Diagnosis and recovery from severe acute respiratory syndrome coronavirus 2 infection is challenging in kidney patients: tests are an issue

To the editor A novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA, detected by reverse transcription–polymerase chain reaction (RT-PCR) was identified as the cause of a cluster of pneumonia cases in Wuhan, China.[1] It spreaded rapidly, at first in China and then resulting in an epidemic in other countries around the world.[1] In a recent publication by Flisiak et al,[2] the diagnostic workup for the infection is discussed, with RT-PCR being the basis for the diagnosis of active SARS-CoV-2 infection. The role of serological methods is briefly presented in the paper, and more extensive discussion is provided by Tomasik et al.[3]

In the course of an epidemic, mass serological testing with rapid tests "on request," especially for detecting IgM class antibodies, can be used to identify asymptomatic infections once other means of reducing the epidemic have been used. Detection of IgG or IgM/IgG antibodies can be useful in epidemiological studies as suggested by Flisiak et al.[2] With these tests, it is possible to estimate the number of people who have been in contact with the virus and developed antibodies and in the population-based studies.

Even though rapid antibody tests are simple, easy to use, fast, and cheap, they have important limitations as reported previously.[3] They missed the infection in the early and even mid-phase. They yielded a substantial number of false-negative results, as shown in some countries including Poland.[4] Moreover, to definitively rule out or confirm SARS-CoV-2 infection, the test must be performed with the use of RT-PCR molecular diagnostics. Rapid molecular tests recently registered by the Food and Drug Administration (FDA) may offer a possible fast-track diagnostic workup of SARS-CoV-2 infection in emergency departments. It should be emphasized that typically RT-PCR of nasopharyngeal swabs has been used to confirm the clinical diagnosis of SARS-CoV-2 infection. Wang et al[5] showed that only 32% of pharyngeal swabs and 63% of nasal swabs were positive, while bronchoalveolar lavage yielded 93% positivity. Thus, we may face the problem with false test results, both positive and negative. Therefore, the European Center for Disease Control and Prevention in their latest 9th update discussed tests performance criteria and validation.[6]

Every coin has two sides, the former is diagnosis of infection, the latter is its resolution. Recovery from coronavirus disease 2019 (COVID-19) is defined as absence of fever for more than 3 days, resolution of symptoms and radiologic improvement, and 2 negative PCR tests taken 24 hours apart.[7] Kidney disease, in particular, requiring renal replacement therapy is associated with profound alterations in the immune system.[8] Infections are the second leading cause of death among hemodialysis patients, mainly due to the impairment of both innate and acquired immunity.[8] The accumulation of uremic toxins is believed to be the main cause of immune deficiency observed in advanced kidney disease.[8] On the basis of the published literature, we present a patient with acute kidney injury who recovered from COVID-19 pneumonia and transiently tested positive as well as results of 6 hemodialyzed patients also transiently tested positive. We discuss the clinical relevance of these findings.

A 35-year-old man with paranoidal schizophrenia was admitted on February 28, 2020 to a regional hospital due to ethylene glycol ingestion (0.75 l of radiator coolant) in a suicide attempt, who developed acute kidney injury requiring renal replacement therapy. He developed pneumonia induced by SARS-CoV-2 infection and was transferred on March 26, 2020 to the Central Clinical Hospital of Ministry of the Interior and Administration in Warsaw (CSK MSWiA). Data from the regional hospital were very scarce and details unavailable. During the hospitalization in the CSK MSWiA, he was in a stable clinical condition, without dyspnea and with normal oxygen saturation. High-resolution computed tomography performed on April 4, 2020 showed a picture of

Table 1 Time course and results of testing in patients with end-stage renal disease/acute kidney injury

Patient, (age, sex)	Positive test (date)	Control test	Control test	Control test	Control test	Control test	Control test	Control test
72F	Mar 30	Apr 7 (+)	Apr 14 (+/–)	Apr 21 (–)	Apr 22 (+)	NA	NA	NA
64M	Mar 30	Apr 11 (+/–)	Apr 14 (+)	Apr 21 (+)	Apr 16 (+/–)	Apr 19 (+/–)	Apr 21 (–)	Apr 23 (–)
77M	Mar 29	Apr 7 (+)	Apr 13 (+/–)	Apr 14 (+/–)	Apr 17 (+/–)	Apr 20 (–)	Apr 21 (–)	NA
63M	Mar 26	Apr 7 (+)	Apr 14 (–)	Apr 16 (+/–)	Apr 17 (+/–)	Apr 20 (–)	Apr 21 (–)	NA
57F	Mar 28	Apr 7(+)	Apr 14 (–)	Apr 16 (–)	NA	NA	NA	NA
65M	Mar 27	Apr 5 (+)	Apr 12 (–)	Apr 13 (–)	Apr 22 (+/–)	NA	NA	NA
35M (AKI)	Mar xx	Apr 2 (–)	Apr 6 (–)	Apr 9 (+)	Apr 11 (–)	Apr 14 (+/–)	Apr 16 (–)	Apr 17 (–)

Test results are presented as: (+) positive, (+/–) doubtful, (–) negative

Abbreviations: Apr, April; AKI, acute kidney injury; F, female; M, male; Mar, March; NA, not applicable

ground-glass opacification in the left lung lingula and small consolidative abnormalities in the lower part of the right lung (fibrosis? atelectases?) consistent with viral pneumonia. Hydroxychlorochine (250 mg twice daily, March 26 to April 2, 2020), meropenem 1 g intravenously once daily, (March 27 to April 7, 2020), and azithromycin (500 mg once daily, April 5–7, 2020) were administered. He was dialyzed 3 times a week until April 3, 2020. After 2 negative tests (April 3 and April 6, 2020) he was considered as recovered and on April 7, 2020 admitted to our department in a stable clinical condition, without fever, with productive cough, crackles in the lower parts of lungs, oxygen saturation of 98%, C-reactive protein level of 100.4 mg/l, creatinine levels of 6.55 mg/dl, and diuresis of 2500 ml/d.

