High-dose glucocorticoids pulse-therapy for beta-coronaviridae pneumonia: a systematic literature review and case-series of Coronavirus disease-2019

G. Dolci¹, G. Cassone², F. Venturelli³,4, G. Besutti³,5, M. Revelli⁵, R. Corsini⁶, F. Sampaolesi⁶, P. Pavone⁶, G. Contardi⁶, N. Riva⁶, G. Marini⁶, C. Lazzareschi⁶, S. Mezzadri⁶, J. Milic³, M. Massari⁶, M. Costantini⁷, C. Salvarani²,⁸

¹Infectious Disease School, University of Modena and Reggio Emilia, Modena; ²Rheumatology Unit, IRCCS Arcispedale Santa Maria Nuova, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia; ³University of Modena and Reggio Emilia PhD Program, Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Modena; ⁴Epidemiology Unit, ¹Radiology Unit, Department of Imaging and Laboratory Medicine, ²Infectious Disease Unit, Azienda USL-IRCCS di Reggio Emilia; ⁵Scientific Director, Azienda USL-IRCCS di Reggio Emilia; ⁶Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy.

Giovanni Dolci, MD
Giulia Cassone, MD
Francesco Venturelli, MD
Matteo Revelli, MD
Romina Corsini, PhD
Fabio Sampaolesi, MD
Paolo Pavone, MD
Giada Contardi, MD
Nicoletta Riva, MD
Giulia Marini, MD
Claudia Lazzareschi, MD
Sergio Mezzadri, MD
Jovana Milic, MD
Marco Massari, MD
Massimo Costantini, MD
Carlo Salvarani, MD

Please address correspondence to: Carlo Salvarani,
Unità Operativa di Reumatologia,
Azienda Ospedaliera-IRCCS di Reggio Emilia,
Viale Risorgimento 80,
42100 Reggio Emilia, Italy.
E-mail: salvarani.carlo@ausl.re.it

Abstract

Objective. The results of the RECOVERY trial identified dexamethasone as the first pharmacological therapy that reduces mortality in patients with COVID-19. The aim of this paper is to conduct a systematic literature review on safety and efficacy of pulse glucocorticoid therapy for Severe Acute Respiratory Syndrome (SARS)-Coronavirus CoV (CoV), Middle East Respiratory Syndrome (MERS)-CoV or SARS-CoV-2 infections and describe a case-series of COVID-19 patients treated with off-label pulse doses of methylprednisolone.

Methods. We performed a systematic literature review on safety and efficacy of pulse therapy for betacoronaviridae infections as described in the protocol registered on PROSPERO (CRD42020190183). All consecutive patients admitted to Arcispedale Santa Maria Nuova di Reggio Emilia or Guastalla Hospital with COVID-19 between March 1st and April 30th, 2020 and treated with methylprednisolone 1 gram/day for at least three days were included in the case series. A retrospective review of available computed tomography (CT) scan and chest x-ray was performed independently by two radiologists blinded to clinical data, and discordanes were resolved by consensus.

Results. Twenty papers were included for SARS, but only two were comparative and were included in the primary endpoint analysis. Likewise, eleven papers were included for COVID-19, four of which were comparative and were considered for the primary outcome analysis. Included studies for both SARS and COVID-19 are mostly retrospective and highly heterogeneous, with lethality ranging from 0% to 100% and ICU admission rate ranging from 9% to 100%. Fourteen patients were included in our case series, 7 males and 7 females.

Conclusion. No randomised controlled trial is available yet for corticosteroids pulse-therapy defined as at least ≥500mg/day methylprednisolone in patients with emerging coronavirus pneumonia. Lethality among our cohort is high (4/14), but this finding should be interpreted with caution due to the fact that in our setting pulse-steroids were used in patients not eligible for other treatments because of comorbidities or as rescue therapy. The incidence of steroid-related adverse events seems low in our cohort.

The quality of the evidence on glucocorticoid pulse-therapy in SARS, MERS and COVID-19 is poor. Randomised controlled trials are greatly needed.

Introduction

Pharmacologic treatments for Coronavirus Disease 2019 (COVID19) pneumonia are still under investigation. In the preliminary results of the RECOVERY trial, dexamethasone was identified as the first pharmacological therapy able to reduce mortality in COVID-19 (1). Dexamethasone 6mg for ten days improved survival in patients with respiratory failure. Off-label therapies have been widely used and there are many ongoing clinical trials, but no solid evidence of any other effective treatment is available yet.

