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Recommended Citation

Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, Miller J, Kenney RM, Alangaden G, and Ramesh MS. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. Clin Infect Dis 2020.

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Early Short-Course Corticosteroids in Hospitalized Patients With COVID-19

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Background. There is no proven antiviral or immunomodulatory therapy for coronavirus disease 2019 (COVID-19). The disease progression associated with the proinflammatory host response prompted us to examine the role of early corticosteroid therapy in patients with moderate to severe COVID-19.

Methods. We conducted a single pretest, single posttest quasi-experiment in a multicenter health system in Michigan from 12 March to 27 March 2020. Adult patients with confirmed moderate to severe COVID were included. A protocol was implemented on 20 March 2020 using early, short-course, methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days. Outcomes of standard of care (SOC) and early corticosteroid groups were evaluated, with a primary composite endpoint of escalation of care from ward to intensive care unit (ICU), new requirement for mechanical ventilation, and mortality. All patients had at least 14 days of follow-up.

Results. We analyzed 213 eligible subjects, 81 (38%) and 132 (62%) in SOC and early corticosteroid groups, respectively. The composite endpoint occurred at a significantly lower rate in the early corticosteroid group (34.9% vs 54.3%, $P = .005$). This treatment effect was observed within each individual component of the composite endpoint. Significant reduction in median hospital length of stay was also observed in the early corticosteroid group (5 vs 8 days, $P < .001$). Multivariate regression analysis demonstrated an independent reduction in the composite endpoint at 14-days controlling for other factors (adjusted odds ratio: 0.41; 95% confidence interval, .22 – .77).

Conclusions. An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes.

Clinical Trials Registration. NCT04374071.

Keywords. Corticosteroids; outcomes; COVID-19; SARS-COV-2; coronavirus.

BACKGROUND

As of 9 April 2020, the United States has over 400 000 cases of confirmed coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Most patients will have mild illness, but older persons and those with comorbidities may develop severe disease necessitating hospitalization and time in the intensive care unit (ICU) [2, 3]. The disease pathophysiology presents in 2 distinct overlapping phases, the initial pathogenic viral response

followed by host inflammatory response with grades of severity associated with distinct clinical findings [4, 5]. The pathological progression in severe COVID-19 includes an excessive and unregulated proinflammatory cytokine storm resulting in immunopathological lung injury, diffuse alveolar damage with the development of acute respiratory distress syndrome (ARDS), and death [6–9].

In the absence of any proven antiviral therapy, the current clinical management is primarily supportive care, supplemental oxygen, and mechanical ventilatory support [1, 10]. Adjunctive therapy with immunomodulatory agents targeting the inflammatory cytokine storm are being evaluated [5, 10]. Studies of corticosteroid therapy for phylogenetically similar coronavirus infections showed no benefit and potential harm [11]. Despite the frequent use in treating patients with COVID-19 in China, the role of corticosteroids is undefined [3, 5, 10–13]. A more recent observational study reported improved outcomes in patients with COVID-associated ARDS that received corticosteroids [14].

Received 23 April 2020; editorial decision 13 May 2020; accepted 15 May 2020; published online May 19, 2020.

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Clinical Infectious Diseases® 2020;XX(X):1–7

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DOI: 10.1093/cid/ciaa601

We postulated that early treatment with a short course of corticosteroids in patients with COVID-19 may attenuate the excessive host respiratory and systemic inflammatory responses. We report the clinical characteristics and early outcomes of patients with COVID-19 receiving short courses of methylprednisolone.

