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CHEST

SARS CoV-2 Detection From Upper and Lower Respiratory Tract Specimens

Diagnostic and Infection Control Implications

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One of our most important tools to navigate the coronavirus disease 2019 (COVID-19) pandemic is rapid and accessible testing to identify people who are infected with this novel coronavirus (SARS CoV-2). Timely and accurate diagnostics are essential for clinical treatment of infected patients, public health decision-making and contact tracing, infection control practices and personal protective equipment (PPE) use, and avoidance of overwhelming our health-care system. Diagnostic testing for infection with SARS CoV-2 has been performed most commonly through real-time reverse transcriptase-polymerase chain reaction (RT-PCR) molecular assays to detect viral RNA from upper respiratory tract (nasopharyngeal/oropharyngeal or nasal swabs, saliva) or lower respiratory tract (sputum, tracheal aspirate, BAL) specimens.[1-3] In the research setting, SARS CoV-2 RNA has also been detected in feces, blood, urine, and breast milk, although the transmissibility of the virus from these fluids is unknown.[1,4]

Although multiple commercial- and laboratory-developed RT-PCR assays have shown excellent analytical sensitivity and specificity from respiratory specimens, false-negative testing has also been a concern, especially in the setting of patients presenting with symptoms characteristic of COVID-19 infection in an area with high local prevalence or with findings consistent with viral pneumonia on chest imaging that is not otherwise explained.[5] False-negative nasopharyngeal RT-PCR testing has been attributed to poor quality specimen collection, testing too early in the incubation period of disease, and specimen processing errors; the adequacy of the use of upper respiratory specimens for diagnosis of clinically and radiographically predominant lower respiratory tract disease (ie, pneumonia) has also been questioned.[2,5] Studies have shown increased sensitivity of lower respiratory tract specimens compared with upper respiratory tract specimens[2,6,7]; however, it can be technically challenging and create additional safety and exposure concerns to obtain sputum or BAL samples, particularly in patients who are not intubated. In this issue of *CHEST*, Wang et al[8] also found that of 68 patients with confirmed COVID-19 infection, 20.6% had negative initial and follow-up nasopharyngeal swabs, but a positive sputum specimen, when tested for SARS CoV-2 by RT-PCR molecular assay. SARS CoV-2 detection by RT-PCR from respiratory specimens remains the primary diagnostic strategy for COVID-19 infection. In the setting of compatible clinical or radiographic findings and initial negative upper respiratory tract RT-PCR testing, the testing of lower respiratory tract specimens can aid in the accuracy of diagnosis and should be considered, if it can be obtained safely.

Similar to other large studies of patients infected with COVID-19,[1,3,5] Wang et al[8] found the median duration of SARS CoV-2 RNA detection from either upper or lower respiratory tract specimens was 21 days, with elderly age as an independent risk factor for prolonged viral shedding (hazard ratio, 1.71; 95% CI, 1.01-2.93). Duration of viral genetic shedding was shorter from nasopharyngeal swabs than sputum samples, at 19 and 34 days ($P < .001$), respectively.[8] More prolonged RT-PCR detection of viral RNA in lower respiratory specimens has also been shown in other studies when compared with upper respiratory samples.[2,6] Wang et al suggest that this more-prolonged shedding in lower respiratory specimens compared with nasopharyngeal

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specimens may impact infection control policies if a "test based" clearance strategy is used for removing patients from COVID-19 isolation precautions. However, RT-PCR-based assays cannot differentiate between degraded viral genetic remnants or intact infectious virus; increasing evidence supports the use of a "time- and symptom-based" strategy to end isolation precautions for these patients.

To date multiple studies have shown that SARS-CoV-2 virus can no longer be cultured from respiratory tract specimens after 8 to 9 days from illness onset.[9] A study in pre-print by van Kampen et al[10] of 129 patients who were hospitalized with severe COVID-19 showed a median duration of culturable virus of 8 days after symptom onset (range, 0-20 d), with higher viral loads, absence of serum neutralizing antibodies, and immunocompromised status all associated with culturable virus. As Wang et al[8] found in two patients in their study, some patients have a recurrence of positive SARS CoV-2 RNA detection from respiratory samples after clinical recovery and prior negative PCR-based testing, which has not been shown in other studies to indicate replication-competent virus.[11] The Korean Centers for Disease Control monitored 285 patients with COVID-19 infection who had been "cleared" from isolation precautions after negative nasopharyngeal testing and who subsequently tested positive again on surveillance nasopharyngeal swab testing >14 days after discharge from the hospital.[12] They found no culturable virus from the respiratory specimens of 108 of the patients that they tested and no cases of transmission on review of 790 close community contacts of these patients.[12]

The reliance on repeat PCR-based testing to discontinue isolation precautions or monitor for infectivity has varied between countries and health systems. In the United States, the Centers for Disease Control and Prevention now favors a "time and symptom based" strategy for discontinuing isolation precautions, without additional testing.[9] For patients with mild-to-moderate illness, they recommend discontinuing isolation precautions if patients are at least 10 days from symptom onset, afebrile for at least 24 hours, with improving symptoms.[9] Longer isolation (at least 20 days from symptom onset) is recommended for patients who are severely ill or immunocompromised who may have more prolonged shedding of infectious virus.[9] Given the prolonged and intermittently positive respiratory tract SARS CoV-2 PCR testing commonly seen in patients who have clinically recovered from COVID-19, more information is needed regarding the potential for and timing of reinfection, and at present the Centers for Disease Control and Prevention does not recommend retesting within 3 months of clearance from isolation.[9] The protective role and duration of serologic immunity also need further investigation.

Since the start of the COVID-19 pandemic, public health leadership and health systems have issued guidance surrounding isolation of patients with COVID-19 in the hospital and at home to prevent transmission and to protect health-care workers and our communities. Test-based clearance strategies require testing resources, coordination, and availability of repeat testing and may result in prolonged personal protective equipment use and limitations of care if patients remain isolated longer than warranted based on their infectivity. These strategies should continue to be reevaluated as we learn more regarding the duration of shedding of replication competent infective virus.

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