There has been growing evidence that hyperinflammation is linked to severe pneumonia in COVID-19 (2-6). In most patients with severe disease...
Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV2) infection is associated with a cytokine-storm characterised by a rise of pro-inflammatory cytokines leading to an aberrant immune response (4, 7-13). An abnormal inflammatory response is also involved in the lung damage secondary to other betacoronaviridae, as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) infections (11, 14). A study by Huang et al. showed that people with more severe COVID-19 admitted to intensive care unit (ICU) had higher blood levels of several cytokines such as IL2, IL7, IL10, G-CSF, IP10, MCP1, MIC1A and TNFα (4). An increment of IL6 in severe cases of betacoronaviridae infections has been described and was confirmed in SARS-CoV2 infection (12, 15-17). Neutrophils play an important role in COVID-19-induced lesions, both in the peripheral blood and lungs (3, 18). Thus, macrophage-activation syndrome-like immune activation in COVID19-associated acute respiratory distress syndrome (ARDS) has been hypothesised (19).

Consequently, researchers and clinics have been focusing on immune-modulating therapies to treat ARDS in patients with COVID-19 (3, 20, 21), including chloroquine (22), hydroxychloroquine (23), IL1-inhibitors (24), JAK-inhibitors (25) and IL-6 inhibitors (26-31). Corticosteroids are under investigation too. They inhibit numerous pro-inflammatory cytokines, including IL-6, IL-8, MCP-1 and IL-10, that can be involved in SARS-CoV2-induced lung damage (32). Furthermore, as showed by Fauci et al., they block the efflux of neutrophils and monocytes to the inflammatory sites (33). Finally, research on glucocorticoids for COVID-19 can be particularly relevant for low-and-middle income countries, where expensive biologic agents may not be available on a large scale.

While low and moderate dose corticosteroids have been widely used in SARS-CoV2 infection, we sought to investigate a potential role of high dose pulse glucocorticoid therapy. In COVID-19 the cytokine storm represents the acme of the inflammatory process, suggesting the need for a prompt and strong anti-inflammatory effect, which pulse glucocorticoid therapy can provide better than non-pulse treatment. This therapy has already proven effective to treat the most severe complications of autoimmune diseases.

We designed a systematic review to further explore literature on steroid pulse therapy in SARS, MERS and COVID-19 to assess lethality, ICU admissions and the main glucocorticoids-related adverse events in these patients. The aim of this paper is to conduct a systematic literature review on safety and efficacy of pulse glucocorticoid therapy for SARS, MERS or SARS-CoV2 infection and describe a monocentric case-series of COVID-19 patients treated with off-label pulse doses of methylprednisolone.

Materials and methods
Systematic review
The review protocol was registered on PROSPERO database with ID CRD42020190183 (34). Any discrepancy with original protocol was discussed in the methods. Only papers including a methylprednisolone therapy of at least 500mg/day for at least 3 days or equivalent doses were considered. Full materials and methods of the systematic review are reported in the Supplementary file.

Patients
All consecutive patients admitted to Arcispedale Santa Maria Nuova di Reggio Emilia or Guastalla Hospital between March 1st and April 30th 2020 with COVID-19 and treated with Methylprednisolone 1 gram/day for at least three days were included in the study.
Therapeutic scheme

An internal off-label therapeutic schedule was used:
Methylprednisolone intravenous 1gr single daily dose for the first 3 days;
Then methylprednisolone per os:
16mg tablet 3 times a day for 3 days;
Then methylprednisolone per os:
8mg tablet 3 times a day for 3 days;
Then methylprednisolone per os:
4mg tablet 3 times a day for 3 days;
Then methylprednisolone per os:
2mg tablet 3 times a day for 3 days.
This schedule was chosen based on rheumatologists’ experience with steroid pulses in auto-immune diseases, with a 12-day tapering to avoid inflammatory rebound.

Data collection

The data were collected from both electronic and paper clinical records. Data on comorbidities, oxygen support, ventilation and infection were collected manually. A retrospective review of available computed tomography (CT) scan and chest x-ray was performed independently by two radiologists blinded to clinical data, and discrepancies were resolved by consensus. On the CT scan, presence of ground-glass opacities, consolidation, crazy-paving pattern, pleural effusion and lymphadenopathies (>1 cm in the short axis), as well as bilateral distribution and extension of parenchymal findings estimated by a visual scoring system (<20%, 20–39%, 40–59%, ≥60%) were collected (35). On the chest x-ray, the presence of interstitial pattern and consolidation, and the estimation of parenchymal change extension by means of the Radiographic Assessment of Lung Edema (RALE) score, were collected (36). Laboratory exams were extracted electronically.