METHODS

Study Population

Consecutive patients hospitalized from 12 March 2020 through 27 March 2020 were eligible for inclusion if they were ≥ 18 years, had confirmed COVID-19 infection, with radiographic evidence of bilateral pulmonary infiltrates, and required oxygen by nasal cannula, high-flow nasal cannula (HFNC), or mechanical ventilation. Patients were excluded if they were transferred from an out-of-system hospital, died within 24 hours of presentation to the emergency department (ED), or were admitted for < 24 hours. A confirmed case of COVID-19 was defined as a patient that had a positive reverse-transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 in a nasopharyngeal sample tested by the Michigan Department of Health and Human Services (MDHHS) or the Henry Ford Health System (HFHS) centralized clinical microbiology laboratory. Beginning 16 March 2020, testing for hospitalized patients was performed by the centralized clinical microbiology laboratory.

Patients were risk stratified by severity of symptoms on presentation to the hospital as mild, moderate, or severe COVID-19. Patients without hypoxia or exertional dyspnea were considered to have mild COVID-19. Patients with mild COVID-19 were treated with symptom relief only and not admitted to the hospital. Patients who presented with infiltrates on chest radiography and required supplemental oxygen by nasal cannula or HFNC were classified as having moderate COVID-19. Patients who had respiratory failure requiring mechanical ventilation were classified as having severe COVID-19.

Study Design

This was a multicenter quasi-experimental study at HFHS, composed of 5 hospitals in southeast and south-central Michigan. The study was approved by the institution's Investigational Review Board (13739) with waiver of consent. Patients in the standard of care (SOC) group from 12 March 2020 through 19 March 2020 were compared to an early corticosteroid group that included patients from 20 March 2020 through 27 March 2020.

Patients in both study groups received standard care, composed of supplemental oxygen, HFNC, invasive ventilation, antibiotic agents, antiviral agents, vasopressor support, and renal-replacement therapy, as determined by the primary team. Patients who progressed to ARDS were managed with SOC [15].

Intervention Standard of Care

Patients with moderate or severe disease who presented to HFHS within the first week of the COVID epidemic in Detroit were

initially treated with supportive care with or without a combination of lopinavir-ritonavir and ribavirin or hydroxychloroquine according an institutional guideline developed by Infectious Diseases Physicians and Pharmacists. The institutional guidelines were developed by consensus, and based on the available literature, experience from Wuhan, China, and other centers around the world affected by COVID-19 before Michigan. Intravenous (IV) remdesivir compassionate use was requested for eligible mechanically ventilated patients. On 17 March 2020 lopinavir-ritonavir with ribavirin was removed from the COVID-19 institutional protocol [16]. Steroids were considered on a case-by-case basis.

Early Corticosteroid Group

As a result of observed poor outcomes, clinical rationale based on immunology, clinical course of COVID-19, and more recently best available evidence, the HFHS early corticosteroid protocol was developed (Supplementary Materials) [14, 15, 17]. We hypothesized that early corticosteroids would combat the inflammatory cascade leading to respiratory failure, ICU escalation of care, and mechanical ventilation. The early corticosteroid protocol was incorporated in the institutional COVID-19 guidelines on 20 March 2020. Patients with confirmed influenza infection were not recommended to receive early corticosteroids. The decision to prescribe hydroxychloroquine and early corticosteroids was at the discretion of the primary medical team.

Moderate COVID-19 was treated with hydroxychloroquine 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2–5. Patients with moderate COVID-19 who required 4 liters or more of oxygen per minute on admission, or who had escalating oxygen requirements from baseline, were recommended to receive IV methylprednisolone 0.5 to 1 mg/kg/day in 2 divided doses for 3 days. Patients who required ICU admission were recommended to receive the above regimen of hydroxychloroquine and IV methylprednisolone 0.5 to 1 mg/kg/day in 2 divided doses for 3–7 days. ICU patients were also evaluated for tocilizumab on a case-by-case basis. Oral switch was performed to prednisone at a ratio of 1 to 1 when determined clinically appropriate by the primary medical team.

Data Collection

Data were ascertained from each institution's electronic medical record and recorded in a standardized electronic case report form. Demographic data, information on clinical symptoms or signs at presentation, and laboratory and radiologic results during admission were collected. All laboratory tests and radiologic assessments, including plain chest radiography and computed tomography of the chest, were performed at the discretion of the treating physician.

