

# **NCCN Best Practices Guidance: Management of COVID-19 Infection in Patients with Cancer (March 2021)**

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## **Introduction: COVID-19 knowledge is extensive - and limited.**

A scientific understanding of COVID-19 disease, caused by the virus SARS-CoV-2, in humans continues to rapidly emerge, even as the pandemic broadens. However, most information about COVID-19 in patients with cancer is based on observational data and extrapolation from larger population studies that may have included individuals with malignancies. Randomized controlled trials in patients with cancer in the context of COVID-19 are lacking. Accordingly, these National Comprehensive Cancer Network (NCCN) best practice recommendations should be regarded largely as provisional and subject to change with the advancement of scientific and clinical knowledge as further credible data are generated.

This “best practices guidance” extends and updates that provided by NCCN in April 2020<sup>1</sup> and addresses indications for SARS-CoV-2 testing in patients with cancer, management of cancer-directed therapies during the COVID-19 pandemic, and therapy of COVID-19 infection in this patient group. These recommendations are based on previously published guidelines set forth by other specialty societies and organizations, as well as on rapidly emerging data. Specific guidance regarding cancer surgery, radiation oncology, and supportive care may be found in the guidelines from organizations below.

- [National Institutes of Health: Special Considerations in Adults and Children with Cancer](#)<sup>2</sup>
- [American Society of Hematology](#)<sup>3</sup>
- [American Society of Clinical Oncology](#)<sup>4</sup>
- [Society of Surgical Oncology](#)<sup>5</sup>
- [American Society for Radiation Oncology](#)<sup>6</sup>
- [American Society for Transplantation and Cellular Therapy \(ASTCT\)](#)<sup>7</sup>

## **Cancer and COVID-19: Current Understanding**

Patients with cancer are at increased risk for severe disease and increased mortality due to SARS-CoV-2.<sup>8</sup> Case fatality rates (CFRs) reported among patients with cancer are higher than those for the general population, 29.4% versus 10.2% ( $P < .0001$ ), respectively, for hospitalized COVID-19 patients.<sup>9</sup> Large cohort studies have consistently demonstrated that all-cause mortality and the likelihood of intensive care unit (ICU) admission are higher in cancer patients, even after adjustment for older age, sex, diabetes, smoking, cardiovascular and pulmonary disease, and other common risk factors for COVID-19 severity.<sup>9-12</sup> Notably, COVID-19 infection presenting with bilateral infiltrates and tumor pulmonary involvement are predictive of higher mortality in cancer patients.<sup>13</sup>

COVID-19–associated mortality varies widely among cancer types, treatments administered, and stages of therapy (eg, patients who are in active treatment compared to those in remission). Patients with hematologic malignancies have a high mortality rate nearly twice that of patients with solid organ cancers (50% vs. 26.1%).<sup>9</sup> Numerous studies have since confirmed that CFRs are highest among patients with hematologic malignancies, including acute leukemia and non-Hodgkin lymphoma (NHL), as well as with lung cancer.<sup>14-18</sup> Metastatic malignancy and age >60 years may also confer increased mortality in patients with cancer and COVID-19. Data analyzed from the COVID-19 and Cancer Consortium (CCC19) Registry, including 928 patients from the United States, Canada, and Spain, further found that cancer patients in remission or with no evidence of ongoing malignancy were at a lower risk of death from COVID-19 than those receiving active treatment for stable or progressive disease.<sup>15</sup>

Whether certain cancer treatments exacerbate COVID-19–related patient morbidity and mortality has become a paramount question for both hematologists and oncologists. A recent meta-analysis of studies exploring the relationship between anti-tumor treatments and outcomes of cancer patients infected by SARS-CoV-2 demonstrated that the receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of severity of disease or mortality among cancer patients.<sup>19</sup> In contrast, the effects of cytotoxic chemotherapy in the month prior to COVID-19 onset are mixed. While several studies from earlier in the pandemic linked recent chemotherapy with unfavorable outcomes,<sup>11,20-22</sup> subsequent larger observational studies show no evidence of increased severity or death during active cytotoxic cancer treatment.<sup>14-16</sup> A prospective observational study from the United Kingdom involving 800 patients with active cancer (primarily solid tumors) and documented symptomatic SARS-CoV-2 infection found that although risk of death was significantly associated with age, male sex, and comorbidities, there was no correlation between having received anticancer treatments within 4 weeks before testing positive for SARS-CoV-2 and subsequent COVID-19 morbidity or mortality.<sup>23</sup> Generally, studies consistently suggest that solid tumor patients fare relatively well with COVID-19 acquired during cancer treatments, while hematologic malignancy patients exhibit worse outcomes, particularly in intensive therapy settings.<sup>14-18,23</sup> The safety of immune checkpoint inhibitors (ICIs) in the setting of COVID-19 infection remains an area of particular uncertainty.<sup>16,24</sup>

## **A. COVID-19 Testing in Cancer Patients**

### **Question 1: What SARS-CoV-2 tests are available, and what are their strengths and weaknesses? When should each test be considered, and which patient samples are most appropriate to test?**

#### **Rationale:**

- A number of COVID-19 testing platforms are currently available. Both the appropriate selection and interpretation of testing depend upon patient's clinical presentation, sample type, timing of testing, host immunocompetence, community disease prevalence, and test parameters.
- Nasopharyngeal and nasal turbinate swabs, bronchoalveolar lavage (BAL), and sputum and saliva specimens are appropriate samples to be submitted for PCR testing.<sup>25</sup> Saliva samples may be suitable in lower resource settings and when patient self-collection or least invasive procedure is preferred.<sup>26,27</sup>