Despite 2 negative tests, we followed all the necessary precautions: patient was isolated, masks, gowns, gloves, and eye protection were worn by medical staff. Second high-resolution computed tomography was performed 4 days later and revealed abnormalities similar to those observed previously. On April 9, 2020 after 1 unit packed red blood cell transfusion, he developed fever with cramps, and the test was ordered. Hemodialysis catheter was removed (urine and blood cultures were negative). As the test yielded a positive result, he was again transferred to the CSK MSWiA hospital, where 4 repeated tests for SARS-CoV-2 were performed (April 11, 2020, negative; April 14, 2020, doubtful; April 16, 2020, negative; and April 17, 2020, negative). We would like to note that despite 2 negative tests done in the interval of 48 hours, the third test performed 3 days later became positive. The first 2 were performed in the private medical laboratory ALAB (RdRp-P2, E and N sequence), next in the National Institute of Hygiene (RdRp-P2, E sequences). It was positive in the 37th cycle of RT-PCR suggesting a small number or copies. Then, 3 tests were negative (last on April 17, 2020).

We identified 6 more case with similar results. They included 2 women and 4 men on chronic hemodialysis due to end-stage kidney disease. All data concerning the tests are presented in Table 1. These are the first Polish data on dialyzed patients. When a test was positive, the patient was dialyzed in the CSK MSWiA in Warsaw. We would like to emphasize that even in the situation after 2 negative tests with other clinical sings, that is, lack of fever for more than 3 days, resolution of symptoms, we may experience problems with the interpretation of test results.

The accuracy and predictive values of SARS-CoV-2 testing have not been systematically evaluated, and the sensitivity of testing likely depends on the precision of the test as well as the type of specimen obtained.[5] Both false-positive and false-negative test results were described, even in recovery.[9] It appears that it is also related to the type of test used with its cut-off value. It seems reasonable to assume that quantitative measurement instead of qualitative will be more valuable for disease monitoring. In a study by Wang et al,[5] the mean (SD) cycle threshold values of all specimens were more than 30 ($<2.6\times10^4$ copies/ml), whereas in nasal swabs, the mean (SD) cycle threshold value was 24.3 ($<1.4\times10^6$ copies/ml), indicating higher viral loads. It is of utmost importance to obtain the swab specimen in a correct way (preferably nasal swabs than nasopharyngeal), following strictly the instruction provided by the laboratory. We do need validated tests and certified laboratories. Last but not least, correlation with clinical findings and repeated tests as needed should also be considered. Kidney disease itself is a risk factor for severe COVID-19.[10] Patients with kidney disease can be either asymptomatic, have atypical symptoms, or severe disease. Dyspnea in dialyzed patients may be in the vast majority caused by hypervolemia, chronic heart failure, exacerbation of chronic pulmonary obstructive disease, or simply common infections. Since many patients, including the dialysis population, take nonsteroidal anti-inflammatory drugs as pain killers, it might be difficult to detect fever when temperature is measured before the start of dialysis. Some of them will not reveal their health problems when they are asked not to be isolated, taken to another hospital as suspected for COVID-19. It may create a huge epidemiological issue for any dialysis unit, when a patient tests positive, in particular for other patients and

health professionals. One solution might be regular testing with swabs taken. However, the question is whether we have enough resources and laboratory capacity. Serological tests in dialysis population are a very challenging issue. Dialysis patients are also characterized by weakened response to vaccinations; especially, the effectiveness of hepatitis B virus vaccination was found to be lower in patients with end-stage renal disease compared with healthy controls,[11] thus, the development of antibodies could be impaired, as well as response to a potential future vaccine. As of April 18, 2020, the FDA "is not aware of an antibody test that has been validated for diagnosis of SARS-CoV-2 infection."[12] The FDA authorized 4 antibody assays. The tests measure IgM or IgG antibodies, but IgM antibodies may not develop at all, and IgG antibodies usually do not develop until later in the course of the disease. Thus, they are not optimal to diagnose COVID-19. We are still waiting for a validated test to assess neutralizing antibodies as they may help identify who has been infected and developed antibodies protecting from future infection as well as identify those still at risk. Moreover, they may also help to assess the possibility of blood donation to manufacture convalescent plasma, an investigational product for use with those who are seriously ill from COVID-19, that is, kidney transplant recipients and patients during active oncohematological therapy.

In conclusion, as our preliminary results demonstrate, we should exercise caution in the population with kidney disease, and infection control precautions for COVID-19 should continue while repeat evaluation is being performed, as immunocompromised state may yield doubtful test results.

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