Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia

G. Umberto Meduri1,2*, Mei-Chiung Shih3,4, Lisa Bridges1,2, Thomas J. Martin5,6,7, Ali El-Solh8,9, Nitin Seam10, Anne Davis-Karim11, Reba Umberger2, Antonio Anzueto12,13, Peruvemba Sriram14, Charlie Lan15, Marcos I. Restrepo12,13, Juan J. Guardiola16,17, Teresa Buck18, David P. Johnson18, Anthony Suffredini10, W. Andrew Bell19, Julia Lin3, Lan Zhao3, Lauren Uyeda3, Lori Nielsen3 and Grant D. Huang20 on behalf of the ESCAPe Study Group

Abstract

Purpose: Severe community-acquired pneumonia (CAP) requiring intensive care unit admission is associated with significant acute and long-term morbidity and mortality. We hypothesized that downregulation of systemic and pulmonary inflammation with prolonged low-dose methylprednisolone treatment would accelerate pneumonia resolution and improve clinical outcomes.

Methods: This double-blind, randomized, placebo-controlled clinical trial recruited adult patients within 72–96 h of hospital presentation. Patients were randomized in 1:1 ratio; an intravenous 40 mg loading bolus was followed by 40 mg/day through day 7 and progressive tapering during the 20-day treatment course. Randomization was stratified by site and need for mechanical ventilation (MV) at the time of randomization. Outcomes included a primary end-point of 60-day all-cause mortality and secondary endpoints of morbidity and mortality up to 1 year of follow-up.

Results: Between January 2012 and April 2016, 586 patients from 42 Veterans Affairs Medical Centers were randomized, short of the 1420 target sample size because of low recruitment. 584 patients were included in the analysis. There was no significant difference in 60-day mortality between the methylprednisolone and placebo arms (16% vs. 18%; adjusted odds ratio 0.90, 95% CI 0.57–1.40). There were no significant differences in secondary outcomes or complications.

Conclusions: In patients with severe CAP, prolonged low-dose methylprednisolone treatment did not significantly reduce 60-day mortality. Treatment was not associated with increased complications.

Keywords: Community-acquired pneumonia, Glucocorticoids, Intensive care, Methylprednisolone, Randomized clinical trial

*Correspondence: gmeduri@uthsc.edu

1 Pulmonary, Critical Care and Sleep Medicine Services, Memphis VA Medical Center, Memphis, USA

Full author information is available at the end of the article

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Introduction

Pneumonia is the leading cause of community-acquired infection requiring intensive care unit (ICU) admission and a common precipitant of septic shock and acute respiratory distress syndrome (ARDS) [1]. Hospital mortality is higher for patients who are older, bacteremic [2], have more comorbidities [3], meet criteria for healthcare-associated pneumonia (HCAP), require mechanical ventilation (MV) or vasopressor support, or are transferred to the ICU from a medical ward [4]. Most hospital deaths occur after eradication of bacteria from tracheal secretions and the bloodstream [5, 6], implying that adequate antibiotic treatment alone may be insufficient in further improving outcomes. Importantly, patients surviving hospitalization remain at risk for long-term morbidity [7], re-hospitalizations [4], and increased post-discharge mortality at 1 year (21–40%) [4] and up to 5 years [8]. Evidence points to the host’s inability to fully down-regulate systemic inflammation and restore tissue homeostasis as the dominant pathophysiological processes contributing to acute and chronic adverse outcomes in community-acquired pneumonia (CAP) [9, 10].

Glucocorticoids were investigated in multiple randomized trials, with a signal for benefit in patients with severe pneumonia [11, 12]; however, a large confirmatory study was lacking. The Department of Veterans Affairs (VA) Cooperative Study #574 evaluated the efficacy of prolonged methylprednisolone treatment on short- and long-term morbidity and mortality in patients admitted to the ICU with severe CAP. We hypothesized that a 20-day low-dose methylprednisolone treatment would reduce 60-day mortality and improve clinical outcomes. The rationale for a 20-day treatment was to support the resolution phase of the disease [13], incorporate adequate glucocorticoid tapering [14], and to reduce post-hospitalization low-grade systemic inflammation.