Results

Literature review

The results found for each disease considered and the systematic review’s flow-chart are depicted in Figure 1. Eighteen papers were included for SARS, but only two were comparative and were included in the primary end-point analysis (Table Ia). Eleven papers were included for COVID-19, four of which were comparative and were considered for the primary outcome analysis (Table Ib).

COVID-19 case series

Hussein et al. (40) described a single case of a woman with an anti-neutrophilic cytoplasmic antibody (ANCA) Vasculitis presenting as pulmonary haemorrhage. She was treated with steroid pulses and eventually passed away. Maideniuc et al. (41) described a single case of acute necrotising myelitis treated with steroid pulses, that survived and at the time of the report was undergoing rehabilitation.

Merab Sauﬁe et al. (42) described two patients treated at home with steroid pulses as rejected by medical institutions and that had favourable outcomes. Parsons et al. (43) described a case of a woman developing acute disseminated encephalomyelitis (ADEM) on day 18 of hospitalisation and was treated in ICU with 5 days- 1gr methylprednisolone-pulse therapy starting on day 31. The patient was then extubated and began a rehabilitation process, being fully oriented on day 59.
Steroids pulse-therapy for COVID-19 and SARS / G. Dolci et al.

Table IIa. Patients’ comorbidities at baseline.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/Males</td>
<td>7/7</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Cough/dyspnoea</td>
<td>10/14 (71.42%)</td>
</tr>
<tr>
<td>Myalgia/Asthma</td>
<td>12/14 (85.71%)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9/14 (64.29%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5/14 (35.71%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>3/14 (21.42%)</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>2/14 (14.29%)</td>
</tr>
<tr>
<td>COPD</td>
<td>2/14 (14.29%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>2/14 (14.29%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Active smoker</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>Metastatic solid tumour</td>
<td>1/14 (7.14%)</td>
</tr>
<tr>
<td>HIV-infection</td>
<td>1/14 (7.14%)</td>
</tr>
</tbody>
</table>

Pugin et al. (44) described 5 cases of COVID19-related encephalitis treated in ICU with methylprednisolone 500 mg pulse-therapy for 5 days. After 48–72 hours, awakening with a dramatic change of the level of consciousness was observed in all patients allowing extubation in 3/5 patients (2 had been tracheostomised). Five to ten days after the first steroid pulse 3/5 patients had fully recovered and the remaining two were fluctuating with variations of arousal, but when awake their Glasgow Coma Scale (GCS) was 14.

Sheianov et al. (45) reported a case series of 3 patients treated first with 125mg/day of methylprednisolone, then with intravenous tocilizumab after ICU admission and intubation. Eventually, due to clinical worsening, they were treated with 1gr methylprednisolone and intravenous immunoglobins for 3 days. Notably, all of them recovered and were discharged home by day 30 after admission.

So et al. (46) described a series of seven intubated patients treated with 3 days-pulse therapy (500mg or 1gr of methylprednisolone) and a total duration of 13 days of corticosteroids. They were all extubated (2–7 days of mechanical ventilation) and discharged home. Piperacillin/tazobactam plus azithromycin or levofloxacin were administered for 7 days. Interestingly, in this case series no superinfection observed, while 2 cases of hyperglycaemia and delusions were reported.

The remaining results of the literature review are reported in the Supplementary file.

Case series
Fourteen patients were included in our case series, 7 males and 7 females. The patients’ characteristics at baseline are described in Table IIa. Three of them (patients no. 1, 2 and 7) were previously treated with off-label tocilizumab but did not experience any significant improvement, thus steroids pulse-therapy was used as rescue therapy with a subsequent respiratory recovery and decrease of oxygen requirement. Table IIb describes the radiological characteristics of the patients at baseline. CT scans were available in 13/14 patients, in all cases with presence of ground-glass opacities and bilateral distribution. Consolidation and cazy-paving pattern were recognised in 8/13 and 11/13 patients, respectively, while pleural effusion and lymphadenopathy were present in 4/13 patients. The visual extension of disease was <20% in 2 patients, 20–39% in 5 patients, 40–59% in 3 patients and ≥60% in 3 patients. The patient without available CT scan was judged with a high parenchymal involvement based on chest x-rays, with presence of both interstitial pattern and consolidation, and a RALE score of 17.

The patients’ outcomes are shown in Table III. Four out of fourteen patients died, while two returned to the nursing homes where they lived before hospital admission. Of the remaining 8 patients, 4 returned to hospital accident and emergency but only one of them needed hospital re-admission for suspected vasculitis. Episodes of delirium were witnessed for the four deceased patients and the two patients that lived in nursing homes with cognitive impairment. For the other 8 patients no episode of delirium nor psychosis was reported.