#### **Reverse Transcription Polymerase Chain Reaction (RT-PCR)**

- Molecular testing by RT-PCR is the most commonly used and reliable method to detect SARS-CoV-2 viral genetic material, with 71%–98% sensitivity and up to 99% specificity depending upon specimen source and timing of testing.<sup>28-30</sup> Numerous commercial tests are available, and assay performance is affected by viral inoculum, timing of testing, and sample collection site as well as test parameters such as gene target site.<sup>31,32</sup>
- Combination (multiplex) PCR tests have been developed by the Centers for Disease Control and Prevention (CDC) and various commercial vendors to simultaneously detect influenza A and B viruses, or a range of other respiratory viral and bacterial pathogens, in addition to SARS-CoV-2 virus in respiratory samples.<sup>33</sup> Influenza, respiratory syncytial virus (RSV), parainfluenza, adenovirus, and other respiratory viruses may cause severe pneumonitis in certain patients with cancer, especially during “respiratory virus season,” and those at highest risk for infection, eg, acute leukemia or hematopoietic cell transplant (HCT)/chimeric antigen receptor (CAR) T-cell recipients.<sup>34</sup>
- PCR testing does not discriminate infectious/replicating virus from inactive virus or viral RNA fragments. Detection of viral RNA by PCR (or antigen testing), particularly in patients who are asymptomatic or recovering from clinical COVID-19 illness, does not necessarily reflect viable or transmissible SARS-CoV-2 virus. There is no currently FDA-approved test to make this distinction.

#### **Antigen Testing**

- Antigen tests are immunoassays to detect SARS-CoV-2 protein fragments in upper airway samples.
- Rapid results (often <20 minutes) and up to 99.5% specificity are attractive features of antigen tests, but they are generally less sensitive compared to PCR (41%–90% depending upon type and duration of symptoms and the specific assay used).<sup>31,35-37</sup> Antigen test positive predictive value in asymptomatic patients can be as low as 33%, depending upon community infection prevalence.<sup>36</sup>

- False-positive antigen testing has been reported; the FDA recommends RT-PCR testing within 48 hours of any positive antigen test for confirmation of infection.<sup>38</sup>

### Serology

- Serology tests for antibodies (IgG, IgM) against SARS-CoV-2 spike (S) or nucleocapsid (N) antigens may indicate either prior infection with the virus (detection of S or N antibodies) or prior vaccination (detection of S antibodies triggered by vaccines that are directed toward S antigen).
- Serology testing generally is not informative within the first 2 weeks after onset of clinical symptoms due to delays in humoral antibody production and low assay sensitivity;<sup>39</sup> assay performance is best at least 3–4 weeks after onset of clinical symptoms.<sup>40</sup>
- Note that patients with cancer and impaired immunity, especially with B-lymphocyte depletion, may not develop robust antibody responses after either infection or vaccination, thereby further limiting the utility of serology testing in such patient populations. Serology testing may help in assessing the benefit of passive immunization therapy.<sup>41</sup>
- Tests measuring neutralizing antibody titers are not yet commercially available. It is not yet clear how serologic test results correlate best with protection.<sup>39</sup>

### Culture

- Cell line viral culture is considered the “gold standard” for identification of viable, replication-competent virus.
- Hazards to laboratory personnel requiring Biosafety level 3 (BSL3) laboratory precautions, time-delays in culturing virus, and cost are prohibitive for most clinical laboratories.

### **Recommendations:**

- Acutely symptomatic patients should have an RT-PCR or antigen test performed to evaluate for COVID-19.
- RT-PCR is the gold standard test for detection of SARS-CoV-2 RNA.
  - A combination multiplex PCR is recommended when considering other respiratory pathogens in addition to SARS-CoV-2.
  - In symptomatic patients, a negative RT-PCR usually excludes a COVID-19 diagnosis. However, a negative test in the setting of suspicious symptoms for COVID-19 should prompt a repeat RT-PCR for SARS-CoV-2, in addition to a multiplex PCR for other respiratory pathogens.
- Nasopharyngeal or nasal turbinate swabs are the most accessible and appropriate diagnostic samples. Aerosol-generating procedures to obtain BAL or induced sputum should be limited and reserved for situations when testing from deep sampling is required to clarify the diagnosis.
- Antigen testing has poor positive predictive value in asymptomatic patients; a positive antigen test result should be confirmed with a PCR test for SARS-CoV-2. Antigen tests should not be used as a sole basis for making clinical decisions in cancer patients.
- Serology is not currently recommended for assessment of COVID-19 immune status in cancer patients until further data are available to define its accuracy in this setting.
- Viral cultures for SARS-CoV-2 are not indicated (and generally unavailable) for clinical management.

## Question 2: What is the timeline for positive viral RNA detection and how should it be interpreted?

### Rationale:

- RT-PCR testing detects SARS-CoV-2 RNA but does ***not distinguish*** replication-competent virus (eg, positive growth in cell line culture) from inactive virus. *A positive RT-PCR test, therefore, does not necessarily confirm the presence of viable and potentially transmissible virus.*
- **SARS-CoV-2 RNA Detection by RT-PCR**
  - In immune-competent individuals, SARS-CoV-2 RNA detection is usually highest during the first week after onset of COVID-19 symptoms and generally declines thereafter.<sup>42-45</sup>
  - In one review of 28 studies, the overall pooled median duration of RNA shedding from respiratory sources was 18.4 days with wide heterogeneity (range 1–63 days) and relatively little difference based on disease severity.<sup>46,47</sup>
    - Longer durations of viral RNA detection (up to 150 days) have been noted in patients with hematologic malignancies and others with profound immunocompromise.<sup>17,48-53</sup>
  - Both symptomatic and asymptomatic individuals have been reported as testing positive for viral RNA again after a period of negative testing.<sup>31,35,54</sup> Whether this reflects re-infection, persistent infection, or viral shedding is unclear.
- **Positive Viral Cultures**
  - Viral cultures (indicating presence or absence of replication-competent virus) from upper respiratory tract samples are typically negative by 8 days and rarely positive beyond 20 days after onset of COVID-10 symptoms in most patients, including those with severe disease or who are immunocompromised.<sup>42,54,55</sup>
  - Prolonged SARS-CoV-2 detection of replication-competent virus (for up to 100 days or more) has been reported in immunocompromised patients and has often been associated with a weak or absent antibody response to the virus.<sup>49,56</sup>

