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Recurrence of coronavirus disease 2019 (COVID-19), future paths and challenges

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To the Editor— Currently, coronavirus disease 2019 (COVID-19) recurrence is a poorly understood phenomenon concerning recently initiated vaccination efforts, novel genotypic variants of SARS-CoV-2, and population-level transmission dynamics. To comprehend the true impact of recurrence for both the patient and population, it is imperative that different possible mechanisms of recurrence are identified and appropriately investigated.

In this regard, we propose that symptom chronology, serial reverse transcription-quantitative polymerase chain reaction (RT-qPCR) tests, viral culture, and viral genome sequencing are important components in the investigation of suspected COVID-19 recurrence cases. These techniques allow differentiation between recurrence[1–5] and persistence[6] and estimation of viral load. They are useful for determining viral viability for infectiousness[7] and for confirming reinfection via the detection of distinct genetic variants of SARS-CoV-2.[5,8] Together, these variables confer sufficient data for classifying cases according to relevant clinical and laboratory parameters to guide decision making on both patient and population levels. Such enhanced decision making may be essential considering the impact of the novel SARS-CoV-2 variants of concern (B.1.1.7, B.1.351, P.1, B.1.427 and B.1.429) on patient outcomes and infectiousness.[8]

In COVID-19 recurrence, recurring positive patients present with a new positive RT-qPCR test after the apparent resolution of the initial SARS-CoV-2 infection.[1–3] Although purely a laboratory classification, positive recurrence is a relatively common phenomenon, with 9%–16% of hospitalized patients being susceptible to positive recurrence in an RT-qPCR test.[1–3] It is important to distinguish patients with RT-qPCR recurrence from those with clinically significant symptom relapse, defined as an intermission in symptoms marked by apparent clinical cure.[4] Symptom chronology becomes particularly useful in such cases, especially because COVID-19 symptom persistence, known as long COVID-19 or postacute COVID-19 syndrome,[6] is a common but separate entity concerning COVID-19 recurrence.

To evaluate the clinical characteristics of reinfection, positive recurrence, and symptom relapse, we reviewed 61 reported cases of COVID-19 recurrence in nonimmunodeficient patients indexed in MEDLINE, EMBASE, Web of Science, and LitCovid before December 3, 2020. Among the 3 current categories of recurrence, we found 18 cases of isolated positive recurrence, 44 cases of symptom relapse, and 9 cases of reinfection. In patients with reinfection or symptom relapse, the median patient age was 46 years (IQR, 32–67), and 41.7% of patients were female. Also, 49% of patients presented no clinically significant comorbidity. Interestingly, 57.9% of cases reported a more clinically important second episode of disease in comparison to the first. Additionally, fever of any grade and cough of any type were the most frequent symptoms in both episodes of disease, with a notable decrease of headaches in the second episode. For further data, refer to the Supplementary Materials (online).

The frequency of reinfection is relatively unknown, possibly due to the challenges associated with obtaining viral genome sequencing in both episodes of disease. However, there is no doubt about the possibility of reinfection by distinct SARS-CoV-2 genetic variants.[5,8] Detailed investigation is still needed to determine whether there is a consistent difference between the severity of reinfection compared to the original episode and how viral-host interactions with different variants alter reinfection dynamics. To answer these questions, institutions must either increase the number of sequenced samples or develop the means to preserve samples for posterior sequencing in case of suspected reinfection.

With regard to positive recurrence, the literature shows that several factors may be relevant to the risk of positive recurrence in RT-qPCR tests: the presence of anti-RBD IgG, viral load estimated by RT-qPCR CT values, patient age, the severity of the first episode, and the total time of hospitalization.[1–3] Although