Methods

Trial design and oversight

A double-blind, randomized, placebo-controlled trial was conducted at 42 VA Medical Centers from January 1, 2012 to August 31, 2016. Eligible patients were randomly assigned in a 1:1 ratio to receive methylprednisolone or placebo. The trial protocol and the statistical analysis plan are provided in the Supplement Appendix.

The trial was approved by the VA Central Institutional Review Board and conducted in accordance with Good Clinical Practice Guidelines. An independent Data Monitoring Committee monitored patient safety, study conduct, and data. The authors vouch for the accuracy and completeness of the data and statistical analyses and for the fidelity of the trial to the protocol.

Outcomes

The primary outcome was all-cause mortality at 60 days. Secondary outcomes included: (1) During

Take-home message

In this double-blind, randomized, placebo-controlled clinical trial of 584 participants hospitalized with severe community-acquired pneumonia, prolonged methylprednisolone treatment did not significantly reduce 60-day all-cause mortality or improve secondary outcomes during initial hospitalization or up to 1 year of follow-up. The risk for complications was similar to the control group.

Participants

Adult patients presenting with a clinical diagnosis of severe CAP/HCAP were enrolled within 72–96 h (additional 24 h in patients not yet meeting severity criteria) of hospital presentation. Inclusion criteria required the presence of one major or three minor modified American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for severe pneumonia [15] as well as admission to intensive or intermediate care. Eligibility criteria are detailed in the Trial Protocol (Supplement Appendix).

Treatment and other trial procedures

Written informed consent was obtained from each participant or their legally authorized representative if they were unable to provide consent. Participants were randomly assigned in a 1:1 ratio to receive methylprednisolone or placebo using random permuted blocks of sizes 2 and 4, stratified by study site and need for MV at enrollment.

Methylprednisolone or placebo was given in a double-blind fashion. On the day of randomization (day 0), an intravenous loading dose of 40 mg was given, followed by maintenance infusion. The full 20-day treatment course included 40 mg/day on days 1–7, 20 mg/day on days 8–14, 12 mg/day on days 15–17 and 4 mg/day on days 18–20. Study drug was given by continuous infusion during ICU stay and changed to twice per day, via intravenous or enteral administration, after ICU discharge. Participants in both groups received standardized care following consensus recommendations [15, 16].

Participants were assessed daily up to day 8 during the initial ICU stay, at hospital discharge, and on days 28, 60, and 180. The final 1-year follow-up for mortality and re-hospitalizations was performed through review of records. We attempted to assess all participants regardless of treatment continuation. Monitoring for serious adverse events (SAEs) continued until the final follow-up contact. Safety monitoring and reporting procedures are detailed in the Trial Protocol.
hospitalization: post-randomization development of vasopressor-dependent shock or ARDS; number of multiple organ dysfunction syndrome (MODS)-free days to day 8; MV-free days up to days 8 and 28; duration of ICU and hospital stay; potential complications associated with methylprednisolone treatment; and hospital mortality; (2) Post-discharge: cardiovascular complications within 180 days of randomization; quality of life and functional status at days 28, 60, and 180; number and causes of re-hospitalization at VA hospitals within 1 year; SAEs and complications; and all-cause mortality at days 180 and 365. Exploratory outcome included duration of MV. MODS was assessed using the Sequential Organ Failure Assessment score [17]. Health-related quality of life was measured by the Veterans RAND 12 Item Health Survey [18, 19]. Functional status was measured by the Activities of Daily Living Scale and the Instrumental Activities of Daily Living Scale [20, 21]. Outcome definitions are detailed in the protocol.