## Question 3: What is the PCR cycle threshold (Ct) value and how should it be used?

### Rationale:

- The RT-PCR Ct refers to the number of amplification cycles it takes for an RT-PCR reaction to detect viral RNA in a patient sample. The Ct is a semi-quantitative measure of viral genomic load.
- The lower the Ct value, the higher the corresponding quantity (load) of virus present in the sample tested.<sup>57</sup>
- Ct values typically increase as disease symptoms improve, corresponding to decreasing amounts of detectable replication-competent virus.<sup>44,58</sup>

- Ct values below 35 generally correlate with replication-competent virus isolation; however, this is not a broadly confirmed or standardized laboratory value and must be interpreted with extreme caution.<sup>55,57,59,60</sup> Serial assessment of Ct kinetics by the same PCR assay over the course of COVID-19 infection may assist in identifying which patients continue to shed infectious virus.
- Some studies correlate early RT-PCR Ct values with disease severity and mortality.<sup>61-63</sup>
- Due to numerous confounders (eg, PCR machine, sample collection methods, time from sample to test) the College of American Pathologists has raised concerns about the routine use and current lack of standardization of RT-PCR Ct measurements.<sup>64</sup>

#### **Recommendations:**

- The use of Ct measurements for routine COVID-19 disease management is limited by lack of clinical validation, and clinical decisions should not be based solely on the Ct value. Nonetheless, it is recognized that Ct measurements may be the only available tool to help interpret whether detection of viral RNA might represent potentially viable virus.
  - Serial Ct values provide information about changes in viral loads that should be interpreted in the context of the patient's immunologic status and COVID-19 clinical course. Increasing Ct values over time likely indicates a decrease in viable, infectious virus.
  - A Ct value of 35 or greater is used by some clinicians to suggest the presence of non-viable virus, but *this number is neither firmly established nor validated*.
  - Comparisons of serial Ct values should be determined on the same sample type and performed by the same PCR platform.
- Interpretation of Ct measurements should be performed in concert with infectious disease specialists and laboratory personnel familiar with the test parameters, limitations, and variability.

### **Question 4: For patients with cancer or HCT recipients, who should be tested for COVID-19?**

#### **Rationale:**

- Patients with cancer and symptomatic COVID-19 often have similar clinical presentations to those without cancer, typically including fever, dry cough, dyspnea and/or diarrhea, and patients with these symptoms require testing.<sup>8</sup>
- Other COVID-19–related complications, including thromboembolic events, cardiomyopathy and dysrhythmia, encephalopathy, and multi-organ inflammatory syndromes, may masquerade as complications of cancer or its treatment and patients who present with these symptoms should be tested for COVID-19.
- COVID-19–related pulmonary and systemic inflammatory manifestations may be very similar to those of cytokine release syndrome (CRS) in CAR T-cell recipients.
- Febrile neutropenia due to recent cytotoxic chemotherapy is a common occurrence in patients with cancer but may be complicated by COVID-19 infection. The impact of concomitant COVID-19 infection and febrile neutropenia on patient outcomes is not known.
- Asymptomatic patients are being routinely tested at many centers prior to invasive procedures or immunosuppressive therapies.<sup>3,7,65</sup>

### Recommendations:

- **Symptomatic patients:** A low threshold for SARS-CoV-2 RT-PCR testing in patients with cancer should be maintained, especially when COVID-19 is prevalent within local communities. A multiplex PCR assay that tests for other viruses and respiratory pathogens combined with SARS-CoV-2 is strongly recommended. Patients in whom SARS-CoV-2 testing is recommended include:
  - Any patient who has new upper or lower respiratory symptoms *or* new/worsening pulmonary infiltrates;
  - Patients with new onset of fever; and
  - Patients with new non-pulmonary symptoms suggestive of COVID-19 infection, including gastrointestinal symptoms, new thrombotic events, loss of taste or smell, and multisystem inflammatory syndrome.
- **Febrile neutropenic patients:** A SARS-CoV-2 RT-PCR test should be part of the initial workup (ie, blood cultures, indicated radiology, physical examination), especially if any respiratory symptoms are present or if there is a high prevalence of COVID-19 in the community.
- **Asymptomatic patients prior to starting HCT conditioning, CAR T-cell therapy, biological therapy, intensive chemotherapy, or invasive procedures:**
  - COVID-19 testing is recommended within 48–72 hours prior to these procedures or therapies.
  - A positive result in asymptomatic patients should prompt clinicians to consider a delay of the planned treatment (if oncologically safe) and instigate isolation precautions.
  - Routine testing of asymptomatic patients is otherwise discouraged.

## **B. Isolation Considerations for Patients with Cancer**

### **Question 5: What isolation procedures are recommended for COVID-19 patients or those suspected of having SARS-CoV-2 infection?**

#### **Rationale:**

- SARS-CoV-2 is predominantly transmitted from person to person by respiratory droplets (defined as large-particle droplets >5 µm in size) that are generated when coughing, sneezing, or talking and to a lesser extent by airborne transmission of small particles (<5 µm in size).<sup>66-68</sup>
- Contact and fomite transmission appear to play a less prominent role.
- SARS-CoV-2 can be transmitted from persons who are infected but without any symptoms.<sup>69-72</sup>
- Hospital infection control practices for highly communicable respiratory pathogens emphasize patient isolation through the use of single-patient and airborne infection isolation (negative pressure) rooms, and this approach has been adopted for patients with COVID-19 by the CDC based on SARS-CoV-2 transmission characteristics.<sup>73</sup>
  - Positive pressure rooms might pose a theoretical risk for airborne spread of SARS-CoV-2 into the hallway.<sup>74</sup>

#### **Recommendations:**

- All patients, regardless of COVID-19 status, should wear a face mask when interacting with health care providers (HCPs). Also, as part of universal standard precautions, face masks and eyewear are recommended for HCPs during all patient encounters.

