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Closing the Brief Case: "Not Positive" or "Not Sure"—COVID-19-Negative Results in a Symptomatic Patient

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ANSWERS TO SELF-ASSESSMENT QUESTIONS

1. Which of the following best describes potential reasons for false-negative molecular testing for SARS-CoV-2?
    a. Analytical errors involving improper transport and storage of specimens
    b. Preanalytical errors stemming from the limited sensitivity of the molecular test
    c. Analytical errors due to incorrect sampling by the clinician obtaining the specimen for testing
    d. Preanalytical errors related to interfering substances inhibiting molecular testing

    Answer: d. Possible preanalytical issues related to false-negative molecular testing for SARS-CoV-2 include the presence of interfering substances such as blood and intranasal medications. Additional preanalytical causes for false-negative results include inadequate specimen collection, improper transport and/or storage of specimens, virus not being present at the site of collection secondary to biology, and testing too early or late in the course of disease. Analytical considerations include the use of assays with poor sensitivity, poor assay performance, and instrument errors. Choices a and c describe preanalytical errors, while choice b relates to an analytical issue.

2. A patient in acute respiratory distress is admitted to the ICU, with strong clinical suspicion of SARS-CoV-2 infection. Initial molecular testing on admission is negative for SARS-CoV-2 RNA. What should additional clinical management of this patient include?
    a. Assume the patient is negative to avoid overuse of personal protective equipment
    b. Test lower respiratory tract samples if available to help confirm the diagnosis of COVID-19
    c. Perform chest X-ray to confirm negative result and definitively rule out COVID-19
    d. Perform antibody testing to confirm negative result and definitively rule out COVID-19

    Answer: b. As described in this case presentation, the patient has a high pretest probability for infection. As such, alternate specimen types should be considered for diagnosis. The nasopharyngeal swab should not be considered the "gold standard" for diagnostic purposes, as the virus may not always be present at that site in COVID-19 patients. Patients who are symptomatic and suspected of having

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COVID-19 should be immediately placed under appropriate infection control settings, regardless of test results (choice a). Chest X-ray has been shown to be positive for characteristic ground-glass opacities in certain patients with pulmonary involvement though this cannot be used alone to rule out disease (choice c). Finally, serology can take up to 14 days to become positive and therefore cannot be used to rule out COVID-19 (choice d).

3. Which of the following described processes would result in the best sampling of the nasopharynx for COVID-19 testing?
    a. A single flocked swab inserted into the nares to a depth equal to the distance from the nares to the opening of the ears
    b. A single flocked swab inserted into the oral cavity to the back of the throat past the palatine tonsils
    c. A single flocked swab inserted 3 cm deep into the right nares and then reinserted 3 cm deep into the left nares
    d. A single flocked swab inserted into the nares to a depth equal to the distance from the nares to the eyes

    Answer: a. Proper sampling of the nasopharynx is essential when submitting nasopharyngeal swabs for SARS-CoV-2 testing. This requires insertion of a single flocked swab into the nares to a depth equal to the distance from the nares to the opening of the ears. This process often causes some patient discomfort though is necessary to test for viruses that replicate in the nasopharynx. Swabs not inserted as far into the nares as recommended should be regarded as nasal swabs. Testing of nasal swabs is offered under the EUA of select manufacturers. Choice b refers to the process of collecting an oropharyngeal swab, which is also offered by some manufacturers as an acceptable specimen type. More data are needed to determine the overall suitability of these specimen types compared to others for SARS-CoV2 testing.

TAKE-HOME POINTS

- SARS-CoV-2 is a novel coronavirus, responsible for the COVID-19 pandemic. Infection with SARS-CoV-2 can result in a spectrum of symptoms ranging from mild shortness of breath and fever to respiratory failure and death. The diagnosis of SARS-CoV-2 has relied almost exclusively on molecular testing on nasopharyngeal (NP) swabs, the most commonly submitted specimen type.
- With the increasing availability of various SARS-CoV-2 assays, there is an abundance of options with a lack of clinical performance data. Appropriate validation of molecular tests offered by the lab for SARS-CoV-2 diagnostics is essential prior to clinical use.
- Multiple explanations for false-negative results have been proposed. The diagnostic performance of the assay is commonly suspected as a cause of erroneous results; however, this encompasses only one of many possibilities, including preanalytical, analytical, and postanalytical errors.
- The timing of specimen collection and viral infection kinetics influence the clinical sensitivity of SARS-CoV-2 molecular detection. Studies have demonstrated great variability in the presence of virus in the upper respiratory tract during the course of infection. While viral loads are highest earlier in the disease course, it is not clear why in certain individuals virus is detected only in locations other than the upper airways.
- The reliance on a single test from a single specimen type to rule out SARS-CoV-2 can be problematic. Clinical suspicion and epidemiological information should not be ignored due to a negative molecular test result.