Statistical analysis
We estimated that 1406 participants randomized 1:1 to the two treatment groups would provide 85% power to detect a 7% absolute reduction in 60-day mortality (21% in the methylprednisolone group vs. 28% in the placebo group). The original plan was to randomize 1420 participants (accounting for 1% attrition in primary outcome) over 5 years (January 2012–December 2016) and conduct two interim analyses at approximately 50% and 75% of the target number of participants to allow early discontinuation for efficacy (based on two-sided boundaries[22]) or futility (based on conditional power). Because of low recruitment, an ad hoc interim futility analysis was conducted on April 8, 2015 based on data as of February 6, 2015. At that time, 431 participants were randomized and the primary outcome was available for 372 participants. A one-sided non-binding futility boundary was calculated [22]. Conditional power was calculated for a range of differences in 60-day mortality (0–10%) and for two different target numbers of patients with 60-day mortality (the original target 1406 and the projected sample size 800 by December 2016). Based on the information, the DMC supported continued recruitment until the end of the planned recruitment period (December 2016). Study enrollment was stopped on April 30, 2016 due to persistent low recruitment; the final number of randomizations was 586. No additional interim analysis was done. Study follow-up ended in August 2016, which allowed collection of primary outcomes for all randomized participants. We report data for 584 participants, because two participants were improperly consented, and their data cannot be used for analyses.

Primary analyses were performed on the intention-to-treat sample (n=584). Sixty-day all-cause mortality was compared by Chi-square test. The difference in percentages of 60-day mortality and the 95% confidence interval (CI) were calculated. Generalized linear mixed effect models were used to adjust for site (as a random effect) and baseline patient characteristics (as fixed effects), including MV status at randomization, age, Acute Physiology and Chronic Health Evaluation (APACHE) III score, bacteremia, use of anti-inflammatory medications, and use of macrolide antibiotics at baseline. Pneumonia Severity Index [23] class and Simplified Acute Physiology Score (SAPS) III score [24] were not included in the model to reduce collinearity of the covariates. Sensitivity analyses were performed to assess robustness of results and included using the per-protocol sample and different imputation methods for 21 participants missing primary outcomes (all due to early study withdrawal). The results from imputations were similar and not shown. Kaplan–Meier estimate of survival probability at day 60 was also calculated. Pre-specified subgroup analyses included MV status at randomization, APACHE III score quartiles, and CAP versus HCAP; post hoc subgroup analyses included severity of CAP, adequacy of initial antibiotic treatment, ARDS at baseline, and time of study treatment initiation (within 48 h vs. > 48 h of hospital presentation). Logistic regression was used to examine subgroups by treatment interactions.

Secondary outcomes were compared using Chi-square test or Fisher’s exact test for categorical outcomes, two-sample t tests or Wilcoxon rank-sum tests for continuous outcomes, and log rank tests and Kaplan–Meier curves for time to death and duration of MV up to day 28. Survival up to 180 days was compared by the restricted mean survival time (RMST) [25].

All p values are two-sided. The p values for secondary and exploratory outcomes were adjusted for multiplicity by the Bonferroni method, separately for in-hospital outcomes and post-discharge outcomes. The widths of the confidence intervals for the treatment differences in secondary and exploratory outcomes were not adjusted for multiplicity. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for analysis. Unless specified otherwise, results are reported as methylprednisolone vs. placebo.

Results
Patients
Of the 3936 patients who were assessed for eligibility, 584 were randomized; 70% were randomized within 48 h of hospital presentation and 94% within 72 h (median time to randomization, 37 h). Two hundred and ninety-seven participants were assigned to the methylprednisolone group and 287 to the placebo group (Fig. 1); 193 (33%)
were receiving MV at the time of randomization. A total of 382 (65%) participants started study treatment within 48 h of hospital presentation and 513 (88%) within 72 h (median time from hospital presentation to study treatment initiation, 40 h). The study flow diagram is shown in Fig. 1, which also provides information on study drug withdrawal and reasons.