Study Definitions

We ascertained coexisting conditions from electronic medical record and physician documentation. The National Early

Warning Score (NEWS) was collected to evaluate baseline illness severity based on vital signs obtained in the ED [18]. Additionally, the quick Sequential Organ Failure Assessment was used to evaluate severity of illness of included patients based on ED vitals and examination [19]. All patients were followed for at least 14 days after initial presentation. Patient data were censored on 9 April 2020.

OUTCOME MEASURES

Primary Endpoint

The primary composite endpoint was escalation to an ICU from a general medical unit, progression to respiratory failure requiring mechanical ventilation after hospital admission, or in-hospital all-cause mortality. Patients directly admitted to the ICU from the emergency room were evaluated for the latter 2 outcomes, and those requiring mechanical ventilation in the emergency room were evaluated for mortality.

Secondary Endpoints

Secondary endpoints included development and severity of ARDS, days to ventilator liberation, shock, acute kidney injury (AKI), and length of hospital stay (LOS). LOS was reported only for patients who were discharged alive within the 14-day minimum follow-up period. ARDS was diagnosed and classified according to the Berlin definition [20]. AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes definition [21].

Statistical Analysis

Continuous variables were reported as median and interquartile range (IQR) and compared using the Mann-Whitney test or *t*-test, as appropriate. Categorical data were reported as number and percentage (no., %) and compared using the χ^2 test or Fisher exact test, as appropriate. No imputation was made for missing data points. The sample size was derived from all eligible consecutive hospitalized patients during the study period. A 2-sided $\alpha < 0.05$ was considered statistically significant. Bivariate and multivariable logistic regression analysis was planned a priori to test the association between the composite endpoint and exposure to the corticosteroid protocol. Covariates in the bivariate analysis with a *P*-value $< .2$ and clinical rationale were included in a multivariable regression model that was restricted to a subject-to-variable ratio of 10:1. To evaluate the implementation timing of the in-house RT-PCR SARS-CoV-2 testing a post hoc sensitivity analysis were conducted on the composite outcome. A nonequivalent dependent variable, receipt of, and time to empiric antibiotic therapy for pneumonia, was utilized to account for potential maturation in the management of COVID-19. Statistical analysis was performed using IBM SPSS version 25 (Chicago, IL) and SAS 9.4 (Cary, NC).

RESULTS

Two-hundred and fifty consecutive patients were evaluated for inclusion. Ten were hospitalized for ≤ 24 hours, 23 did not require oxygen by nasal cannula, HFNC, or mechanical ventilation, and 4 expired within 24 hours of admission (Figure 1). Two-hundred and thirteen patients were included, 81 (38%) in the SOC group and 132 (62%) in the early corticosteroid group. The median age of the SOC group and early corticosteroid group was 64 (IQR: 51.5, 73.5) and 61 (IQR: 51, 72) years, respectively. Black patients comprised 61.7% of the SOC group and 79.5% of the early corticosteroid group ($P = .005$). Of the comorbid conditions evaluated, chronic obstructive pulmonary disease was more frequent in the SOC group compared to the early corticosteroid group (18.5% vs 9.1%; $P = .045$). The presenting COVID-19 symptoms, baseline severity of illness, and other demographics are presented in Table 1. One patient had a concomitant influenza infection in the early corticosteroid group.

Overall, corticosteroids use was 56.8% and 68.2% in the SOC group and early corticosteroid group, respectively ($P = .094$). The early corticosteroid group had a greater proportion of corticosteroids initiated within 48 hours of presentation (12.4% vs 41.7%, $P < .001$), with a median time to initiation of 2 days (IQR: 1–3, range 0–8) as compared to 5 days (IQR: 3–7, range 1–9) in the SOC. The median time to hydroxychloroquine initiation was greater in the SOC group compared to the early corticosteroid group (3 [IQR: 1, 4] vs 1 [IQR: 0, 2] days, $P < .126$). Additional treatment characteristics are described in Table 2.

