

## CLINICAL DECISIONS

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### Doctor, How Long Should I Isolate?

*This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.*

#### CASE VIGNETTE

## A Woman with Covid-19

Siri R. Kadire, M.D.

A 24-year-old woman with no relevant medical history presented to the emergency department with a 1-week history of cough and shortness of breath. She stated that she had not had any contact with people who were sick but had recently attended a small event. She reported no fever, diarrhea, or loss of taste or smell. On physical examination, she was found to have hypoxemia, with an oxygen saturation of 88%, and crackles were heard on lung auscultation. A chest radiograph showed bilateral interstitial opacities, and a polymerase-chain-reaction (PCR) assay was positive for SARS-CoV-2. She was given supplemental oxygen, delivered by nasal cannula at 2 liters per minute, and was placed in an isolation observation unit overnight for monitoring. The next day, she continued to require oxygen and was admitted to a ward bed. Her oxygen requirements increased, and she was given supplemental oxygen at a rate of 15 liters per minute through a nonrebreather mask and was admitted to the intensive care unit (ICU). Her condition improved over the course of the week, and her need for supplemental oxygen decreased. The remainder of her course was uneventful, and she was transferred back to a ward bed.

It has now been 1 week since her admission to the hospital, and discharge planning has started. The patient plans to go home to stay with her parents, both of whom are over the age of 65 years, while she recuperates. She is concerned about the risk of transmission of SARS-CoV-2 to her parents. Her father is taking immunosuppressive medication after recent kidney transplantation. She has requested that PCR testing be performed again on a repeat nasopharyngeal swab. The PCR test is performed, and the result is positive.

You must advise the patient about the risk of transmitting the virus to her parents, given the time since the onset of Covid-19 symptoms and the positive repeat PCR test.

#### TREATMENT OPTIONS

Which one of the following approaches would you take? Base your choice on the literature, your own experience, published guidelines, and other information sources.

1. **Recommend continued isolation.**
2. **Reassure the patient of the low risk of transmission.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

#### OPTION 1

## Recommend Continued Isolation

Valeria Fabre, M.D.

Recommendations on the duration of isolation for patients with Covid-19 continue to evolve with increased understanding of SARS-CoV-2 transmis-

sion dynamics. Early in the Covid-19 pandemic, recommendations from the Centers for Disease Control and Prevention (CDC) included discontinuing isolation when there was clinical improvement and a negative molecular SARS-CoV-2 test. This recommendation was replaced by a time-based approach (rather than a test-based one) when it became apparent that shedding of nonviable

SARS-CoV-2 RNA in the upper respiratory tract can continue for days to weeks after recovery from illness.<sup>1</sup> Early, albeit small studies showed that SARS-CoV-2 detected by PCR in respiratory specimens beyond day 10 after the onset of symptoms did not grow in cell culture and was probably not transmissible.<sup>2,3</sup> Large population-based studies conducted by CDC South Korea indicate that the infectious potential of SARS-CoV-2 declines after the first week following symptom onset, irrespective of resolution of symptoms.<sup>4</sup>

However, a few studies have recently challenged this concept. One study showed viable virus by *in vitro* growth in cell culture in 14% of patients (4 of 29) with persistent positive SARS-CoV-2 PCR tests from upper respiratory specimens obtained after the first week following the initial positive PCR test; one patient was never hospitalized, and one had been hospitalized with mild symptoms.<sup>5</sup> Complete viral genome sequencing indicated that these cases represented the same infection rather than reinfection. Age, immunocompromised status, and severe illness have been associated with prolonged SARS-CoV-2 RNA shedding<sup>1</sup>; however, data are insufficient regarding factors associated with prolonged shedding of *viable* SARS-CoV-2. One recent study showed that some patients with immunosuppression after treatment for cancer could shed viable SARS-CoV-2 for at least 2 months.<sup>6</sup> A study of 129 severe cases of Covid-19 showed that the probability of detecting viable virus beyond day 15 after symptom onset was 5% or less.<sup>7</sup> The CDC currently recommends isolation precautions for 10 days after symptom onset (with fever resolution lasting at least 24 hours without the use of fever-reducing medications), with extension to 20 days for immunocompromised patients or those with severe illness. The patient described in the clinical vignette had severe infection according to the World Health Organization severity scale and CDC criteria; thus, continuing isolation for a total of 20 days seems reasonable and in accordance with current evidence. No studies to date have reported person-to-person transmission occurring from the observed late shedding of viable SARS-CoV-2; thus, it may be reasonable to customize decisions regarding duration of isolation on the basis of individual circumstances. In the current case, a household member is a kidney transplant recipient, a condition in which Covid-19 infection is associated with high morbidity and

mortality, which further justifies a 20-day isolation period.