The two treatment groups were balanced in demographics and baseline patient characteristics (Table 1). The mean age was 68.8 years, 96% were male, and 83% were White. Patients had an average of four major comorbidities (Table S1). Thirty-four percent of participants met HCAP criteria, 69% had multi-lobar involvement on chest radiograph, 15% had bacteremia, 11% had ARDS at enrollment, and 13% had vasopressor-dependent shock at enrollment. Pathogens potentially responsible for the pneumonia were identified in 250 (43%) of the 577 participants with specimens from the respiratory tract, pleural fluid, blood or urine. The most common pathogens isolated were Staphylococcus aureus (10%), Streptococcus pneumoniae (9%), Pseudomonas aeruginosa (3%), and Escherichia coli (3%). Initial antibiotic treatment was deemed adequate in 96% of the participants based on ATS/IDSA guideline recommendations (Fig. 2).

**Primary outcome**

There was no significant difference in 60-day all-cause mortality (16% vs. 18%; unadjusted absolute risk difference −2%, 95% CI −8 to 5%; unadjusted odds ratio (OR) 0.89, 95% CI 0.58–1.38; p = 0.61) (Table 2). The result was similar when adjusted for site and MV status at randomization (adjusted OR 0.90; 95% CI 0.57–1.40; p = 0.63) and when also adjusted for baseline patient characteristics (adjusted OR, 0.87; 95% CI 0.53–1.42; p = 0.58). Kaplan–Meier estimate of 60-day mortality was 16% (95% CI 12–21%) in the methylprednisolone group and 18% (95% CI 14–23%) in the placebo group. No significant variation was found in the treatment effect across study sites. Results were similar in the per-protocol sample (Table S2 and Table S3). There was no significant between-group difference in the subgroup analyses (Table S4 and Fig. 3).

**Secondary outcomes**

**In-hospital morbidity and mortality**

There were no significant differences between the treatment groups in development of vasopressor-dependent shock, development of ARDS, MV-free days up to days 8 or 28, duration of ICU stay (median 3 vs. 4 days; p = 1.00), duration of hospital stay (median 7 vs. 8 days; p = 1.00), or hospital mortality (12% vs. 10%; p = 1.00) (Table 2). Among the 25 (12 vs. 13) participants who developed new shock or ARDS, 5 (1 vs. 4) stopped study medication to receive open label glucocorticoid treatment. Among participants who required MV at randomization, there was a 3-day reduction in median duration of MV (median 4 vs. 7 days; hazard ratio (HR) 1.44; 95% CI 1.04–1.99; p = 0.21 after Bonferroni correction).

**Post-discharge morbidity and mortality**

There were no significant between-group differences in cardiovascular complications, quality of life, functional status, or re-hospitalizations (Table 2). The most common reasons for re-hospitalization were pneumonia (20%), congestive heart failure (18%), and chronic obstructive pulmonary disease (COPD) (17%).

The two treatment groups had similar 180-day mortality (21% vs. 24%; OR 0.86; 95% CI 0.58–1.29; p = 1.00) and RMST up to day 180 (151 days vs. 149 days; difference 2.5 days; 95% CI −7.7 to 12.6 days; p = 1.00) (Table 2). Kaplan–Meier estimate of mortality by 180 days was 20% (95% CI, 16% to 26%) in the methylprednisolone group and 23% (95% CI 19–29%) in the placebo group. The two groups also had similar 1-year mortality (30% vs. 33%; OR 0.90; 95% CI 0.61–1.27; p = 1.00) and time to death (HR 0.90; 95% CI 0.66–1.22; p = 1.00) (Table 2 and Fig. 2A). Results of secondary outcomes were similar in the per-protocol sample (Table S2) and within the MV (Table S5 and Fig. 2B) and non-MV strata (Table S6 and Fig. 2C). Within each stratum, the two treatment groups had similar baseline characteristics (Table S7 and Table S8).

