

## **Infectious Disease Management and Considerations in Cancer Patients with Documented or Suspected COVID-19**

(Contributions from: Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute, Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Fred & Pamela Buffett Cancer Center, Huntsman Cancer Institute at the University of Utah, Memorial Sloan Kettering Cancer Center, and Robert H. Lurie Comprehensive Cancer Center of Northwestern University)

The current COVID-19 pandemic presents some unique issues related to caring for cancer patients, and we realized that our current standard-of-care NCCN Guidelines do not adequately address some of these issues. These interim guidelines have been developed to align with the overarching priorities of providing optimal care for cancer patients while making efforts to lessen the risk of nosocomial transmission, maintain health care system integrity, and ensure that those at highest risk of severe infection are rapidly identified and triaged appropriately. Given the highly fluid state of changing epidemiology and of our understanding of the SARS-CoV-2 virus biology, it is anticipated that these guidelines will be updated frequently as more information becomes available.

**It is critically important to treat fever and neutropenia according to existing guidelines in all patients regardless of COVID-19 positivity or suspicion.**

The Centers for Disease Control and Prevention (CDC), American Society for Clinical Oncology (ASCO), American Society of Hematology (ASH), and American Society for Transplantation and Cellular Therapy (ASTCT) have provided websites with excellent guidance and resources for clinicians caring for patients.

- <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html>
- [www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19](http://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19)
- <https://www.astct.org/communities/public-home?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5>
- <https://www.hematology.org/covid-19>

This guidance covers *General Infection Prevention and Policy Approaches*, *COVID-19 Testing Considerations in Cancer Patients*, and *Cancer Treatment Considerations* during the pandemic circulation of the SARS-CoV-2 virus.

## General Infection Prevention and Policy Approaches

1. Patients with symptoms who are tested for COVID-19 should ideally be masked (if not already) and then placed in a private room with the door closed for assessment. Health care personnel performing COVID-19 testing should wear personal protective equipment (PPE) appropriate for airborne pathogens, including N95 masks. While awaiting results, patients should remain isolated either at home or under standard precautions in the medical facility if they require admission. While the CDC favors airborne precautions, this is a matter of debate and it is not feasible in many health care facilities when availability of beds, negative pressure rooms, and PPE are limited. Some centers place patients on droplet precautions in a non-pressurized or negative-pressurized room while awaiting test results; note that these patients should not go into positive pressure rooms.
2. Cohorting of patients in private rooms on a designated COVID-19 unit in a health care facility is recommended to avoid nosocomial spread among cancer patients. Teams dedicated to caring for COVID-19 positive patients can also help to conserve PPE.
3. Health care centers should develop infection prevention policies for persons under investigation (PUI) for COVID-19 infection, in both inpatient and outpatient settings, to avoid excess movement within facilities. Outpatients who have symptoms that place them in the PUI category should be tested at the safest location; all non-essential clinic visits should be rescheduled pending determination of COVID-19 status.
4. Telephone calls to pre-screen patients prior to scheduled clinic appointments or elective admissions should be organized to limit exposures in clinical areas and to facilitate identifying patients who may have COVID-19.
5. Screening to identify those with new fever, cough, or shortness of breath is advised for all patients (and visitors) upon arrival to the medical center. All those with active symptoms should be masked upon arrival to limit risk for transmission, and decisions about testing may subsequently be made by center policies or at the discretion of the provider.

## COVID-19 Testing Considerations in Cancer Patients

Most patients with confirmed COVID-19 have developed fever and/or symptoms of acute respiratory illness (eg, cough, difficulty breathing). There are insufficient data at present to determine whether patients with cancer or those undergoing cytoreductive or immunomodulating therapies have different presentations of COVID-19 disease. Therefore, these clinical symptoms remain the best guide to identifying cancer patients who may have infection. Clinicians should immediately implement recommended infection prevention and control practices if a patient is suspected of having COVID-19.

### 1. Fever and Neutropenia

Fever is a common presenting symptom of COVID-19 although it is unclear how often it occurs as an isolated symptom among cancer patients, particularly in the absence of respiratory symptoms. Institutional decisions regarding testing should be made based on the local epidemiology and testing capacity. However, if testing is available and there is widespread community transmission, it is recommended that patients with unexplained fever and neutropenia be tested for COVID-19.

If patients have other symptoms associated with febrile neutropenia—including cough with or without sputum, sinus or nasal congestion, sore throat, myalgias, chest discomfort with breathing, or shortness of breath, or if they are diagnosed with new-onset pneumonia—they should be tested for COVID-19 promptly. (see 2.)

