosocomial infections	Included in the SOLIDARITY WHO trial. However, a recent randomized study, using lopinavir or ritonavir as monotherapy, in China failed to meet primary endpoint (time to clinical improvement) and had no effect on viral shedding	Moderate diarrhea and nausea with LFT abnormalities. Drug – drug interactions: amiodarone, cyclosporine, tacrolimus, phenytoin, rifampin, voriconazole

Favipiravir — RNA polymerase inhibitor	Developed for influenza, and used for Ebola, Lassa, and other severe infections	Tested in China and Japan, with media reporting efficacy in relation to viral shedding and improvement in patients with pulmonary symptoms. Trials are underway	Limited
Ribavirin — nucleoside inhibitor	Used for HCV and off-label for RSV	In some reviews, it has been used as combination therapy, but with no clear benefit. Trials underway using this in combination with IFN-beta and lopinavir/ritonavir	Hemolysis
Tocilizumab — monoclonal antibody	Recombinant humanized monoclonal antibody against the IL-6 receptor that inhibits IL-6 mediated pro-inflammatory response. Often used for CRS following CAR-T, which appears to be part of the pathology of COVID-19	Open label study in 20 patients in China with COVID-19: reduced oxygen requirement, normalized CRP, increased lymphocyte count to normal. 19/20 were discharged. **Not recommended for routine use, only in severely ill patients once risks and benefits have been assessed**	LFT abnormalities, increased risk of serious infections, loss of fever as response to infection

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; LFT, liver function test; MERS-CoV, middle eastern respiratory syndrome coronavirus; PCR, polymerase chain reaction; RNA, ribonucleic acid; RSV, respiratory syncytial virus; SARS-CoV, severe acute respiratory syndrome coronavirus; WHO, World Health Organization

Corticosteroids are another therapeutic option considered for patients with COVID-19. In SARS-CoV-1, steroids were associated with increased need for intensive care unit (ICU) admission or mortality. In MERS-CoV, steroids (evaluated by dose and duration) had no impact on mortality. One study in SARS-CoV-2 indicates delayed use of steroids may increase risk of death in the ICU. In a different cohort, methylprednisolone was associated with increased risk of death in patients who developed ARDS. Routine use of steroids is not recommended in patients with mild disease, but may be considered as part of a supportive care regimen for patients with ARDS on a case-by-case basis.

Vaccines are in development, with human clinical trials underway. However, this is a solution that is many months from reality. Intravenous immunoglobulin is also unlikely to provide protection as no blood donors with antibodies are available. Other agents that may be investigated, in addition to those in **Table 1**, include JAK inhibitors, mesenchymal stem cells for patients with ARDS, immunoglobulins for anti-inflammatory effects, and umifenovir.

Contraindications

- There is some evidence that angiotensin conversion enzyme inhibitors and angiotensin II receptor blockers contribute to renal failure in patients with COVID-19, but there is not enough evidence to recommend patients discontinue these
- Non-steroidal anti-inflammatory drugs may have negative effects, with acetaminophen and paracetamol being preferred anti-pyretics

European experience

In Europe, at the time of Per Ljungman's presentation, 15 patients had been diagnosed (and reported to the EBMT) with COVID-19 following HSCT. The median age of these patients was 59 years, with 12 being allogeneic and three being autologous HSCTs. Ten were upper and five were lower respiratory infections. One patient had died at the time of presentation. The EBMT continue to gather information on these cases to best inform future clinical practice.

The EBMT request all diagnosed cases in transplant and CAR-T recipients are reported to the prospective EBMT survey. The form can be obtained from idwp.ebmt@lumc.nl.

References

1. Ljungman P. COVID-19 in stem cell transplant patients. What do we know? European Society for Blood and Marrow Transplantation. Webinar series. Mar 20, 2020.
2. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med.* 2020. DOI: 10.1056/NEJMc2004973
3. EBMT. Coronavirus disease COVID-19: EBMT recommendations update Mar 23, 2020. European Society for Blood and Marrow Transplantation (EBMT). https://www.ebmt.org/sites/default/files/2020-03/EBMT%20COVID-19%20guidelines%20v.4.3%20%282020-03-23%29.pdf. Published Mar 23, 2020. Accessed Mar 24, 2020.