- HCPs should use the following personal protective equipment (PPE) for patients suspected or confirmed to have COVID-19: gown, gloves, eye protection, and a NIOSH-approved N95 respirator or equivalent, or higher-level respirator (or face mask if a respirator is not available).
- N95 respirators or equivalent or higher-level respirators are required when performing an [aerosol-generating procedure](#)<sup>75,76</sup> (AGP).
- Preferred inpatient location for patients with COVID-19:
  - Airborne infection isolation rooms (AIIRs) (negative pressure rooms). If AIIR room availability is limited, AIIRs should be prioritized for performing an AGP.
  - Single-person room with a dedicated bathroom and with door closed.
  - Cohorting of patients with confirmed SARS-CoV-2 infection is acceptable if single rooms are not available AND if other transmittable infections are not identified.

## Question 6: When can patient isolation for SARS-CoV-2 be discontinued?

### Rationale:

- The likelihood of recovering replication-competent virus declines after onset of symptoms.<sup>43</sup>
  - For patients with mild to moderate COVID-19, replication-competent virus has not been recovered after 10 days following symptom onset.<sup>43,53,55,69,77</sup>
  - Recovery of replication-competent virus between 10 and 20 days after symptom onset has been documented in some patients with severe COVID-19 and/or with significant immunosuppression.<sup>48,49,53,54,56,78,79</sup>
- Severity of COVID-19 illness and degree of immunosuppression are important in deciding on the appropriate duration of isolation for individual patients with cancer.

### Recommendations:

- For most persons with COVID-19 illness, isolation and precautions can generally be discontinued 10 days *after symptom onset* and resolution of fever for at least 24 hours, without the use of fever-reducing medications, and with improvement of other symptoms.<sup>43</sup>
- Patients who have critical illness due to COVID-19 and/or are severely immunocompromised (including those receiving intensive cytotoxic chemotherapy, patients with prolonged neutropenia, HCT recipients, or CAR T-cell recipients) may produce replication-competent virus beyond 10 days that may warrant extending duration of isolation and precautions for up to 20 days after symptom onset; consider consultation with infection control experts.<sup>43</sup>
- For persons who never develop symptoms, isolation and other precautions can be discontinued 10 days *after the date of their first positive RT-PCR test for SARS-CoV-2 RNA*.<sup>80</sup>
- A *test-based strategy* for discontinuation of isolation precautions could be considered for some patients (eg, those who are severely immunocompromised) in consultation with infectious disease experts. This approach requires patients to symptomatically improve with resolution of fever and have at least two consecutive respiratory specimens collected  $\geq 24$  hours apart testing negative using RT-PCR.<sup>80</sup>

## Question 7: What measures are recommended for patients with “significant” SARS-CoV-2 exposure?

### Rationale:

- Significant SARS-CoV-2 exposure may be defined as a patient who has had close contact (within 6 feet for a total of 15 minutes or more in 24 hours) with a person known to be infected.<sup>81</sup>
- The exact risk of viral transmission after significant exposure is unknown and depends upon many variables (eg, symptoms of infected person, duration and proximity of contact, room ventilation). Household contacts (up to 10%) have the highest risk of secondary infections.<sup>82,83</sup>
- If viral transmission does occur to the patient, the upper bound of COVID-19 incubation period is 14 days.<sup>84</sup> During this period, the patient may develop symptoms, although up to 40% may remain asymptomatic.<sup>69</sup>
- Reinfection with a new SARS-CoV-2 virus (including new circulating variants) can occur, especially as immunity wanes to initial infection. Reports have demonstrated reinfection occurring at least 90 days after infection onset, although others have shown as early as 45 days after onset.<sup>85-88</sup>

### Recommendations:

- A 14-day quarantine is recommended for patients who have had a significant exposure to a person with known SARS-CoV-2 infection.
- Infection prevention measures used during the quarantine period are the same as employed for those with confirmed SARS-CoV-2 infection.
  - Isolation in a single-person room at home or in a hospital is strongly advised. Cohorting with patients who are infected with SARS-CoV-2 should not be permitted.
  - HCPs should use the recommended PPE, including gowns, gloves, eye protection, and N95 respirators (or face mask if N95 respirators are not available), and patients should wear masks when in proximity with other people.
  - During the quarantine period, these patients should be closely monitored for development of symptoms.<sup>73</sup>
- Recently, the CDC provided two acceptable alternatives to shorten the quarantine period while maintaining a safety margin:
  - Quarantine can end after day 10 without testing and if no symptoms have been reported during daily monitoring.
  - Quarantine can end after day 7 if a diagnostic specimen tests negative within 48 hours before the time of planned quarantine discontinuation and if no symptoms were reported during daily monitoring.<sup>89</sup> In both strategies, continued symptom monitoring and masking through day 14 must be maintained as cases of COVID-19 have been diagnosed up to day 14 after exposure.
- For patients who have recovered from prior COVID-19, have met criteria to end isolation, and have subsequently had a new or re-exposure to someone with suspected or confirmed COVID-19, repeat testing is recommended **only if**:<sup>43</sup>
  - New symptoms suggestive of COVID-19 develop, or
  - Greater than 90 days have passed since the original laboratory confirmed SARS CoV-2 infection.

## **C. Cancer Treatment Considerations for SARS-CoV-2–Positive Patients**

The heterogeneity of cancers, the complexity and number of different cancer treatment regimens, as well as the uncertainties about COVID-19 clinical course in individual patients preclude definite guidelines about cancer therapy management in those who have a positive SARS-CoV-2 test. However, the National Institutes of Health (NIH) and other society organizations and specialty groups are the most reliable sources for guidance on individual types of cancer and cancer treatments (**see Introduction**).