- Fever and neutropenia should be treated promptly with empirical antibiotics as outlined in NCCN Guidelines, following initial evaluation and while awaiting COVID-19 test results. It is critical to use standard approaches for evaluation of the febrile neutropenic patient and to institute broad-spectrum antibiotics to avoid missing important infectious causes of fever, especially in high-risk patients.
- Low-risk febrile neutropenia patients should be treated at home with oral or home infusions of IV antibiotics as per the NCCN Guidelines, whenever possible. Daily telephone or telehealth follow-up should be employed as often as possible, if considered medically safe by the treating physician. Although blood draws are often needed in follow-up, teams should minimize requirements to return for testing when possible.
- Granulocyte colony-stimulating factor (G-CSF) administration is recommended for all those who develop febrile neutropenia, and not just those at with a risk for complication, if they are not already receiving growth factor, with the primary goal of minimizing days of hospitalization ([Hematopoietic Growth Factor \[HGF\] guidance](#)). This guidance applies to patients who do not have clinical suspicion or confirmed evidence of COVID-19 infection.

- Prophylactic use of G-CSF is recommended to minimize risk of febrile neutropenia, with the goal of reducing cases flowing into emergency rooms (ERs) and hospitals. ([HGF guidance](#))
  - Change threshold for use of G-CSF with regimens from only high risk (>20% risk of febrile neutropenia) to intermediate (10%–20% risk of febrile neutropenia) or high risk (for reference to usual standard of care, see MGF-1 in the NCCN Guidelines for Hematopoietic Growth Factors).
  - *Cautionary statement: Physicians may wish to avoid use of or discontinue G-CSF in case of respiratory infection, respiratory symptoms, or confirmed or suspected COVID-19 to avoid increase in pulmonary inflammation or hypothetical risk of increasing inflammatory cytokines associated with adverse outcome.*

## 2. Respiratory Symptoms (regardless of fever)

- New onset of cough, shortness of breath, or upper respiratory (URI) symptoms (eg, sore throat, myalgias) should prompt COVID-19 testing of those patients. First-line testing should be nasopharyngeal swab for SARS-CoV-2–specific polymerase chain reaction (PCR); nasopharyngeal swabs are thought to have higher sensitivity than nares or oropharyngeal samples. For patients who develop a productive cough, sputum can be collected and tested for COVID-19. Sputum quantitative viral loads of SARS-CoV-2 from patients with confirmed infection are typically higher than those found in throat or nasal swabs; **the induction of sputum is not recommended.**
- Patients with high-risk symptoms (eg, pneumonia, respiratory failure) should be strongly considered for repeat testing if initial testing is negative.
- Bronchoscopy is discouraged in COVID-19–infected patients or PUI due to the aerosolizing of the virus and risk to health care workers. In selected cases (eg, those receiving invasive mechanical ventilation), a lower respiratory tract sample can be collected if deemed essential for diagnostic or therapeutic purposes, using airborne precautions in a negative pressure room, if possible.
- COVID-19 testing should be considered in patients with fever and malaise, myalgias, diarrhea or gastrointestinal discomfort, or even mild URI symptoms. Clinicians should be aware of anosmia and ageusia, which can be early and isolated presenting symptoms. Older patients at highest risk may present with confusion and delirium, so a high index of suspicion among the highest risk patients is important.
- Appropriate isolation practices in the hospital (or in the home) must be instituted until test results return. The CDC provides information about isolation; however, many centers have developed their own guidelines for COVID-19 isolation practices, adjusted to their PPE levels and community prevalence of disease.

- Evaluation should also include testing for other common respiratory viral pathogens using one the currently available multiplex PCR panel.
- Bedside chest x-ray should be performed in all patients with respiratory symptoms (including those limited to the upper respiratory tract) at initial evaluation. CT scans should be limited or delayed until testing is complete, but if deemed necessary, should be reviewed with the radiology department in advance.
- Inflammatory markers such as C-reactive protein, ferritin, lactate dehydrogenase (LDH), and d-dimer may be elevated in COVID-19 (+) patients but are non-specific and can be elevated at baseline in some cancer patients. COVID-19 (+) patients with respiratory disease and elevated inflammatory markers are thought to be potentially at increased risk for severe disease.
- For outpatients with respiratory virus symptoms, the decision to hospitalize patients should be made on the basis of symptoms and clinical review. Patients with documented COVID-19 or COVID-19 symptoms should be monitored closely, using daily telehealth/telephone visits, home pulse oximetry, and fever monitoring; if symptoms or signs progress then admission is required. Close coordination with inpatient units and/or ER physicians is required to assure safe transitions from outpatient to inpatient care. In these cases.

### **3. Unexplained Fever in Non-Neutropenic Patients**

- Unexplained fever in non-neutropenic cancer patients—including those undergoing cancer treatment or those who have completed therapy but may still be considered to be immunocompromised—should be considered for COVID-19 testing. If there is documentation of ongoing COVID-19 symptoms in addition to new-onset fever, patients should be appropriately isolated and tested for COVID-19.

