When to rule out COVID-19: How many negative RT-PCR tests are needed?

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Abstract

Amidst the COVID-19 pandemic, clinicians have been plagued with dilemmas related to the uncertainty about diagnostic testing for the virus. It has become commonplace for a patient under investigation (PUI) to repeatedly test negative but have imaging findings that are consistent with COVID-19. This raises the question of when the treating team should entertain alternative diagnoses. We present such a case to help provide a framework for how to weigh repeatedly negative test results in clinical decision making when there is ongoing concern for COVID-19.

1. Introduction

The spread of Coronavirus disease 2019 (COVID-19) has resulted in a global pandemic and has altered many aspects of daily practice both inside and outside of medicine. While various methods of molecular testing for COVID-19 are now available [1], low reported sensitivities for these tests [2–4] have lowered clinical confidence in their efficacy in ruling out COVID-19 infection. In this setting, CT evaluation of PUIs has become more popular as a supplement to RT-PCR testing given imaging findings that have been reported as characteristic of infection [5]. While the radiographic appearance of COVID-19 can be striking, concerns over the true sensitivity and specificity of this modality further complicate the clinical picture [6,7]. Clinicians now find themselves in a position where patients have imaging findings suggestive of COVID-19 but also have one (or multiple) RT-PCR tests that are negative. We present such a case here and cover the applied clinical statistics to address how many serial RT-PCR tests are needed to effectively rule out COVID-19 infection.

2. Case presentation

An otherwise healthy 35-year-old presented to the emergency department in April 2020 with three days of subjective fever, cough, chills, myalgia, and diarrhea. He denied sick contacts and had been observing social distancing policies. He had four roommates, none of whom were ill. His labs were notable for a white count of 17.9 K/cmm. A chest radiograph (Fig. 1A) showed bilateral lower lung opacities reported as “typical of viral pneumonia including COVID-19.” The respiratory viral panel was negative and a nasopharyngeal COVID-19 RT-PCR swab was obtained. The patient was discharged in stable condition with instructions for supportive care and home self-isolation. Following discharge, the RT-PCR test returned negative.

Radiograph at initial presentation shows subtle lower lung opacities interpreted as likely viral pneumonia (A). Follow-up radiograph at time of representing to the ED two days later (B). The lower lung opacities are more confluent. This was interpreted as “consistent with COVID-19 pneumonia.” Axial images from CT pulmonary angiogram performed four days after initial presentation (C and D). There are confluent groundglass opacities particularly in the lower lobes indicative of lung injury. The upper lobes, however, show more discrete airway-centric nodules, a finding that is typical of EVALI and has not been described in the setting of COVID-19 pneumonia.

Two days later, the patient represented to the emergency department with worsening respiratory distress, productive cough, and 10–12 episodes per day of watery, non-bloody bowel movements. His temperature was 101.3°F and oxygen saturation was 88% on room air. A repeat chest
radiograph (Fig. 1 B) showed worsening lower lung opacities and was interpreted as “most consistent with COVID-19 pneumonia.” A repeat nasopharyngeal swab RT-PCR was obtained, and the patient was admitted to the respiratory isolation unit for presumptive COVID-19 pneumonia. He was treated with intravenous antibiotics for community-acquired pneumonia and hydroxychloroquine. Stool samples were sent to evaluate for infectious etiologies of diarrhea (Clostridium difficile testing and PCR-based testing for a panel of pathogens). A second nasopharyngeal swab RT-PCR also returned negative.

Over the next three days, his respiratory status continued to decline, eventually requiring transfer to the ICU and high flow nasal cannula at 25 L per minute (LPM) with the fraction of inspired oxygen at 0.7. A third RT-PCR test returned negative. No infectious cause of diarrhea was identified by laboratory analysis. A chest CT was then performed (Fig. 1C and D) to further evaluate his worsening respiratory status. While the imaging findings did not exclude COVID-19, the radiologist suggested an alternative diagnosis for the patient’s respiratory distress, which prompted a re-evaluation of the presumptive diagnosis of COVID-19.

