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Letter to the Editor

Relapse in the first 8 weeks after onset of COVID-19 disease in outpatients: Viral reactivation or inflammatory rebound?


Letter to the editor Journal of Infection

Dear editor,

We read with interest the study by Gousseff et al. about 4 mild cases with clinical recurrences of COVID-19 on day 24–36 after start of symptoms¹. Our findings in 41 outpatients with a relapse may further help to unravel which mechanism plays a role in similar cases: viral reactivation, reinfection or inflammatory rebound.

Reinfection of COVID-19 is commonly defined as clinical recurrence accompanied by a positive PCR test more than 90 days after onset of the primary infection². Within that timeframe re-positive PCR results following negative tests occur in more than 10% of recovering COVID-19 patients^{1,3–5}. The combination of a clinical recurrence ('relapse') after a symptom-free interval and re-positive PCR results has not been explored extensively and may be rare: 0.1% in outpatients with median 25 days (max. 84) between 2 positive results⁶. To minimize transmission risk the Dutch guideline proposes a timeframe of 8 weeks instead of 90 days after disease onset to consider reinfection; only patients with a relapse 8 or more weeks after disease onset are advised to isolate and retest⁷. To provide evidence to support this approach, we aimed to determine whether an early relapse in outpatients is accompanied by concurrent SARS-CoV-2 positive PCR results with low Cycle threshold (Ct) values ('viral reactivation').

Outpatients were identified during source investigation and contact tracing by the public health service (PHS) of Rotterdam-Rijnmond in local COVID-19 testing sites that became operational on 1 June 2020. Samples from nose and throat swabs from patients experiencing COVID-19-like symptoms are processed in 14 local laboratories. Not all laboratories report a Ct value in all positive RT-PCR test results due to technical characteristics of some of their RT-PCR platforms. The PHS is mandatorily notified by laboratories in case of positive SARS-CoV-2 results and all test-positive patients are routinely contacted to record clinical data.

During the study period of 1 June–15 November 2020 340,916 tests were performed; 46,073 were positive. Outpatients with a relapse were retrospectively identified from the register in two ways: 1) patients who called the PHS to enquire about the need to retest because of recurrent COVID-19-like symptoms and who were subsequently retested ($n = 17$), and 2) patients with recurrence of symptoms and who self-initiated testing within 8 weeks after the first test ($n = 24$).

The median age of the 41 patients was 33 years (range 11–58); 14 (34%) were female; none were immunocompromised nor admitted during either disease episode. The first symptomatic period lasted a median of 8 days (range 0–31), and patients re-

ported headache (55%), muscle ache (55%), nasal cold (48%), loss of taste or smell (48%), cough (45%), sore throat (37%) and fever (35%) (Table 1 & 2). The median symptom-free interval was 12 days (range 2–30). During relapse they most frequently reported cough (45%), nasal cold (39%), headache (26%) and sore throat (21%). Fever was reported by 2 patients as a new symptom among the 4 who reported fever during the relapse.

RT-PCR Ct values and RT-PCR platforms used were requested from the diagnostic laboratories. The first PCR test was performed a median of 4 days (IQR 2–6) after disease onset with a median Ct value of 22.1 (range 16.0–34.8, $n = 27$, Table 1). Out of 41 relapse patients, 33 had been retested a median of 28 days (range 10–58) after the first test and a median of 4 days (range 1–34) after relapse onset. The second test result was positive in 27 cases (82%). In 17 patients a Ct value could be retrieved, median was 34.8 (range 29.2–38.0). Paired comparison of Ct values in 10 patients showed a median increase of 14.9 cycles (range –1.0–20.0) in the second test (one case with lower Ct value in the second test: both >33).

Consequently, in mild COVID-19 cases without risk factors such as old age or immunosuppression a relapse may occur in the first 8 weeks after disease onset without viral reactivation. Sometimes PCR results were negative or - in case of positivity of the second test - high or consistently increased Ct values can be found. This is considered to reflect the gradual decline of the initial viral load with prolonged shedding of non-replicating virus². Possibly inflammatory rebound may explain the clinical recurrence, but this was not measured in these outpatients. Furthermore, onward viral transmission is improbable because Ct values around 30 or higher, as determined in our outpatients during the relapse, are unlikely to result in spread of viable virus^{8,9}. Similarly, in the studies examining SARS-CoV-2 PCR re-positivity in non-immunocompromised patients, virus cultures were negative^{1,3,4,10}. These data support the Dutch guidelines that do not advise re-isolation or retesting of outpatients with an early relapse⁷. Only in case of severe disease manifestations during relapse or new symptoms after direct contact with another proven COVID-19 case the standard measures of isolation and retesting are applicable also in the first 8 weeks.

