Journal of Infection 85 (2022) e134–e136

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

## Rapid COVID-19 rebound in a severe COVID-19 patient during 20-day course of Paxlovid

*Dear Editor*,

We read with interest the article reported by J. M. Coulson et al. that three cases of COVID-19 rebound were associated with nirmatrelvir/ritonavir pre-hospital therapy.[1] Paxlovid (nirmatrelvir tablets + ritonavir tablets) is an oral antiviral drug that reduces the risk of hospitalization or death for mild-to-moderate COVID-19 patients who are at risk for progression to severe disease.[2] The Chinese National Medical Products Administration issued an emergency use authorization for Paxlovid on February 31, 2022. Although Paxlovid was reported to reduce viral load and prevent COVID-19-related hospitalization among mild to moderate patients,[2,3] Paxlovid treatment in severe COVID-19 patients or long term Paxlovid treatment in COVID-19 patients have not been investigated. Case reports have reported that some patients who have completed a 5 day course of Paxlovid experienced rebound COVID-19 infections,[1,4,5] here we describe a case of COVID-19 rebound in a severe COVID-19 patient during long term (20 days) treatment of Paxlovid.

On 20 May 2022, an 83-year-old male COVID-19 patient attended our hospital without any respiratory symptom (hospital day 1), his coexisting diseases included type 2 diabetes, hypertension and sequelae of cerebral hemorrhage. Oxygen saturation at room air was 99% and the physical exam was unremarkable. The Chest computed tomography (CT) showed bilateral interstitial infiltrates. Low volume oxygen inhalation was initiated on day 1 (Fig.1).

The patient showed clinical worsening with cough, shortness of breath and persistent fever since day 2. His-oxygen saturation at room air was 70% with a respiratory rate of beats 30–40/min and he was treated with 2 L of oxygen by nasal cannula on Day 6, and the Chest CT on Day 6 showed bilateral interstitial infiltrates which was worse than the result of day 1. Blood tests showed increased neutrophils count ($12.94 \times 10^9$/L) and normal lymphocyte count ($1.13 \times 10^9$/L) (Table 1). He was considered as bacterial coinfection in COVID-19, treatment with Paxlovid, methylprednisolone (GEM-P) and antibiotic was initiated on day 6 (Fig.1), and Paxlovid was treated as prescribed for 5 days (day 6–10).

Although the oxygen saturation was 94–99% and the respiratory rate was 20–25 beats/min after continuous oxygen inhalation, his clinical symptom was not improved and Chest CT showed no obvious changes, blood tests showed normal neutrophils count ($4.78 \times 10^9$/L) and decreased lymphocyte count ($0.91 \times 10^9$/L) on day 11 (Table 1). The results of severe acute respiratory syndrome coronavirus 2 (SARS CoV- 2) real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) by nasopharyngeal swabs remain positive (Fig.1), therefore, the therapeutic course of Paxlovid was then been prolonged (day11–19). The patient's conditions gradually improved, and two consecutive negative SARS-CoV-2 RT-PCR tests from nasopharyngeal swabs were reported on day17–18 (Fig.1), although he had moderate fever, the other clinical symptoms were improved, neutrophils count was reduced (Day 19), and oxygen saturation maintained at a stable high level, and he was then transferred to a COVID-19-free department and continued to receive antibiotic agents and oxygen therapy (day 20).

Surprisingly, SARS-CoV-2 RT-PCR test was performed on day 20 in COVID-19-free department and proved to be strongly positive (cycle threshold (Ct) value: N gene:25.5, ORF1ab gene:26.32), clinical symptoms were improved except moderate fever, the therapeutic course of Paxlovid was then been prolonged again (day 20–25) (Fig.1). SARS-CoV-2 RT-PCR tests became negative on days 21, 22, 25, and 28. The patient's conditions, laboratory results and radiological results improved significantly and he was discharged on day 28 (Fig.1). Treatment with Paxlovid for 20 days didn't induce obvious dysgeusia, headache, nausea, vomiting, elevated alanine aminotransferase and lowered creatinine renal clearance (Table 1) in this patient.

The reason of COVID-19 rebound after Paxlovid treatment is not clear, treatment with Paxlovid might transiently suppress the viral replication and the patient could not develop an efficacious immune response during Paxlovid treatment, this might allow for a short interval SARS-CoV-2 viral rebound.[2,6] The first 2 courses of Paxlovid treatment seem to have no obvious effect on virus shedding (Fig. 1), suggesting that Paxlovid therapy was ineffective or the emergence of treatment-resistant mutations might be happened in this patient. In addition, viral sequencing was not performed, so we can't distinguish between relapse and re-infection. The results of SARS-CoV-2 RT-PCR test seem to be fluctuant, the Ct value proved to be strongly positive on day 20 and then suddenly turn to be negative on day 21, infection with a different strain or contamination may be another explanation. The limitation of this study was that we didn't perform repeatedly SARS-CoV-2 RT-PCR test for this patient on day 20 to verify the positive result.