The primary composite endpoint occurred at a significantly lower rate in the early corticosteroid group compared to the SOC group (34.9% vs 54.3%, $P = .005$). A significant reduction in each of primary composite endpoints was also noted (Table 3). In the sensitivity analysis subgroup, after the implementation of the in-house RT-PCR SARS-CoV-2 testing, 34.9% (46 of 132 patients) and 55% (33 of 60 patients) experienced the primary composite endpoint in the early corticosteroid group and SOC group, respectively ($P = .009$). After adjustment for male sex, NEWS of ≥ 7 , and age ≥ 60 , early corticosteroid initiation was independently associated with a reduction in the composite endpoint at 14 days (adjusted odds ratio: 0.41; 95% confidence interval [CI], (.22 – .77) (Table S2, Supplemental Materials).

The median LOS was significantly reduced from 8 days in the SOC group, to 5 days in the early corticosteroid group ($P < .001$). ARDS occurred in 38.3% and 26.6% in the SOC group and early corticosteroid group, respectively ($P = .04$). Outcomes at 14 days also included 9 (11.1%) of SOC patients remaining admitted as compared to 26 (19.7%) of early corticosteroid patients. Table 3 describes additional outcomes before and after implementation of the early corticosteroid protocol.

Table 1. Baseline Demographics and Clinical Characteristics of Study Patients

Characteristics	Total (n = 213)	SOC (n = 81)	Early CG (n = 132)	P value
Demographics				
Median age (IQR), y	62 (51–62)	64 (51.5–3.5)	61 (51–72)	.400
Male sex, no. (%)	109 (51.2)	41 (50.6)	68 (51.5)	.899
Black race, no. (%)	155 (72.8)	50 (61.7)	105 (79.5)	.004
Median body mass index (IQR) - kg/m ²	32 (27.3–38.7)	30 (25–39)	33.2 (28.9–38.5)	.007
Coexisting conditions, no. (%)				
Asthma	33 (15.5)	16 (19.8)	17 (12.9)	.180
Chronic kidney disease	98 (46)	41 (51.9)	57 (43.5)	.240
Chronic obstructive pulmonary disease	27 (12.7)	15 (18.5)	12 (9.1)	.045
Congestive heart failure	26 (12.2)	10 (12.5)	16 (12.2)	.951
Coronary artery disease	38 (17.8)	18 (22.2)	20 (15.2)	.192
Diabetes	105 (49.3)	37 (45.7)	68 (51.5)	.411
Hypertension	158 (74.2)	62 (76.5)	96 (72.7)	.925
Malignancy	24 (11.3)	11 (13.6)	13 (9.9)	.405
Smoking history	88 (41.3)	40 (49.4)	48 (36.4)	.062
Symptoms				
Cough, no. (%)	158 (74.2)	62 (76.5)	96 (72.7)	.536
Fever, no. (%)	150 (70.4)	57 (70.4)	93 (70.5)	.989
Myalgia, no. (%)	85 (39.9)	32 (39.5)	53 (40.2)	.926
Shortness of breath, no. (%)	148 (69.5)	50 (61.7)	98 (74.2)	.054
Median duration of symptoms (IQR), d	5 (3–7)	5 (2–7)	6 (3–7)	.107
Severity of illness in ED				
Median qSOFA (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	.850
Median NEWS (IQR)	7 (4–10)	7 (4–10)	7 (4–9)	.668
Requiring mechanical ventilation in ED, no. (%)	22 (10.3)	10 (12.3)	12 (9.1)	.448
Direct admission to ICU, no. (%)	26 (12.2)	11 (13.6)	15 (11.4)	.631

Abbreviations: CG, corticosteroid group; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; NEWS, National Early Warning Score; qSOFA, quick Sequential Organ Failure Assessment; SOC, standard of care.