Discussion
To date, no randomised controlled trial is available for the use of corticosteroids pulse-therapy defined as ≥500mg/
The extremely different populations described in the SARS and COVID-19 studies reflect the extreme severe patients that did not improve after other treatments. This is particularly evident in the SARS most-described cohorts in Hong Kong. The statistics were retrospective and did not particularly focus on pulse-therapy, the secondary outcomes of this systematic review were not reported for patients treated with pulse-therapy. Even for the avascular osteonecrosis and bone mineral density, the most investigated steroid-related adverse events in SARS patients, the results are inconsistent. While there is some agreement on the duration of steroidal therapy as a major risk factor associated with avascular necrosis, it is unclear if high-dose but short duration therapies might be detrimental. Furthermore, avascular osteonecrosis seems to stop or even ameliorate once glucocorticoids are ceased.

### Table IIc. Patients’ laboratory characteristics at baseline.

<table>
<thead>
<tr>
<th>CRP (mg/dl)</th>
<th>LDH (mg/dl)</th>
<th>D-dimer (ng/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>P/F</th>
<th>CRP (mg/dl)</th>
<th>LDH (mg/dl)</th>
<th>D-dimer (ng/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>P/F</th>
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<tbody>
<tr>
<td>Median</td>
<td>10.6</td>
<td>854</td>
<td>1624.5</td>
<td>66.3</td>
<td>Median</td>
<td>51.5</td>
<td>359</td>
<td>195.4</td>
<td>2.39</td>
</tr>
<tr>
<td>1</td>
<td>4.26</td>
<td>628</td>
<td>340</td>
<td>25.9</td>
<td>0.53</td>
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<td>242.5</td>
</tr>
<tr>
<td>2</td>
<td>1.34</td>
<td>590</td>
<td>1097</td>
<td>20.23</td>
<td>0.06</td>
<td>509</td>
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<td>NA</td>
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<tr>
<td>3</td>
<td>6.13</td>
<td>1512</td>
<td>1632</td>
<td>182.8</td>
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<td>1298</td>
<td>1675</td>
<td>176</td>
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<tr>
<td>4</td>
<td>15.2</td>
<td>359</td>
<td>918</td>
<td>112.5</td>
<td>1.88</td>
<td>380</td>
<td>421</td>
<td>NA</td>
<td>99.8</td>
</tr>
<tr>
<td>5</td>
<td>10.1</td>
<td>500</td>
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<td>NA</td>
<td>2.39</td>
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<td>476</td>
<td>NA</td>
<td>136</td>
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<tr>
<td>6</td>
<td>1.85</td>
<td>922</td>
<td>2510</td>
<td>5</td>
<td>2.38</td>
<td>523</td>
<td>828</td>
<td>19.4</td>
<td>151.3</td>
</tr>
<tr>
<td>7</td>
<td>32.8</td>
<td>1020</td>
<td>1301</td>
<td>265.4</td>
<td>5.06</td>
<td>727</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>8</td>
<td>11.1</td>
<td>530</td>
<td>NA</td>
<td>66.3</td>
<td>1.15</td>
<td>472</td>
<td>1722</td>
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<tr>
<td>9</td>
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<td>1023</td>
<td>9572</td>
<td>192.8</td>
<td>10.18</td>
<td>4823</td>
<td>13246</td>
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<td>82</td>
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<td>1502</td>
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<td>31.59</td>
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<td>11</td>
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<td>2686</td>
<td>89.5</td>
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<td>2525</td>
<td>24.3</td>
<td>0.38</td>
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<td>469</td>
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<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>13.2</td>
<td>829</td>
<td>4396</td>
<td>49.1</td>
<td>0.75</td>
<td>564</td>
<td>NA</td>
<td>NA</td>
<td>176</td>
</tr>
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</table>