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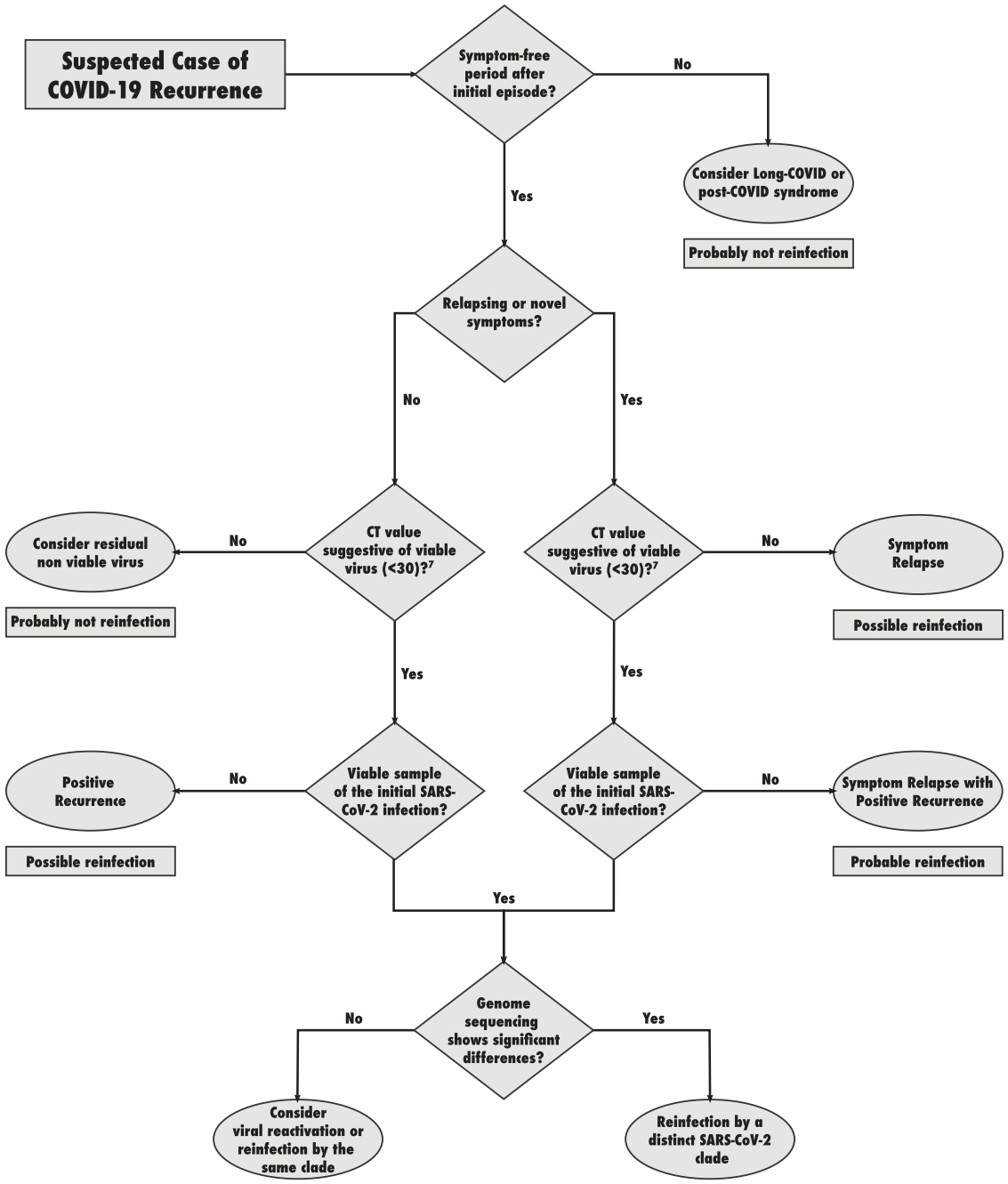

Fig. 1. A flowchart-based framework for investigating suspected cases of COVID-19 recurrence. Note. RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

anti-RBD IgG may influence the risk of positive recurrence, anti-SARS-CoV-2 IgG, in general, appears not to have a significant effect on recurrence. An overwhelming 93.5%–100% of reported recurring positive patients present positive IgG assay results between episodes.[1,2] IgG avidity has been positively correlated with patient age and disease severity, but its association with positive recurrence remains uncertain.[9]

Concerning transmission potential, though data on asymptomatic patients with recurrence suggests that the second episode poses no threat in terms of infectiousness,[10] to the best of our knowledge, no studies have successfully evaluated viral cultures using samples from symptom relapse and reinfection patients.

To investigate recurrent COVID-19, we must distinguish between recurrence and persistence of symptoms. To do so, it is necessary to analyze the chronology of symptoms, to detail the viral load with serial RT-qPCR tests, to evaluate infectiousness through viral cultures, and to exclude reinfection with viral genome sequencing. To incorporate such techniques into future studies

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and clinical practice, we suggest a framework for the investigation of suspected recurrence cases (Fig. 1). However, the challenge of this detailed investigation lies in the high resource load required to allow truly robust conclusions, especially considering complicating factors in a postvaccination setting.

Nonetheless, we propose that studies that employ such techniques must be undertaken to appropriately answer the multitude of pressing questions that pertain to COVID-19 recurrence. These investigations are particularly significant considering recent reports of reinfection by novel SARS-CoV-2 variants, which may lead to a more severe second episode of disease.[8] Thus, only when we comprehend the complex interplay between COVID-19 recurrence and the other components of the pandemic will we be able to quantify and react to its impact on both the patient and population levels.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.226

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Coronavirus disease 2019 (COVID-19) outbreak on an inpatient psychiatry unit: Mitigation and prevention

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To the Editor—Severe acute respiratory coronavirus virus 2 (SARS-CoV-2) is primarily spread through respiratory droplets with increased risk of transmission in households and congregate settings.[1–3] Asymptomatic and presymptomatic transmission of SARS-CoV-2 have also made containment difficult.[1,4] Inpatient psychiatry units present unique challenges in controlling infectious disease outbreaks.[5,6] Here, we describe the management of a coronavirus disease 2019 (COVID-19) outbreak on an inpatient psychiatry unit, highlighting unique considerations for this patient population.

Beth Israel Deaconess Medical Center (BIDMC) is a 655-bed, academic, tertiary-care center in Boston, Massachusetts, with a 25-bed inpatient psychiatry unit including multiple 2- and 4-bed patient rooms and communal living spaces. In March 2020, Infection Control/Hospital Epidemiology (IC/HE) was notified of an asymptomatic inpatient with concern for COVID-19 due to a community exposure prior to admission. The index patient, who had been admitted to a double room the day prior (hospital day 0), was placed on precautions and

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