Table 2. Treatments Received by Groups

Treatment	Total (n = 213)	SOC (n = 81)	Early CG (n = 132)	P value
Antimicrobials				
Empiric antibiotic prescribed for pneumonia, no. (%)	163 (76.5)	65 (80.2)	98 (74)	.316
Median time to empiric antibiotics (IQR), d	1 (0–1)	1 (0–1)	0 (0–1)	.631
Median duration of antimicrobials (IQR), d	4 (2–5)	5 (3–5)	3 (2–5)	.009
Hydroxychloroquine use, no. (%)	161 (75.6)	57 (70.4)	104 (78.8)	.167
Median time to hydroxychloroquine initiation (IQR), d	2 (1–3)	3 (1–4)	1 (0–2)	.126
Lopinavir/ritonavir and ribavirin use, no. (%)	10 (4.7)	9 (11.1)	1 (0.76)	.001
Remdesivir use, no. (%)	5 (2.3)	5 (6.2)	0 (0)	.004
Tocilizumab use, no. (%)	14 (6.6)	8 (10.1)	6 (4.5)	.126
Corticosteroid treatment				
Median time to steroid initiation from admission (IQR), d	2 (1–4)	5 (3–7)	2 (1–3)	<.001
Corticosteroids received in first 48 h, no. (%)	65 (30.5)	10 (12.4)	55 (41.7)	<.001
Corticosteroids received at any time, no. (%) ^a	136 (63.8)	46 (56.8)	90 (68.2)	.094
Methylprednisolone use, no. (%)	129 (60.5)	43 (53.1)	86 (64.4)	.688
Median methylprednisolone dose (IQR), mg	40 (40–50)	40 (40–50)	40 (35–50)	.851
Oral prednisone switch, no. (%)	7 (5.4)	5 (11.6)	2 (2.3)	.041
Median duration of corticosteroids (IQR), d ^b	3 (3–3)	3 (3–3)	3 (3–3)	.812

Abbreviations: CG, corticosteroid group; IQR, interquartile range; SOC, standard of care.

^aRefer to [Figure S1](#), supplemental materials for description of timing.

^b29 patients received greater than 3 days; Early corticosteroid group 20 (22.2), 9 SOC (19.5).

Table 3. Outcomes in Standard of Care and Early Corticosteroid Group

Outcomes	SOC (n = 81)	Early CG (n = 132)	Odds Ratio (CI)	P value
Primary outcome				
Primary composite outcome, no. (%)	44 (54.3)	46 (34.9)	.45 (.26–.79)	.005
Death, no. (%)	21 (26.3)	18 (13.6)	.45 (.22–.91)	.024
Respiratory failure requiring mechanical ventilation, no. (%) ^a	26 (36.6)	26 (21.7)	.47 (.25–.92)	.025
Escalation from GMU to ICU, no. (%) ^b	31 (44.3)	32 (27.3)	.47 (.25–.88)	.017
Secondary outcomes				
Overall mechanical ventilation, no. (%)	36 (44.4)	38 (28.8)	.51 (.28–.90)	.020
ARDS, no. (%)	31 (38.3)	33 (26.6)		.040
Mild	3 (3.7)	1 (0.76)		.125
Moderate	8 (9.9)	9 (6.8)		.307
Severe	20 (24.7)	23 (17.4)		.201
Median duration of mechanical ventilation (IQR), d	8 (4–13)	7 (4–9)		.558
Median time to extubation (IQR), d	8 (4–13)	7 (4–9)		.558
Shock, no. (%)	19 (23.5)	17 (12.6)		.069
Acute kidney injury, no. (%)	42 (51.9)	59 (44.7)		.310
Median hospital length of stay (IQR), d	8 (5–14)	5 (3–7)		<.001
Discharged from hospital, no. (%)	51 (62.2)	88 (66.7)		.584
Remain hospitalized, no. (%)	9 (11.1)	26 (19.7)		.102
Remain intubated, no. (%)	7 (8.6)	13 (9.8)		.771

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; CG, corticosteroid group; GMU, general medical unit; ICU, intensive care unit; IQR, interquartile range; SOC, standard of care.