### **Question 8: For what duration should cytotoxic chemotherapy be interrupted or modified in *cancer patients with SARS-CoV-2 infection*?**

#### **Rationale:**

- Observational studies have reported that cytotoxic cancer chemotherapy has not consistently contributed to worse outcomes from SARS-CoV-2 infections in patients with cancer, with studies yielding mixed results.<sup>14,15,90-92</sup> Some studies show adverse effects, however, and differences in underlying disease and stage as well as therapy type and intensity have not been fully accounted for.<sup>20,21,93</sup>
- Treatment delays for cancer patients who have documented SARS-CoV-2 infection, both symptomatic and asymptomatic, are routine (as is the case with any active infection). The duration of delay depends on the severity of clinical SARS-CoV-2 infection (ie, mild, severe, asymptomatic), type and status of malignancy, risk of cancer relapse and progression, patient age and comorbidities, type and intensity of treatments, adverse effects of treatment regimen, and goals of therapy.
- Persistent or prolonged viral RNA detection by RT-PCR is a dilemma for clinicians who must decide whether or not it is safe to provide further immunosuppressive cancer therapy to patients (**see Questions 2 and 3**). As previously noted, replication-competent virus usually clears after 8 days and rarely presents beyond 20 days after onset of COVID-10 symptoms in most patients, including those with severe disease or who are immunocompromised.<sup>40,42,54,55</sup> However, a more prolonged presence of replication-competent virus has been reported in select immunocompromised patients and has often been associated with a weak or absent antibody response to the virus.<sup>48,49,56,78,79</sup>

#### **Recommendations:**

- Ideally, symptoms should be resolved or markedly improved before cytotoxic chemotherapy is administered. Durations for delaying chemotherapy administration are guided by estimated durations of infectious viral shedding, severity of COVID-19 symptoms, type of cancer and treatment, and risk of disease progression as a result of delaying chemotherapy.
- **Patients who test positive for SARS-CoV-2 infection may be treated as follows:**
  - **Mild/moderately symptomatic non-hematologic cancer patients:** Chemotherapy is generally delayed until resolution of all symptoms and *a minimum of 10 days after symptom onset*.

- **Severely symptomatic and/or hematologic malignancy cancer patients:** Chemotherapy is generally delayed until resolution of all symptoms and *a minimum of 20 days after symptom onset*.
- **Asymptomatic patients:** Chemotherapy is generally delayed for a *minimum of 10 days after the date of their first positive RT-PCR test for SARS-CoV-2 RNA, as long as they remain asymptomatic*. Asymptomatic candidates who have been exposed to a person with COVID-19 should be monitored for symptoms for 14 days (*see Question 7*).
- **Prior to planned HCT or CAR T-cell therapy patients:** Procedures are generally delayed for a *minimum of 10 days after symptom onset (or date of first RT-PCR if asymptomatic)* as long as there is significant improvement of symptoms.
- ***In all cases, however, if chemotherapy or other cancer treatment is urgently required due to uncontrolled cancer, then it should be administered at the judgment of the attending physician without delay.***
- Repeat RT-PCR testing for SARS-CoV-2 RNA is not strongly advocated unless patients continue to have symptoms past day 20. As noted, the meaning of persistent RT-PCR positive results is unclear. A Ct measurement could be cautiously interpreted within the context of patient symptoms and level of immunosuppression to aid clinical decision-making regarding timing of chemotherapy (*see Question 3*).

## Question 9: Should HCT or CAR T-cell therapy be delayed?

### Rationale:

- There are scant data, limited to a few retrospective case series, regarding outcomes of SARS-CoV-2 infection in HCT recipients.<sup>94-97</sup> Small sample sizes, heterogeneity of transplant types, patient age, immunosuppression, and timing after transplant (ranging from days to years) in these reports yielded very mixed outcomes.
  - One study of both autologous (n = 14) and allogeneic (n = 20) HCT recipients who developed COVID-19 late after HCT (median 17.4 months) reported 21% mortality and suggested that age >60 years, being on steroids at diagnosis of COVID-19, and COVID-19 diagnosis within 1 year of HCT were associated with poor outcomes.<sup>95</sup>
  - A larger series of allogeneic HCT, autologous HCT, and CAR T-cell therapy recipients (n= 77), all of whom developed COVID-19 at more than one year after last HCT or CAR T-cell therapy (median 782 days), reported better clinical outcomes for patients without active malignancy, with 78% survival at 30 days after COVID-19 onset.<sup>96</sup>
- Little information exists about the effects of COVID-19 occurring early in the course of transplant, eg, during conditioning, neutropenic phase, or soon after engraftment. Poor outcomes are presumed, however, based on the well-known morbidity and mortality linked to other respiratory viral infections such as influenza or RSV in this setting.<sup>46</sup>
- Recommendations below are based on published guidelines from ASTCT and the American Society of Hematology (ASH):
  - [American Society of Hematology](#)<sup>3</sup>
  - [American Society of Transplantation and Cellular Therapy](#)<sup>7</sup>
- The [Center for International Blood & Marrow Transplant Research](#) (CIBMTR) is conducting a prospective global registry study of HCT recipients who became infected with COVID-19.<sup>98</sup>

