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Duration of isolation and contagiousness in COVID-19 patients receiving tocilizumab and dexamethasone: a case series

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Abbreviated title: Isolation for COVID patients post tocilizumab
Abstract:

We describe ten patients with severe COVID-19 who received tocilizumab and dexamethasone. We correlated isolation duration with cycle thresholds (Ct) values of nucleic acid amplification tests, clinical state and viral cultures. Isolation duration exceeded 21 days for seven patients due to positive viral cultures or Ct values < 30.
Introduction

COVID-19 contagiousness is critical in healthcare setting, and varies along with severity of disease, immunosuppression of host and medication\(^1\). In severe cases of COVID-19, viral replication and transmission have been described up to 20 days after the onset of symptoms, sometimes longer in immunocompromised patients.\(^2\,^3\) Still, CDC guidelines recommend deisolation 21 days after the onset of symptoms, after resolution of fever and improvement of symptoms. A test-based strategy “can be considered”\(^4\).

In the province of Quebec, a single dose of tocilizumab along with 10 days of dexamethasone are recommended in severe cases of COVID-19. Considering the relative immunosuppression induced by those drugs,\(^5\,^6\) and the fact that they are used in severe cases, uncertainty regarding the optimal duration of isolation surfaced. One study showed that tocilizumab and dexamethasone treatments were independently associated with prolonged shedding of viral RNA\(^1\).

We can assess contagiousness and viral replication through viral culture\(^7\). Unfortunately, this method takes time and specialised laboratories. Alternatively, we can evaluate viral shedding and extrapolate contagiousness through Cycle thresholds (Ct) values of nucleic acid amplification tests (NAAT) of SARS-CoV-2 RNA\(^7\).

We describe ten patients who received tocilizumab and dexamethasone for severe COVID-19 due to Alpha variant (B.1.1.7). We correlated clinical state, Ct values of NAAT and viral culture results to suggest safe discontinuation of isolation measures.
Methods

Patients selection: We reviewed cases of severe COVID-19 from March 23rd through April 21st, 2021. We included every patient who received tocilizumab and dexamethasone for whom isolation duration was evaluated by an infectious disease (ID) consultant. We reviewed comorbidities, symptomatology and temperature, isolation duration and NAAT and viral culture results.

Setting: CHU de Québec-Université Laval is a 1660 beds, acute care university institution in Quebec City, Canada. COVID-19 patients are hospitalised on COVID-specific units with dedicated staff for the isolation duration, then transferred to non-COVID wards. COVID-19 units comprise approximately 115 beds and 15 ICU beds in two separate sites.

Diagnostic tests: Decision to obtain NAAT or viral culture was delegated to the ID consultant. All specimens were obtained through nasopharyngeal swabs. NAAT were conducted on Simplexa assay (DiaSorin Molecular), targeting genes S and ORF1ab. Viral cultures were done on Vero E6 cells in a Biosafety level 3 laboratory, using a previously described method\(^8\). After a year-long pause (as a biosafety mitigation measure), viral cultures were allowed again in our institution in March 2021, if prescribed by an ID specialist to evaluate patients post tocilizumab and dexamethasone. Our case series includes every viral culture done within the study period.

Infection Control: Per local guidelines, patients presenting with severe illness (defined as intensive care warranting high-flow oxygen or mechanical ventilation) could be deisolated after 21 days if they had been apyretic for 48h and clinically improving for 24h. Isolation duration could be extended by ID specialists, when called upon. As a clinical surrogate for our patients’ contagiousness, we monitored new COVID-19 cases in healthcare workers and other patients on non-COVID wards after deisolation.
Results

Patients, aged 46 to 75, had a severe case of COVID-19, Alpha variant (B.1.1.7) and received a single dose of tocilizumab along with dexamethasone for ten days. They all needed invasive ventilation for a period ranging from five days to over a month. They did not receive any other COVID-19-specific treatment. Every patient but one recovered.

Overall, there is a discrepancy between our results (Table 1) and approved guidelines concerning duration of isolation for severe COVID-19. At Day 21 post onset of symptoms, seven out of ten patients were still in isolation, mostly because of lack of clinical improvement, low Ct values, and, in two cases, positive viral cultures.