Long term Paxlovid therapy in severe COVID-19 patient has not been reported, in this patient, although COVID-19 rebound happened, the results of SARS-CoV-2 RT-PCR tests became eventually negative with continued use of Paxlovid for 20 days (4 courses). Dysgeusia, headache, nausea, vomiting, elevated alanine aminotransferase and lowered creatinine renal clearance are the most common adverse events in patients administered Paxlovid,[2] however, no obvious adverse events were found after long-term treatment with Paxlovid for COVID-19 in this patient, this suggested that prolonging the therapeutic course of Paxlovid might be feasible and safe for severe COVID-19 patients.

In summary, this case suggested that COVID-19 rebound may occur in Paxlovid treated COVID-19 patient even if the therapeu-

https://doi.org/10.1016/j.jinf.2022.08.012

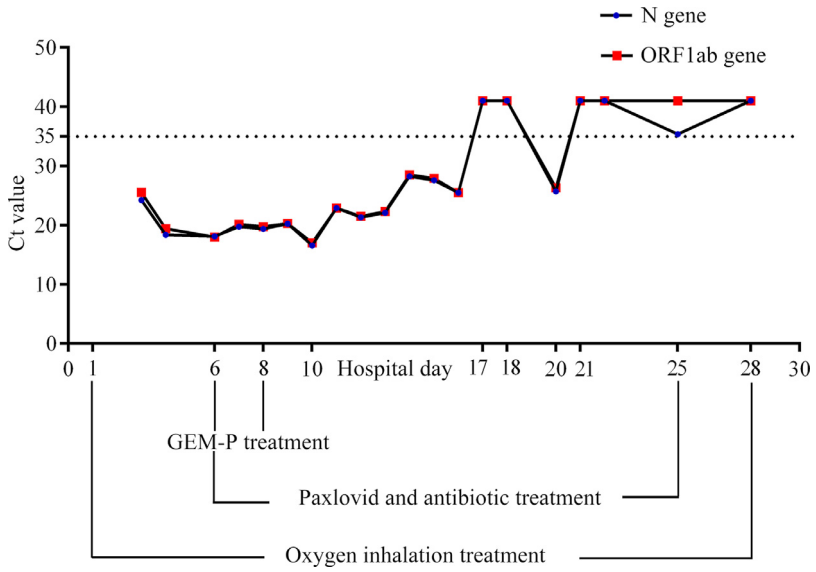


**Fig. 1.** The evolution of SARS-CoV-2 viral load and the different treatments received. Ct, cycle threshold; GEM-P, methylprednisolone.

**Table 1**
Laboratory results.

| Variable | Reference range | Day 5 | Day 8 | Day 11 | Day 13 | Day 17 | Day 19 | Day 21 | Day 26 |
|---|---|---|---|---|---|---|---|---|---|
| Absolute neutrophil count ($\times 10^9$/L) | 1.8–6.3 | 12.94 | 9.19 | 4.78 | 5.65 | 9.27 | 6.95 | 5.28 | 4.49 |
| Absolute lymphocyte count($\times 10^9$/L) | 1.1–3.2 | 1.13 | 0.73 | 0.91 | 1.12 | 1.53 | 1.47 | 1.39 | 1.12 |
| Procalcitonin(ng/ml) | 0–0.046 | 0.2 | 1.02 | 0.27 | 0.27 | 0.17 | | 0.15 | 0.1 |
| C-reactive protein (mg/L) | 0–10 | 65 | 90.5 | 11 | 12.5 | 20 | 35 | 15 | |
| Creatinine (umol/L) | 58–110 | 91.7 | 88.8 | | 69.6 | 79.6 | 67.4 | 63.9 | 47.4 |
| Alanine aminotransferase (U/L) | ≤50 | 13 | 17 | | 20 | 15 | 19 | 16 | 8 |
| Aspartate aminotransferase (U/L) | 17–59 | 38 | 36 | | 56 | 31 | 29 | 28 | 21 |

tic course of Paxlovid is prolonged, doctors should closely monitor the rebound in severe COVID-19 patient with Paxlovid therapy, and prolonging the therapeutic course of Paxlovid might be a feasible and safe strategy for severe COVID-19 patients. Further studies are required to determine the etiology of COVID-19 rebounds and the relation to Paxlovid treatment.

## Ethical statement

The study was approved by the Medical Ethics Committee of Shidong Hospital. The informed written consent was taken from the case under this study.

## Funding

This work was supported by the Key Discipline Construction Fund of Yangpu District (YP19ZA09) and Shanghai Sailing Program (21YF1443300).

## Conflicts of Interest

Authors do not have a conflict of interest among themselves.

## Acknowledgement

The authors would like to thank the patient for granting us the permission to publish this case report.

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