**Cause of death**

No apparent between-group differences in immediate or underlying cause of death were observed for all deaths, deaths up to day 60, deaths during initial hospitalization, or deaths after discharge from initial hospitalization (Tables S9 and S10).

**Adverse events**

During the 180 days after randomization, 365 SAEs occurred in 167 (56.2%) participants in the methylprednisolone group, and 342 SAEs occurred in 162 (56.4%) participants in the placebo group (Table S11). There were no significant differences between treatment arms in SAEs (Table S11) or complications (Table S12) during 180 days after randomization or in in-hospital or post-discharge complications (data not shown).

**Discussion**

The ESCAPE trial showed that, in participants admitted to the ICU with severe CAP or HCAP, a 20-day treatment with low-dose methylprednisolone did not significantly reduce all-cause 60-day mortality, the primary outcome. We observed a 3-day reduction in median duration of MV in participants who required MV at randomization, although the certainty of this finding may be low given
the small sample size in this subgroup, the imprecision of the estimated difference, and lack of multiplicity correction. No other significant differences were found in morbidity or mortality outcomes or complications during 1 year of follow-up.
Table 1 Baseline characteristics

| Characteristic                                      | Methylprednisolone (n = 297) | Placebo (n = 287) |
|-----------------------------------------------------|-------------------------------|-------------------|
| Age—years                                           | 69 ± 10.8                     | 68.6 ± 11.1       |
| Male sex—no./total no. (%)                          | 289/297 (97)                  | 273/286 (95)      |
| Ethnicity—no./total no. (%)                         |                               |                   |
| Not Spanish, Hispanic or Latino                     | 255/286 (89)                  | 251/280 (90)      |
| Mexican, Mexican American, or Chicano               | 16/286 (6)                    | 12/280 (4)        |
| Puerto Rican                                        | 5/286 (2)                     | 8/280 (3)         |
| Cuban                                               | 0 (0)                         | 1/280 (0)         |
| Other Spanish, Hispanic or Latino                   | 10/286 (3)                    | 8/280 (3)         |
| Race—no./total no. (%)                              |                               |                   |
| White                                               | 245/287 (85)                  | 227/281 (81)      |
| Black/African American                              | 36/287 (13)                   | 48/281 (17)       |
| Other                                               | 15/287 (5)                    | 10/281 (4)        |
| BMI ≥ 30—no./total no. (%)                          | 62/297 (21)                   | 70/285 (25)       |
| Smoking status—no./total no. (%)                    |                               |                   |
| Current smoker                                      | 98/294 (33)                   | 89/284 (31)       |
| Prior smoker (not current smoker)                   | 155/294 (53)                  | 139/284 (49)      |
| Lifetime non-smoker                                 | 41/294 (14)                   | 56/284 (20)       |
| Any major comorbidity—no./total no. (%)            | 290/297 (98)                  | 275/285 (96)      |
| No. of major comorbidities                          | 4 ± 1.8                       | 3.9 ± 1.9         |
| Charlson Comorbidity Index                          | 5.77 ± 2.39                   | 5.65 ± 2.24       |
| ACE27 Overall Comorbidity Score—no./total no. (%)   |                               |                   |
| 0                                                   | 6/297 (2)                     | 8/285 (3)         |
| 1                                                   | 38/297 (13)                   | 33/285 (12)       |
| 2                                                   | 51/297 (17)                   | 59/285 (21)       |
| 3                                                   | 202/297 (68)                  | 185/285 (65)      |
| ACE27 Total Score                                   | 2.51 ± 0.79                   | 2.48 ± 0.81       |
| Karnofsky Performance Score                         | 72.4 ± 22                     | 72.9 ± 22.4       |
| HCAP—no./total no. (%)                              | 112/297 (38)                  | 89/287 (31)       |
| Resided in nursing home or long-term care facility immediately prior to hospital admission | 40/297 (13) | 48/287 (17) |
| Hospitalized in acute care hospital for 2 or more days within past 90 days | 81/297 (27) | 58/287 (20) |
| Received intravenous therapy (antibiotic or chemotherapy) within past 30 days | 42/297 (14) | 31/287 (11) |
| Received home wound care within past 30 days        | 18/297 (6)                    | 13/287 (5)        |
| Received hemodialysis within past 30 days           | 10/297 (3)                    | 8/287 (3)         |
| Admission from the ward—no. (%)                     | 66/297 (22)                   | 57/287 (20)       |
| Time from hospital admission to randomization—days, median (IQ R) | 1.7 (1–2.2) | 1.4 (0.9–2) |
| PSI                                                 | 125.6 ± 37.2                  | 122.3 ± 34.4      |
| PSI class—no. (%)                                   |                               |                   |
| I                                                   | 3/297 (1)                     | 4/285 (1)         |
| II                                                  | 13/297 (4)                    | 13/285 (5)        |
| III                                                 | 41/297 (14)                   | 29/285 (10)       |
| IV                                                  | 121/297 (41)                  | 126/285 (44)      |
| V                                                   | 119/297 (40)                  | 113/285 (40)      |
| PIRO                                                | 2.14 ± 1.12                   | 2.15 ± 1.1        |
| CURB-65                                             | 2.69 ± 1.03                   | 2.59 ± 1.03       |
| Chest Radiograph Score                              | 2.09 ± 1.02                   | 1.94 ± 1.08       |
| Bilateral—no./total no. (%)                         | 189/288 (66)                  | 163/276 (59)      |
| Multilobar—no./total no. (%)                        | 216/297 (73)                  | 188/285 (66)      |
| PaO2/FiO2 (if PaO2 is available)a                   | 181 ± 85                      | 188 ± 90          |
| SpO2/FiO2 (if PaO2 is not available)b               | 283 ± 101                     | 286 ± 98          |
To our knowledge, this is the largest trial investigating the efficacy of adjunct glucocorticoids on patients with severe pneumonia requiring ICU admission and the first randomized controlled trial (RCT) designed to evaluate both short- and long-term outcomes. We review our findings in the context of recent literature. In the last 15 years, 11 published RCTs investigated prolonged glucocorticoid treatment in patients hospitalized with bacterial CAP (n = 1808) [11, 26]; six of the largest RCTs (n = 1506) were part of an individual patient data meta-analysis [27].