No secondary COVID-19 infection on non-COVID wards were identified when isolation measures were lifted.
**Discussion**

Our case series advocates against deisolation of severe COVID-19 patients who receive tocilizumab and dexamethasone based on clinical improvement alone at Day 21. Five out of ten patients had Ct values < 30, and two patients had a positive viral culture after Day 20, which contrasts with previous data\(^4\)\(^7\). Use of tocilizumab and dexamethasone in our case series may have contributed to a prolonged viral shedding, along with severe infection. More work is needed to determine the underlying causes and risk factors of prolonged infectivity.

Our work reflects what is currently known on the correlation between high NAAT Ct values and negative culture, past a certain threshold. Ct values may vary with the technology used – five studies reported no growth on viral culture on specimen with Ct values ranging from > 24 to > 35\(^7\). Because Simplexa assay does not require molecular extraction, Ct values can be somewhat lower than other methods (-2.1 cycles compared to CDC’s diagnostic panel)\(^9\).

Ct values fluctuated substantially over multiple days samplings, which might represent variable shedding linked to specimen quality or volume and severity of disease\(^3\). It has also been observed previously that patients with prolonged positive testing (over 28 days) are also the ones in whom Ct values fluctuate the most\(^3\), which was the case for patient 3, notably.

For severe COVID-19 cases post tocilizumab and dexamethasone, our data advocates for a deisolation strategy based on two separate NAAT results (thus mitigating Ct values’ fluctuation): a conservative Ct cut-off value > 30 could be used in clinically improving patients, at least 21 days after symptoms onset. In our case series, Ct values > 30 in clinically improving patients correlated with negative viral culture (and presumed absence of contagiousness\(^7\)). After lifting isolation, no secondary infection was attributed to our patients. It is possible (but unlikely) that they were still contagious but didn’t infect others due to infection prevention and control measures. Conversely, the fact that some
patients have a prolonged viral excretion might explain some of the nosocomial outbreaks seen during the pandemic.

The principal strength of this case series is that we present viral culture results while most previous studies showed RNA viral shedding through NAAT alone. Providing detailed case summaries might also be of use to clinicians. Finally, to our knowledge, few other studies have addressed the impact of tocilizumab and dexamethasone on isolation duration.

The principal limitation of our case series is its small sample size, which precludes strong conclusions and generalisation. Nonetheless, our patients’ age and comorbidities reflect COVID-19 ICU population. All patients presented with Alpha variant, the most prevalent variant at the time in our province. It should also be noted that due to clinicians’ autonomy and laboratory workers’ unavailability on weekends, cultures could not be systematically obtained at Day 21. Reflecting real-life situations, our case series was conducted without a control group.

Relying on NAAT results in addition to clinical criteria is the safest option in our opinion, considering positive viral culture obtained in a clinically improved patient. Additionally, using NAAT as an objective surrogate to contagiousness probably constitutes the best option in view of newer variables: vaccination status, breakthrough infections, and variants of concern, especially Omicron and Delta variants - Delta has been associated with longer duration of Ct values < 30\textsuperscript{10}. Larger trials are needed to confirm our data and explore its applicability in those situations.
Acknowledgements