Table III. Patients’ clinical outcomes and adverse events.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Therapy-to-discharge or death (days)</th>
<th>Oxygen support duration (days)</th>
<th>NIV</th>
<th>NIV duration (days)</th>
<th>Infections</th>
<th>Re-admission</th>
<th>Re-admission cause</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Home</td>
<td>8</td>
<td>13</td>
<td>NO</td>
<td>NA</td>
<td>Nil</td>
<td>NO</td>
</tr>
<tr>
<td>2</td>
<td>Home</td>
<td>7</td>
<td>16</td>
<td>YES</td>
<td>3</td>
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<td>NO</td>
</tr>
<tr>
<td>3</td>
<td>Deceased</td>
<td>9</td>
<td>11</td>
<td>YES</td>
<td>10</td>
<td>Nil</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Home</td>
<td>15</td>
<td>16</td>
<td>YES</td>
<td>8</td>
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<td>NO</td>
</tr>
<tr>
<td>5</td>
<td>Home</td>
<td>10</td>
<td>9</td>
<td>NO</td>
<td>NA</td>
<td>Nil</td>
<td>YES</td>
</tr>
<tr>
<td>6</td>
<td>Deceased</td>
<td>10</td>
<td>14</td>
<td>YES</td>
<td>12</td>
<td>Nil</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Home</td>
<td>28</td>
<td>23</td>
<td>YES</td>
<td>10</td>
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</tr>
<tr>
<td>8</td>
<td>Home</td>
<td>21</td>
<td>23</td>
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<td>NA</td>
<td>Nil</td>
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</tr>
<tr>
<td>9</td>
<td>Deceased</td>
<td>6</td>
<td>6</td>
<td>YES</td>
<td>6</td>
<td>Suspect bacterial infection at baseline</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Deceased</td>
<td>9</td>
<td>10</td>
<td>NO</td>
<td>NA</td>
<td>Nil</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>Home</td>
<td>10</td>
<td>7</td>
<td>NO</td>
<td>NA</td>
<td>Nil</td>
<td>YES</td>
</tr>
<tr>
<td>12</td>
<td>Home</td>
<td>20</td>
<td>14</td>
<td>NO</td>
<td>NA</td>
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<td>NO</td>
</tr>
<tr>
<td>13</td>
<td>Nursing home</td>
<td>29</td>
<td>47</td>
<td>NO</td>
<td>NA</td>
<td>Suspect bacterial infection at baseline</td>
<td>NA</td>
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<td>14</td>
<td>Nursing home</td>
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<td>NO</td>
</tr>
<tr>
<td>Median</td>
<td>10</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NIV: non-invasive ventilation; NA: not applicable; UTI: urinary tract infection.
ID-19. In this study the standard of care group did not receive glucocorticoids. Methylprednisolone pulses group had a significantly higher percentage of improved patients (94.1% vs. 57.1%; p=0.001) and a significantly lower mortality (5.9% vs. 42.9%; p=0.001). Ruiz-Irastorza et al. (56) conducted a comparative observational study in 242 patients with high inflammatory markers at admission. Sixty-one patients (25%) received methylprednisolone 125–250mg/day pulse-therapy for three days in the second week of disease. This pulse-therapy group had a decreased hazard ratio for death (0.35; 95%CI 0.11–1.06) and composite outcome death or intubation (0.33; 95%CI 0.13–0.84) compared to the non-pulse-therapy group.

The lethality in our case series is high (4/14) compared to the overall lethality described for COVID-19 (57). Nevertheless, this finding should be interpreted with caution due to the fact that in our setting pulse-steroids were mostly used as rescue therapy in patients with moderate to severe respiratory failure or not eligible to other treatments due to other comorbidities. The four deceased patients had important comorbidities, with a Charlson’s score ranging from 4 to 7 and age ranging from 68 to 86 years. Notably, the incidence of steroid-related adverse events seems low in our cohort, but a longer follow-up is needed, particularly for avascular osteonecrosis. The previous evidence from SARS survivors suggests that avascular osteonecrosis is often asymptomatic and can improve over time (53, 54).

With regard of super-infections, only one urinary tract infection after the administration of pulse-therapy was found. New onsets of delirium were not present in our cases, as well as clinically relevant episodes of hyperglycaemia. Adverse events and in particular super-infections might be under reported in the examined literature, but this low prevalence of steroid-related adverse events is consistent with the findings of our case series.

The impact of our findings is limited by the small sample and retrospective nature of our study. However, in our small cohort, methylprednisolone pulse-therapy followed by a rapid corticosteroid reduction and suspension seemed relatively safe. While many clinicians and researchers are focusing on immune-modulatory therapies to control the cytokine storm induced by SARS-CoV2 infection, steroid pulse-therapy can be a viable option because of its fast and profound anti-inflammatory effect acting on multiple pathways. This can be particularly important considered the affordability of these treatment.

### Conclusion

The quality of the evidence on glucocorticoid pulse-therapy defined as ≥500mg/day of methylprednisolone in SARS, MERS and COVID-19 is poor due to the lack of prospective studies. Randomised controlled trials are urgently needed.

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