Rereview of the patient’s past medical history was remarkable for vaping of tobacco/cannabis products. Although the history of vaping was elicited at the original ER visit, this detail was not prioritized in the original differential diagnosis, or in his subsequent clinical course. When the history was redressed after the CT, the patient also reported recently switching THC products just prior to presentation. CT findings were typical for the recently described entity called e-cigarette and vaping associated lung injury (EVALI) [8,9]. Despite this, clinical concern for COVID-19 remained and a fourth RT-PCR test was sent which also returned later as negative.

Hydroxychloroquine was stopped after the fourth negative test, and the patient was started on methylprednisolone for presumed EVALI. He received a high dose for 3 days before beginning a taper, despite objection from infectious disease consultants that he might still have COVID-19 pneumonia. Over the first 3 days of steroid therapy, the patient’s respiratory status rapidly improved. His diarrhea resolved, and he was transferred out of the ICU, no longer requiring supplemental oxygen to maintain his saturation. The diagnosis of EVALI was made based on the history of vaping, presentation, four negative RT-PCR tests, imaging findings, and response to steroids. In retrospect, the patient’s original presentation was typical of EVALI (including his lack of sick contacts and gastrointestinal symptoms), however this was difficult to appreciate in the context of the COVID-19 pandemic. Even when the possibility of EVALI was first entertained, despite the patient’s worsening clinical picture, there was concern about administering steroids as this treatment may not be beneficial in COVID-19 and could prolong viral shedding.

3. Discussion

While no robust peer reviewed literature currently exists to reliably calculated the sensitivity and specificity of RT-PCR testing, it is widely agreed upon that the specificity is high, approximately 98% [2]. The sensitivity is contested with reports suggesting that it may be as low as 60–78% [2–4]. Disease prevalence also factors greatly into the negative predictive value of RT-PCR. Unfortunately the reported prevalence of COVID-19 is variable and likely unreliable given limited access to testing [10]. As an exercise to highlight the heuristic pitfall of anchoring bias in this case, we calculated the predicted performance of serial testing with the assumption that each RT-PCR is an independent test. We used this model to estimate the likelihood of COVID-19 infection after serial RT-PCR tests across various values for disease prevalence (Table 1). We have conservatively used a sensitivity of 60% for RT-PCR to demonstrate the efficacy of serial PCR testing under “worst case” conditions. For a more detailed description of how these statistics were calculated please refer to our supplementary materials (Section 5), which include standard two by two tables for serial RT-PCR testing (Table S1.1, S1.2).

Comparison of false negative rates after performing serial RT-PCR testing between various populations each with a different prevalence of COVID-19.

At the time of this patient’s presentation, the prevalence of COVID-19 was...
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19 in symptomatic patients in our care network was estimated to be 5%. Based on our conservative calculations, after the second negative RT-PCR test, the probability of COVID-19 was less than one percent (0.87%). After his fourth negative RT-PCR, the probability dropped to 0.15%.

4. Conclusion

Anchoring to the diagnosis of COVID-19 is easy to do in the setting of the unprecedented uncertainty of the current pandemic. It is for this reason we hope the applied statistics in this case will give providers a practical framework for contextualizing multiple negative RT-PCR tests for various patient populations. In most environments, COVID-19 infection should be effectively ruled out with three negative RT-PCR results (Table 1). In areas of higher disease burden (prevalence of 25%), the false negative rate after four RT-PCR tests is below 1%. Even with a very high prevalence of 50%, the false negative rate is low (2.7%) after four negative tests, suggesting that alternative diagnoses should be strongly considered.

Contributors

All authors participated in the construction and editing of the manuscript and its revisions.

Ethics committee approvals

N/A.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101192.

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Table 1

| Number Of PCR tests | 1% Prevalence | 5% Prevalence | 10% Prevalence | 25% Prevalence | 50% Prevalence |
|---------------------|---------------|---------------|----------------|----------------|----------------|
| First PCR Test      | 0.41%         | 2.1%          | 4.34%          | 11.98%         | 28.99%         |
| Second PCR Test     | 0.17%         | 0.87%         | 1.82%          | 5.26%          | 14.28%         |
| Third PCR Test      | 0.07%         | 0.36%         | 0.75%          | 2.22%          | 6.37%          |
| Fourth PCR Test     | 0.03%         | 0.15%         | 0.31%          | 0.92%          | 2.7%           |

* False negative rates calculated using a sensitivity of 60% and specificity of 98% for the RT-PCR test.