## Recommendations:

- Candidates for HCT should undergo screening testing for SARS-CoV-2 within 2 days of admission for conditioning treatment as a routine. Those who are symptomatic should undergo a second test if the initial test is negative.
  - SARS-CoV-2–positive HCT candidates should have the HCT delayed at least 14 days, with duration guided by severity of COVID-19 disease, underlying disease, status of malignancy, risk of cancer relapse and progression, patient age and comorbidities, type and intensity of treatments, adverse effects of treatment regimen, and goals of therapy.
  - However, if a transplant or CAR T-cell therapy is urgently required, then it should be initiated at the judgment of the attending physician without delay. Infectious disease consultation is recommended in these situations.
  - Asymptomatic candidates who have been exposed to a person with COVID-19 should be monitored for symptoms for a minimum of 14 days before proceeding. If symptomatic infection develops, then delay and isolation for another 14 days is advised.
  - Donors who are healthy do not need to be screened for SARS-CoV-2. Donors who are diagnosed with COVID-19 or who are suspected of having COVID-19, and who have symptomatic disease, should refrain from stem cell or marrow donation for at least 14 days after complete resolution of symptoms. Asymptomatic donors who may have a positive diagnostic test for SARS-CoV-2 (eg, nasopharyngeal swab) should refrain from donating at least 14 days after the date of the positive test result.<sup>99</sup>
- Repeat RT-PCR testing for SARS-CoV-2 is not recommended if the patient is asymptomatic or symptoms resolve. However, it may be considered if symptoms persist, although the meaning of prolonged positive RNA detection is unclear. If used, the PCR Ct measurement should be interpreted with great caution and in the context of patient symptoms and level of immunosuppression.

## Question 10: Should therapy with immune checkpoint inhibitors (ICIs) be delayed or interrupted?

### Rationale:

- ICIs, monoclonal antibodies blocking programmed cell death-mediating receptors, cause hyperactivation of T cells to mount anti-tumor activity but may also incite immune-mediated side effects including pneumonitis. Severe pulmonary distress due to synergistic toxicity from COVID-19 infection and ICI therapy is a concern.<sup>100,101</sup>
- *Data thus far are limited and contradictory regarding clinical outcomes of patients receiving ICIs and developing COVID-19.*<sup>102</sup>
  - Worse outcomes from COVID-19 in patients receiving ICIs have been reported in small series or cases and in one larger study from early in the pandemic.<sup>16,100,101</sup>
  - In contrast, Luo et al examined 69 lung cancer patients with COVID-19, finding ICI exposure was not associated with increased risk of severity of COVID-19.<sup>103</sup>

- Large population analyses have not identified ICIs as a risk factor for worse outcome in cancer patients with COVID-19.<sup>23,92,104</sup>
- There is increasing evidence to suggest that by enabling the restoration of T-cell cytotoxicity, ICIs may enhance antiviral effects and provide a therapeutic option against SARS-CoV-2 infection.<sup>105</sup>

**Recommendations:**

- Patients receiving ICIs and who develop SARS-CoV-2 infection may benefit from interruption of ICI therapy. However, at this point in time, consensus recommendations regarding duration of ICI interruptions are ill-defined and should be patient-individualized including considerations for the specific immune checkpoint inhibitor and severity of COVID-19.

## **D. Treatment of COVID-19 in Cancer Patients**

### **Question 11: When should monoclonal antibody products be used?**

- Relatively limited data led to the FDA to issue an Emergency Use Authorization (EUA) for the use of either bamlanivimab or casirivimab/imdevimab for the treatment of mild to moderate COVID-19 disease in adults and pediatric outpatients (>12 years, weight ≥40 kg) who do not require oxygen therapy and are at high risk for progression to severe disease.
- These antibodies are not authorized for use on patients hospitalized with COVID-19 complications. The EUA includes a warning that “monoclonal antibodies ... may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen.”

**Rationale:**

- Among outpatients with infection not requiring oxygen supplementation, bamlanivimab 700 mg IV x 1 improved symptoms and decreased COVID-19–related hospitalizations or emergency department (ED) visits.<sup>106</sup>
- In a similar group the combination of bamlanivimab 2,800 mg and etesevimab 2,800 mg reduced hospitalization or death from 7% to 2%.<sup>107</sup>
- In a similar group of patients, casirivimab/imdevimab [the REGN-COV2 antibody cocktail] reduced COVID-19 viral loads.<sup>108</sup>
- Bamlanivimab [LY-CoV555], for example, did not improve outcomes in hospitalized patients with COVID-19 without end-organ failure given remdesivir.<sup>109</sup>

**Recommendations:**

- Outpatients
  - People with mild to moderate COVID-19 who are at risk for severe disease (eg, active malignancy undergoing chemotherapy, age ≥65, *diabetes mellitus*, *immunocompromised*):
    - Administer bamlanivimab 700 mg IV alone or in combination with etesevimab 700 mg IV<sup>110</sup> OR

- Administer casirivimab 1,200 mg AND imdevimab 1,200 mg IV<sup>111</sup>
  - Asymptomatic outpatient with newly positive COVID-19 testing who are at risk for severe disease, including patients with cancer:
    - The current EUA does not authorize use of antibody therapy for completely asymptomatic patients.
    - Continuous clinical assessment of such patients for development of any COVID-19 associated symptoms is recommended; if symptoms occur then monoclonal antibody therapy may be instituted.
- Hospitalized patients
  - If COVID-19 is the reason for hospitalization, we recommend against using currently authorized monoclonal antibodies for symptomatic patients.
  - If the reason for hospitalization is not COVID-19 (eg, patient found to have COVID-19 incidentally on screening test) and symptoms are mild, consider monoclonal antibody therapy (if feasible) so as not to deny patients the care they could have received as outpatients.

## Question 12: When to use remdesivir?

### Rationale:

- Remdesivir may lead to more rapid improvement and lower mortality in selected patients.
  - In patients hospitalized with hypoxia and evidence of lower respiratory tract infection from COVID-19, patients receiving remdesivir had shorter time to recovery, clinical improvement, and lower mortality.<sup>112</sup>
  - A study of patients without hypoxia (with oxygen saturation >94% on room air) found inconsistent results, with a 5-day course of therapy with remdesivir resulting in improved clinical status but no impact with longer courses.<sup>113</sup>
  - An earlier study in China of patients found no significant improvement in outcomes in hospitalized patients receiving remdesivir. The reason for the difference between trials is not clear, but may relate to differences in the populations studied and limited statistical power. The authors report numerically faster time to clinical improvement in patients receiving remdesivir with symptom duration of  $\leq 10$  days.<sup>114</sup>
- A trial of 10 days versus 5-days of remdesivir found no significant difference in outcomes, though patients in the 10-day arm had significant worse clinical status at baseline.<sup>115</sup>

### Recommendations:

- Remdesivir is recommended for inpatients hospitalized for COVID-19 pneumonia, with hypoxia, but who are not yet requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO).
  - Remdesivir dose is 200 mg IV x 1 day, then 100 mg/day for 5–10 days (or shorter if discharged from hospital sooner).
  - Monitor liver function tests (LFTs) daily.
  - Weigh risks versus benefits in those with renal insufficiency.