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.
References


<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender and Age</th>
<th>Comorbidities</th>
<th>Date of onset of symptoms (OOS)</th>
<th>Intubation duration (in days)</th>
<th>Evolution at Day 21 after onset of symptoms</th>
<th>NAAT results #Day (Ct gene S/gene ORF1ab)</th>
<th>Viral culture (#Day of sample from OOS)</th>
<th>Reason to lift isolation</th>
<th>Lifting isolation on #Day after OOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 66</td>
<td>Idiopathic pulmonary fibrosis (mild), HTN, Type 2 diabetes, dyslipidemia</td>
<td>March 23rd, 2021</td>
<td>28 (until death 29/04)</td>
<td>Clinical deterioration, hypoxemia, ongoing fever under large spectrum antibiotics</td>
<td>Positive #21 (21,2/21,9)</td>
<td>Positive #30 (28,2/28,5)</td>
<td>Positive #31 (19,3/19,4)</td>
<td>Positive #33 (22,2/21,5)</td>
</tr>
<tr>
<td>2</td>
<td>F, 60</td>
<td>Depression, migraine, obesity</td>
<td>April 15, 2021</td>
<td>12</td>
<td>Clinical improvement, subfebrile on UTI</td>
<td>Mild positive #21 (31,3/ND)</td>
<td>Mild positive #25 (ND/34,3)</td>
<td>Negative (#21)</td>
<td>Negative culture</td>
</tr>
<tr>
<td></td>
<td>M, 60</td>
<td>HTN, Type 2 diabetes, dyslipidemia</td>
<td>April 4th, 2021</td>
<td>39</td>
<td>Persistent hyperthermia, hypoxemia still under mechanical ventilation, bacteremia</td>
<td>Positive #36 (24.3/25.2) Positive #38 (29.9/30.7) Positive #40 (16.4/17.7) Positive #43 (19.9/20.9) Positive #45 (28.8/29.2)</td>
<td>Negative (#37)</td>
<td>Negative culture</td>
<td>45</td>
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<tr>
<td>4</td>
<td>M, 57</td>
<td>HTN, Type 2 diabetes, dyslipidemia</td>
<td>April 21st, 2021</td>
<td>9</td>
<td>Afebrile, clinical improvement</td>
<td>Positive #21 (23.4/24.4) Positive #23 (31.4/33.8)</td>
<td>Positive in 2 days (#21)</td>
<td>Clinical improvement and Ct &gt; 30</td>
<td>23</td>
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<td>5</td>
<td>M, 59</td>
<td>HTN, Previous aortic dissection, chronic renal insufficiency (stage 2), bronchial</td>
<td>April 5th, 2021</td>
<td>38 (tracheostomy at Day 22)</td>
<td>Intermittent hyperthermia, still under mechanical ventilation, large spectrum</td>
<td>Negative #37, Negative #39</td>
<td>Negative (#37)</td>
<td>Two negative nasopharyngeal NAAT</td>
<td>39</td>
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<tr>
<td>Case</td>
<td>Age</td>
<td>Diagnosis</td>
<td>Date of Admission</td>
<td>Duration</td>
<td>Status</td>
<td>Methodology</td>
<td>Isolation Duration</td>
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<tr>
<td>6</td>
<td>M, 75</td>
<td>HTN, obstructive sleep apnea, coronary artery disease, osteoporosis, hypothyroidism</td>
<td>April 21st, 2021</td>
<td>5</td>
<td>Afebrile, clinical improvement</td>
<td>No NAAT done after diagnosis</td>
<td>Negative (#21)</td>
<td>Clinical criteria</td>
<td>21</td>
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<tr>
<td>7</td>
<td>M, 51</td>
<td>Obstructive sleep apnea, oesophageal reflux, previous nasal septal deviation surgery</td>
<td>April 2nd, 2021</td>
<td>10</td>
<td>Afebrile, clinical improvement</td>
<td>Positive #24 (31.2/32.7)</td>
<td>Negative (#24)</td>
<td>Clinical criteria. Isolation extended because date of onset of symptom initially not clear – was thought to be on Day 21 post OOS.</td>
<td>24</td>
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<tr>
<td>8</td>
<td>M, 66</td>
<td>HTN, Hepatitis B undergoing treatment (Entecavir), possible Lymphoma under investigation</td>
<td>April 13th, 2021</td>
<td>10</td>
<td>Afebrile, clinical improvement</td>
<td>Negative #28</td>
<td>Not done</td>
<td>Clinical criteria. Isolation extended because date of onset of symptom initially not clear – was thought to be on</td>
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<td>9</td>
<td>M, 46</td>
<td>Obesity, callous body agenesis</td>
<td>April 17th, 2021</td>
<td>16</td>
<td>Still febrile, clinical amelioration</td>
<td>Positive #23 (27.1/28.2) Negative #32</td>
<td>Note done</td>
<td>Negative NAAT</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M, 70</td>
<td>HTN, obstructive sleep apnea, oesophageal reflux, dyslipidemia, coronary artery disease, migraine, previous prostate neoplasia</td>
<td>April 7th, 2021</td>
<td>13</td>
<td>Afebrile, clinical improvement</td>
<td>Positive #21 (20/20.8) Positive #28 (30/30.2) Positive #29 (32.8/35.4)</td>
<td>Negative (#21)</td>
<td>Clinical improvement and Ct &gt;30</td>
<td></td>
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</tbody>
</table>

**Legend**:  
M male  
F female  
HTN arterial hypertension  
UTI urinary tract infection  
OOS onset of symptoms  
ND Not detected