### **4. Testing Considerations in Other Situations**

- Pre-transplant COVID-19 testing is recommended prior to conditioning/lymphodepletion with results available within 2 days prior to conditioning regardless of the presence of symptoms.
- Depending on testing availability, some centers with high incidence may decide to begin admission screening of all patients for COVID-19.
- Pre-procedure COVID-19 testing for planned surgeries or interventional radiology (IR) procedures should be considered in coordination with procedure areas to limit possible exposures.
- Bronchoscopy, pulmonary function laboratory testing, or endoscopy should be deferred in all patients if possible, but if deemed essential then pre-procedure COVID-19 testing should be performed within 24 hours prior to the procedure.

Based on testing results, appropriate PPE and environmental precautions can be instituted to limit exposure to health care personnel to aerosols created by these procedures.

- Decisions for COVID-19 testing in patients already hospitalized should be made on an individual basis, depending on clinical suspicion, likelihood of an alternative explanation, and other risk factors. Coordination of plans for testing, intubation, and more intensive care of inpatients who develop new COVID-19 symptoms are important to reduce risk of nosocomial transmission. If testing is being considered, we strongly recommend consultation of the appropriate infectious disease and infection control services, while awaiting COVID-19 test results.

## **Cancer Treatment Considerations**

Cancer patients who are COVID-19 (+) need to be followed closely during the course of this disease, because they may quickly develop respiratory insufficiency requiring intensive care; they also pose an infection risk to health care workers. Accordingly, it is important that the charts of COVID-19 (+) patients be flagged as such and that they remain in isolation precautions for COVID-19, as outlined by each health care facility, throughout all clinical encounters—inpatient and outpatient. Obtaining 2 negative COVID-19 nasopharyngeal swab tests that are at least 24 hours apart typically discontinues isolation precautions. However, infection control practitioners at each facility are primarily responsible for clearing a patient from isolation precautions.

### **1. Cyclic Cytotoxic Chemotherapy in COVID-19 Patients**

- The period of time between resolution of infection and initiating or restarting anti-cancer chemotherapy is unclear. However, treatment should generally not be started until COVID-19 symptoms have completely resolved and viral testing is negative.
- Decisions on modifying or withholding chemotherapy should include consideration of the indication for chemotherapy and goals of care, as well as where the patient is in the treatment course and his/her treatment tolerance. For example, if the cancer is rapidly progressing and the risk:benefit assessment favors proceeding with treatment of the cancer, then it may be necessary to proceed.
- Consideration should be given to alternative routes (oral vs. IV) and sites (clinic vs. at home) of delivering chemotherapies if feasible, to reduce travel to health care facilities.

### **2. Hematopoietic Cell Transplantation (HCT) in COVID-19 Patients**

- Candidates for HCT should be tested for COVID-19 within 2 days of admission for conditioning treatment as a routine, per ASTCT guidelines. Those who are symptomatic should undergo a second test if the initial test is negative.
- Candidates who are COVID-19 (+) should have the HCT delayed at least 14 days after symptoms resolve; they should then have 2 negative tests that are 1 week apart.
- Asymptomatic candidates who have been exposed to a person with COVID-19 should be monitored for symptoms for 14, preferably 21, days; they should then have 2 negative tests that are 1 week apart (deferred until day 14) if possible, prior to transplant.
- Donors should be assessed for COVID-19; if they test positive, the donation should be deferred. Extensive guidance on this matter (including recommendations for cryopreservation) is found in the ASTCT website.

### 3. Immunomodulating Therapies in COVID-19 Patients

**There are currently no data on how specific immunomodulating therapies modify risk for COVID-19 complications.** For example, it is unclear if PD1 and other checkpoint inhibitors, which are associated with the rare development of pneumonitis, will worsen outcomes in a COVID (+) patient. The potential harms that may result from delaying or interrupting cancer treatment must be weighed with the theoretical risk from COVID-19. Treatment decisions should be individualized as outlined in various oncology guidelines published by Societies as well as by NCCN.

### 4. Supportive Care Considerations

- Consider withholding infusions that are used for supportive purposes (eg, intravenous immunoglobulin [IVIG], elemental iron, bisphosphonates to minimize exposure of patients and caregivers within health care facilities). Skipping doses of some infusions may not result in harm in certain patients. There may also be oral alternatives that can be prescribed.
- Consideration of lower thresholds for blood and platelet transfusions may be applicable for some patients in whom it would be deemed safe, in order to reduce infusion clinic visits and conserve limited blood supply.
- To limit health care exposures, Mediports may be flushed as infrequently as every 12 weeks, thus reducing face-to-face interactions with health care personnel. Other strategies for catheter management should be explored to this end as well.