Repeat SARS-CoV-2 PCR testing to determine the duration of isolation should not be recommended for this patient because, as noted, a positive PCR test does not mean that she is infectious, and viral tissue culture is not available to assess for viable virus in clinical laboratories. Repeat PCR testing can result in unnecessarily prolonged isolation and anxiety for patients and medical teams. Public awareness of the shortcomings of Covid-19 diagnostic tests and the distinction between shedding of viral RNA and viable virus is essential to ensure that patients and health care workers are comfortable with our current approach to isolation precautions for patients with Covid-19.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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## OPTION 2

### Reassure the Patient of the Low Risk of Transmission

Richard P. Wenzel, M.D.

The scenario in the vignette focuses on the question of how long after symptom onset a patient with Covid-19 can transmit the virus, SARS-CoV-2. Behind that question are additional questions that highlight current shortcomings in testing. First, is a reverse-transcriptase PCR test result a valid surrogate for the presence of transmissible virus? Second, does *in vitro* growth of virus from respiratory specimens predict transmissibility to people?

I'll argue that the answer to the first question is "no" and to the latter "probably," though we don't know the infecting dose for transmission.

Fourteen days after the onset of symptoms, a 24-year-old woman with no underlying coexisting conditions is undergoing discharge planning. Though she spent several days in the ICU, her course was moderate, not severe: she was persistently afebrile, was never intubated, and had only moderate changes on chest radiography.

Some reports suggest that patients with Covid-19 who are older, male, or obese, who are immunosuppressed, or who have severe disease have longer-than-average periods of shedding vi-

rus. This patient has none of the above characteristics and would not be expected to have prolonged viral shedding.

In a retrospective, cross-sectional study of 90 patients with confirmed Covid-19 (severity not described), the investigators placed respiratory specimens on African green monkey (Vero) cell lines. In vitro infectivity was observed in 29%, and the odds ratio for viral growth decreased by 37% for each additional day after the onset of symptoms. No growth was detected in samples collected more than 8 days after the onset of symptoms.<sup>8</sup>

A detailed virologic analysis of nine cases of mild Covid-19 in young and middle-aged professionals showed no virus isolation in serial samples of blood, urine, or stool. Viral growth was found from oral-pharyngeal or nasopharyngeal swabs in all the patients from days 1 through 5 after symptom onset. Although viral RNA was detected in 40% of the patients after day 5, and was even detected up to 28 days, viral growth was not detected after day 8.<sup>2</sup>

Cheng and colleagues prospectively enrolled 100 patients with confirmed Covid-19 and 2761 contacts. The attack rate for 1818 contacts who were exposed within 5 days after symptom onset in the primary pool of patients was 1% (95% confidence interval [CI], 0.6 to 1.6), yet the attack rate among 852 contacts exposed later was 0% (95% CI, 0.0 to 0.4).<sup>9</sup>

A systematic review and meta-analysis of SARS-CoV-2 case series, cohort studies, and randomized trials showed RNA shedding for 17 days after symptom onset (95% CI, 15.5 to 18.6) in upper respiratory samples among a total of 3229 participants in 43 studies and for 14.6 days (95% CI, 14.4 to 20.1) in lower respiratory tract samples among a total of 260 participants in 7 studies. Although RNA could be detected up to 83 days and 59 days in upper and lower respiratory samples, respectively, no study detected live virus beyond day 9 of illness.<sup>1</sup>

In February 2021, the CDC, citing their own unpublished data and those from other sources, stated that in patients with mild or moderate Covid-19, replication-competent virus hasn't been recovered after 10 days following symptom on-

set. Even in severe illness (the vast majority of patients admitted to the ICU had been intubated), the probability of virus isolation after 15 days was 5%.<sup>10</sup>

In summary, a 24-year-old woman with moderate Covid-19 infection and no markers for extended viral shedding has positive RNA detection yet probably has no replication-competent virus. She has little probability of transmitting SARS-CoV-2 to an immunosuppressed family member at home.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article was published on March 10, 2021, at NEJM.org.

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DOI: 10.1056/NEJMcide2100910

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