^aA total of 10 and 12 patients were not included in this analysis because they required mechanical ventilation in the emergency department in the SOC and early corticosteroid groups, respectively.

^bA total of 11 and 15 patients were not included in this analysis because they were directly admitted to the ICU in the SOC and early corticosteroid groups, respectively.

DISCUSSION

In this quasi-experimental study, hospitalized patients with moderate to severe COVID-19 that received an early short course of methylprednisolone had a reduced rate of the primary composite endpoint of death, ICU transfer, and mechanical ventilation, with a number needed to treat of 8 to prevent 1 patient transfer for mechanical ventilation. The reduction in ICU transfer and requirement for mechanical ventilation represents a potential intervention to reduce critical care utilization

during the COVID-19 pandemic [22, 23]. The median reduction of hospital LOS by 3 days observed with the use of corticosteroids could positively impact hospital capacity during the COVID-19 surge.

Corticosteroids are not routinely recommended in patients with COVID-19 without an alternate indication or presence of ARDS [11, 15, 24]. Data are conflicting; corticosteroid use in previous viral respiratory illnesses has demonstrated delayed viral clearance and increased mortality [11, 25]. On the

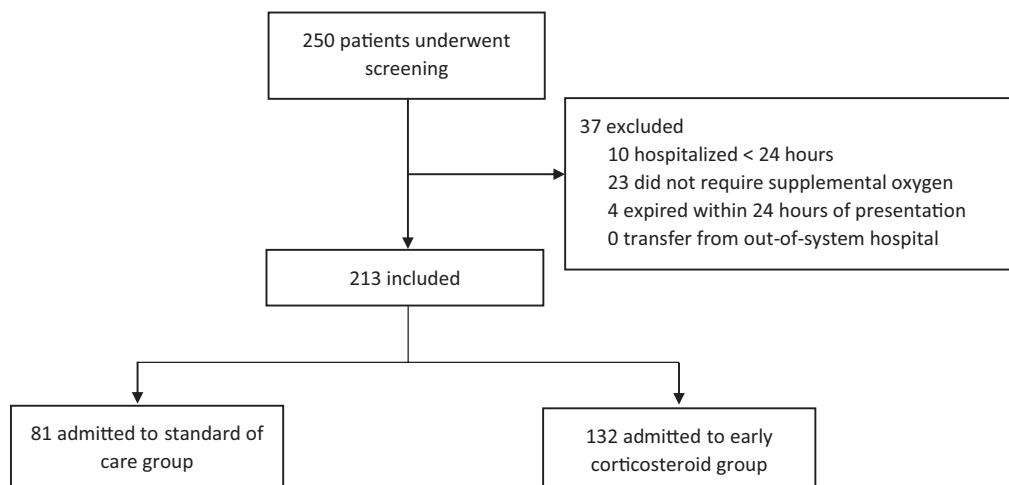


Figure 1. Number of patients screened and included in the trial.

contrary, short-course corticosteroids in some reports are beneficial and safe in critically ill patients with SARS-CoV-2 and were not found to be an independent risk factor of prolonged viral RNA shedding [17, 26, 27]. These discordant findings may be explained by the observational nature of the studies, heterogeneity in patient acuity, inconsistent dosing regimens and duration, and timing of initiation of therapy [10, 17]. Corticosteroids were used in 11–35% of nonsevere and 45–72% of severe COVID-19 cases in China; however, the benefits and risks remain undefined [2, 6, 12–14]. A mortality benefit (hazard ratio, 0.38; 95% CI, .20–.72) with the use of methylprednisolone was reported in 1 retrospective cohort study of COVID-19 patients with ARDS [14].