- Consider giving remdesivir to patients *without* hypoxemia but otherwise admitted for COVID-19. This would depend on the presence of other symptoms (such as shortness of breath), radiographic findings, and the patient's risk of progression of infection.
- Consider giving remdesivir in a 10-day course of therapy depending on the patient's clinical status and comorbid medical conditions (including their degree of immune compromise).

### Question 13: When to use glucocorticoids?

#### Rationale:

- A meta-analysis of seven clinical trials representing 1703 critically ill patients reported decreased mortality with corticosteroid use (dexamethasone, hydrocortisone, or methylprednisolone). The effect only reached statistical significance with dexamethasone.<sup>116</sup>
- Included in the above meta-analysis was an earlier report of the benefit of dexamethasone in hospitalized patients with COVID-19 who were receiving oxygen. Corticosteroids were found to be harmful in those who did not require supplemental oxygen support at baseline.<sup>117</sup>
- A subsequent clinical trial of 299 hospitalized patients with moderate to severe COVID-19 reported improved outcomes (less need for mechanical ventilation and better Sequential Organ Failure Assessment [SOFA] scores) but no significant differences in mortality, though as noted the trial was stopped early.<sup>118</sup>

#### Recommendations:

- Glucocorticoid therapy is recommended for patients with active malignancy hospitalized for COVID-19 pneumonia with hypoxemia.
  - Administer dexamethasone 6 mg/day x 10 days or shorter if discharged from hospital sooner.
  - Alternatives: Hydrocortisone 150 mg/day, methylprednisolone 32 mg/day, prednisone 40 mg/day.
  - Administer corticosteroids with caution in those with diabetes mellitus, with close attention to blood sugar. Weigh risks and benefits carefully.
- There is unclear benefit of corticosteroids if patients are neutropenic or otherwise immune suppressed (eg, in bone marrow transplant patients on immune suppression).

### Question 14: When to use baricitinib?

#### Rationale:

- In a clinical trial of patients receiving remdesivir, the addition of baricitinib was associated with improved clinical status and more rapid recovery. The study was underpowered for 28-day mortality, though numerically mortality was lower in the baricitinib group. Glucocorticoids were not allowed in the study unless being used for a standard clinical indication, including adrenal insufficiency, asthma, laryngeal edema, septic shock, or acute respiratory distress syndrome (ARDS).<sup>119</sup>

**Recommendations:**

- Consider addition of baricitinib (4 mg/day for 14 days or until hospital discharge) to remdesivir in patients requiring high-flow oxygen or noninvasive ventilation when glucocorticoids cannot be used.

**Question 15: When to use convalescent plasma?****Rationale:**

- There is increasing evidence to suggest that high-titer convalescent plasma may provide clinical benefit in some patients with COVID-19.<sup>120</sup>
  - In one relatively low-powered study, administration of non-titer convalescent plasma was not associated with clinical improvement or mortality, though it did result in reduction of viral load.<sup>121</sup>
  - In a second study, published from India, convalescent plasma did not improve the combined endpoint of all-cause mortality and progression to severe disease (at 28 days).<sup>122</sup> However, neutralizing antibody titers were already present in most of the study participants at time of treatment with plasma.
  - In a study published from Argentina, treatment with high-titer convalescent plasma in older adults within 72 hours after the onset of mild Covid-19 symptoms reduced progression to severe respiratory disease from 31% to 16%.<sup>123</sup>
  - In a retrospective study of patients who received convalescent plasma prior to requiring mechanical ventilation, use of high-titer plasma was associated with reduced mortality when compared to low-titer plasma. No effect on the risk of death was observed among patients who had already received mechanical ventilation by the time of transfusion.<sup>124</sup>
- The value of convalescent plasma would be most pronounced early on, prior to the patient's development of a neutralizing antibody (within the initial few days of the hospitalization). In certain immunocompromised patients (those with impairment in their antibody response), this window would be expected to be longer, and there may be a benefit later in the course of illness in some individuals for this reason.<sup>78,125,126</sup>

**Recommendations:**

- Convalescent plasma may be considered as an adjunctive treatment for inpatients with malignancy hospitalized for COVID-19, especially if their ability to produce antibodies is impaired.
- A dose of 1 or more high-titer units is recommended. Best outcomes are likely to occur in those who receive high-titer units within a few days of COVID-19 diagnosis or admission to hospital early in the course of infection.

**A Note on SARS-CoV-2 Variants:**

The rapid global emergence of mutational variants of SARS CoV-2 raises serious concerns about reduced susceptibility of virus variants to available therapies (eg, monoclonal antibodies, convalescent plasma, antiviral small molecules). This situation is evolving. Monitoring for circulation of virus variants in the community and, potentially, variants arising as a result of specific treatments (escape mutants) is an

ongoing public health measure that will be critical for informing treatment and infection control decisions.

## **Section E: COVID-19–Related Complications in Cancer Patients**

### **Question 16: What concomitant infections are seen with COVID-19 disease?**

#### **Rationale:**

- COVID-19 patients may have secondary infections with fungal, bacterial, and/or other viral pathogens. The clinical implication of such co-infections is not entirely clear, but they might contribute significantly to morbidity or mortality, especially among those who required admission to the ICU.