There are limitations to these findings of this retrospective study. Relapse was self-reported and its true incidence, cause, and contributing factors remain unknown. Because we did not perform serology or genomic sequencing, theoretically reinfection within 8 weeks due to lack of protective immunity could not be ruled out. However, viral RNA re-positivity may occur with or without the presence of SARS-CoV-2 protective antibodies⁵. Caution must be used in interpreting Ct values of RT-PCR tests as a surrogate for viral load because these were obtained from various laboratories with distinct RT-PCR platforms or gene targets. Findings in young outpatients with a mild course of disease cannot be extrapolated to hospitalized cases, high-risk groups or viral loads associated with

Table 1

Disease and RT-PCR test result characteristics of COVID-19 patients who reported a second episode of symptoms resembling COVID-19 or suffered from persistent symptoms within 8 weeks after disease onset.

Case	Duration of first episode (days)	Symptom-free interval (days)	Time between first disease day and test (days)	Time between first day relapse and test (days)	Time between test 1 and test 2 (days)	CT value test 1	Result test 2	CT value test 2
1	12	3	5	4	14	34.8	NEG	
2	0	18	7	7	19	34.7	POS	33.7
3	0	30	1	6	35	33.2	POS	NR
4	8	4	-2			32.6	NP	
5	7	14	6	8	23	31.8	NEG	
6	13	12	7	7	25	31.5	POS	36.2
7			17		29	28.6	POS	32.4
8	5	22	8	3	22	27.4	NEG	
9			3			25.2	NP	
10	26		1		31	25.1	POS	NR
11	21	24	3	4	46	24.6	POS	29.4
12			9			24.2	NP	
13	16	5	6	11	25	22.7	POS	NR
14			2	2	42	22.1	POS	36.2
15	11	3	2			20.9	NP	
16	26	23	3	3	49	20.3	POS	36.5
17	8	12	2			20.1	NP	
18	4	28	3	4	33	19.8	POS	35.8
19	10	3	4			19.6	NP	
20	5	4	4	4	10	19.2	NEG	
21			3	4	29	18.9	POS	35.0
22			6	4	52	18.0	POS	33.7
23			7	4	30	17.3	POS	37.2
24	3	14	2	3	18	17.3	POS	NR
25	7	2	4			17.1	NP	
26			2	1	27	16.9	POS	NR
27	6	11	2	3	17	16.0	POS	NR
28	12	8	3	6	23	NR	NEG	
29	10	12	2	34	55	NR	NEG	
30	26	14	5	23	58	NR	POS	38.0
31			5	1	48	NR	POS	35.6
32			-1	3	21	NR	POS	34.8
33	4	14	5	3	16	NR	POS	33.7
34	3	19	11	1	12	NR	POS	33.6
35	31	12	7	3	40	NR	POS	31.7
36	19	10	5	7	31	NR	POS	29.2
37	19	7	5	4	25	NR	POS	NR
38			3	2	32	NR	POS	NR
39			6		33	NR	POS	NR
40	7	8	6	12	21	NR	POS	NR
41	6	24	6			NR	NP	
Summary	8 (0–31)*	12 (2–30)*	4 (-2–17)*	4 (1–34)*	29 (10–58)*	22.1 (16.0–34.8)*	Positive: 27; Negative: 6; No test taken: 8	34.8 (29.2–38.0)*

Abbreviations: NR, not reported (some laboratories could not retrieve Ct values, because of platform type; NP: not performed).

*median (range).

Cases 2, 3 tested because of COVID-19 positive contacts and remained asymptomatic for several weeks.

Cases 4, 32 tested just before start of symptoms because of COVID-19 positive contacts.

Cases 7, 10, 39 did not have a symptom-free interval, but experienced a substantial exacerbation after partial recovery.

Case 6 retested negative one day after the second test.

Case 11 tested negative in the symptom-free interval.

Table 2

Most frequently self-reported symptoms of COVID-19 patients during the first episode and relapse within 8 weeks after disease onset.

Symptom	Present first episode (n = 40)	%	Present relapse (n = 38)	%
Muscle ache	22	55	7	18
Headache	22	55	10	26
Nasal cold	19	48	15	39
Loss of taste and/or smell	19	48	7	18
Cough	18	45	17	45
Sore throat	15	38	8	21
Fever/ cold shivers	14	35	4	11

other SARS-CoV-2 variants than those that were circulating during the study period. We did not verify whether secondary cases arose in the households of these patients.

In conclusion, viral reactivation was unlikely in mildly affected COVID-19 outpatients without risk factors for severe disease with a relapse in the first 8 weeks of illness, and retesting or isolation seems unnecessary.

Supplementary material associated with this article can be found, in the online version, at doi:

Declaration of Competing Interest

None of the authors has any conflict of interest to declare regarding this subject. This work had no financial support.

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