COVID-19 can progress from mild to severe illness characterized by an initial viral infection phase followed by pulmonary inflammation, and then a hyper-inflammation phase [4, 6, 9]. The pulmonary phase is associated with progressive dyspnea and radiographic findings of pneumonia [4]. Symptom onset to dyspnea and ARDS development occurs between a median of 5–7 days and 8–12 days, respectively [6, 12, 28]. The present study findings support that timing is key. An early course of corticosteroid, specifically methylprednisolone, at the onset of dyspnea, may attenuate progression to the hyper-inflammation phase that requires escalation of care in patients with COVID-19. In this study, 3 days of early corticosteroids were administered at a median 2 days into hospitalization and 8 days from symptom onset. However, the administration of a 3-day course of corticosteroids later in the disease course (median 5 days after hospitalization), as occurred in our SOC group, did not appear to confer the same benefit. Hydroxychloroquine with or without azithromycin, remdesivir, and lopinavir/ritonavir with ribavirin were prescribed at similar frequency between groups. These agents have demonstrated mixed efficacy results for COVID-19 in placebo controlled-trials, with hydroxychloroquine being the most promising at this time [10]. Immunomodulatory agents, such as tocilizumab, were infrequently used in this study.

This study has several limitations. Given the pandemic nature of the disease, a pragmatic quasi-experimental design was used, and there are some differences in the baseline characteristics of the comparator groups. The potential for regression to the mean and maturation is an inherent limitation to all quasi-experiments. On 16 March 2020, rapid on-site RT-PCR testing for SARS-CoV-2 testing was implemented, and some of the SOC group experienced delayed diagnosis and treatment. However, the observed association was unchanged in the sensitivity analysis. A nonequivalent dependent variable, empiric antibiotic therapy for pneumonia, suggested no difference in management of COVID-19. Some of the SOC group received corticosteroids after initiation of the updated COVID-19 institutional treatment protocol. Steroids initiated in this group were started significantly later. Additionally, guideline adherence in the early corticosteroid group was not universal, and

may have been subject to channeling bias. Prone ventilation was attempted in a single SOC group patient and then not utilized again until late March. This may have impacted development of the primary outcome in the subset patients who required mechanical ventilation. Finally, the study has a limited follow-up period of 14 days and may be subject to lead-time bias, similar to other recent reports. As of 9 April 2020, 51 (62.9%) of patients in the SOC cohort and 88 (66.7%) of patients in the early corticosteroid cohort were discharged from the hospital. As a result, outcomes for those patients are not known. Anecdotally, we observed hyperglycemia but no severe corticosteroid related adverse effects (ie, gastrointestinal hemorrhage), and data collection is ongoing.

In conclusion, early use of a short course of methylprednisolone, an inexpensive and readily available agent, in patients with moderate to severe COVID-19 may prevent progression of disease and improve outcomes. These findings are crucial given the ongoing COVID-19 pandemic and ICU bed and mechanical ventilator shortages. Research is urgently needed to further define the role of corticosteroids in patients with COVID-19 at a high risk of clinical deterioration, identified early in the disease course using prognostic markers or clinical prediction tools.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Acknowledgments. Eric Scher, MD,⁴ for his leadership and commitment to education in the field of Academic Internal Medicine. Krishna Modi, MD,⁴ Rebecca Bussa, Kelly Curran, MD,⁴ Abigail Entz, MD,⁴ Hafsa Abdulla, MD,⁴ and Charles Hammond, MD,⁴ for data collection and review. The authors thank the entire front-line staff members of the Henry Ford Health System for dedicated and compassionate patient care during the COVID-19 outbreak.

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Potential conflicts of interest. S. H. received speakers' bureau honoraria from Bayer. I. B. received speakers' bureau honoraria from Gilead, ViiV, and Janssen. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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