#### **1) Fungal Co-infections**

- COVID-19–associated pulmonary aspergillosis (CAPA) has been described in severely ill COVID-19 patients since the beginning of the pandemic<sup>127,128</sup> with incidences of ~4% to 34% among those admitted to the ICU.<sup>128</sup> It is typically diagnosed during the first week of ICU admission.<sup>128-130</sup>
- Diagnosis is hampered by non-specific symptoms and radiographic findings. Finding *Aspergillus spp.* in sputum, tracheal aspirates or bronchoalveolar fluid (BAL) specimens suggests CAPA but *does not distinguish it from colonization*. Unlike invasive aspergillosis in neutropenic or HCT patients, angioinvasion is uncommon in CAPA<sup>127,128,131</sup> and serum galactomannan has limited utility with only 23% of suspected cases positive (as compared to ~72% positive in BAL) per one review.<sup>127</sup>
- Patient risk of CAPA is likely multifactorial, but most studies point to severe lung damage from COVID-19, immune deregulation, and corticosteroid therapy as major risk factors.<sup>127,131,132</sup>
- CAPA has been associated with increased duration of hospitalization and mortality of COVID-19 patients. Antifungal therapy may confer better survival.<sup>127,129,132</sup>

#### **Recommendations:**

- CAPA should be considered in critically ill COVID-19 patients in the ICU who fail to improve. Workup should include CT imaging of the thorax, cultures of deep respiratory tract specimens, and testing for fungal markers (eg, galactomannan, beta-D-glucan, PCR) in serum and/or BAL, although their sensitivity and specificity for CAPA are yet to be defined.
- Recovery of *Aspergillus spp.* from respiratory tract specimens or positive fungal markers should raise consideration for CAPA and initiation of appropriate antifungal therapy.
- Currently, data are lacking to recommend anti-fungal prophylaxis to all patients critically ill with COVID-19 in order to prevent CAPA.<sup>133</sup> Standard anti-fungal prophylaxis should be followed for cancer patients. See the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections at: [https://www.nccn.org/professionals/physician\\_gls/pdf/infections.pdf](https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf).

## 2) Bacterial Co-infections

- The incidence of bacterial co-infections is low ( $\leq 3.5\%$ ) with initial presentation of COVID-19, but apparently increases throughout hospitalization.<sup>134-136</sup> The overall rate of bacterial co-infection in hospitalized COVID-19 patients is  $\sim 8\%$  and can increase to  $14\%–28\%$  among those admitted to the ICU.<sup>137-139</sup>
- Most bacterial co-infections were identified in the lungs or blood stream. Major pathogens reported include *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, but many other bacterial pathogens have also been implicated.<sup>137-141</sup>
- Despite an overall low prevalence of bacterial co-infection with SARS-CoV-2, many studies have noted widespread empirical use of antibiotics—up to  $72\%$  of COVID-19 patients in one meta-analysis.<sup>138</sup> Unnecessary antimicrobial prescribing may potentiate antimicrobial resistance and should be minimized.
- Maximal efforts to rule out bacterial co-infections (eg, sending blood and respiratory specimens for culture; sending urine for Legionella or Pneumococcal antigen testing) should be undertaken.<sup>142</sup> Procalcitonin has an excellent negative predictive value ( $94\%$ ) for bacterial co-infection among ICU patients with influenza<sup>143</sup> and might be a potential tool to guide antimicrobial use for COVID-19 patients as well, although its utility in the latter setting has not been evaluated systematically.<sup>144,145</sup>

### Recommendations:

- Routine empiric antibiotic use is not warranted in most patients hospitalized with COVID-19, unless with other indications, such as neutropenic fever or other signs/symptoms of bacterial infection.
- For those who are severely ill, required ICU admission or mechanical ventilation, empiric use of antimicrobials agents is reasonable, given the challenges distinguishing bacterial from viral pneumonia. If antimicrobials are initiated empirically, maximal attempts should be made to rule out bacterial infections by cultures, antigen testing and inflammatory markers such as procalcitonin.
- Antimicrobial use should be reassessed daily based on the patient’s clinical status and microbiological results in order to minimize the adverse consequences of unnecessary antimicrobial therapy.<sup>142,144,146-147</sup>
- If bacterial co-infection is suspected but without confirmatory data, clinicians should follow local and/or national guidelines recommendations on antibiotic stewardship and on antibacterial treatment of community-acquired or health care-associated pneumonia.<sup>148</sup>

## 3) Viral Co-infections

- Among COVID-19 patients, co-infection with another respiratory virus seems infrequent. Most cohort studies noted an overall rate of about  $2\%–6\%$ ,<sup>139,149-151</sup> but as high as  $>20\%$  in one study.<sup>152</sup>
- A variety of respiratory viruses have been implicated, including influenza A or B, RSV, parainfluenza virus, rhinovirus, enterovirus, non-SARS-CoV-2 “seasonal” coronavirus, and others. The likelihood of co-infection with these viruses is certainly affected by seasonality and regional differences of circulating respiratory viruses within the local community.

- Currently, the clinical implications of co-infection with SARS-CoV-2 and other respiratory viruses are unclear. However, COVID-19 patients infected with another respiratory viral pathogen may benefit from specific treatment, such as neuraminidase inhibitors for those with influenza, or among those highly immunocompromised, ribavirin for RSV. Since signs and symptoms of COVID-19 can be indistinguishable from those of other respiratory viruses, routine testing of patients suspicious for a respiratory tract infection should include both SARS-CoV-2 and these other viral pathogens.

**Recommendations:**

- Patients presenting with signs or symptoms suspicious for a respiratory tract infection should be tested for both SARS-CoV-2 and other respiratory viruses.
- It is important to recognize that a positive SARS-CoV-2 test result does not preclude a concomitant infection with another respiratory virus, and vice versa.
- COVID-19 patients also diagnosed with influenza should receive targeted treatment for both viruses.<sup>153</sup>
- Consider infectious diseases consultation for management decisions if other viruses are identified.

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