We did not find a significant reduction in 60-day mortality or mortality up to 1 year, which is contrary to the observed reduction in 30-day mortality in severe CAP meta-analyses [11, 26]. The timing for glucocorticoid administration in this study may have missed the optimal window for intervention. Our study allowed for randomization up to 72–96 h after hospital admission. While 65% of study participants initiated study treatment within 48 h of hospital presentation and 88% within 72 h, the inherent delay in the initiation of anti-inflammatory therapy occurred during the initial peaks of inflammatory mediators in response to invasive microbial pathogens [28] and may have attenuated potential benefits [29]. Second, the methylprednisolone dose of 40 mg/day may be inadequate to achieve the level of glucocorticoid receptor saturation necessary for optimal anti-inflammatory response; a higher dose was found effective in ARDS (most attributed to pneumonia) [30]. Third, compared to the prior largest RCT on severe CAP [31], our patient population was sicker, as evidenced by oxygenation indices, need for MV, and a greater burden of comorbidities associated with glucocorticoid resistance such as chronic pulmonary and cardiovascular diseases [32]. Fourth, the observed mortality in the control group was substantially lower than what was used for the power calculation. Fifth, the broad range of severity across our study cohort

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Table 1 (continued)

| Characteristic                                              | Methylprednisolone (n = 297) | Placebo (n = 287) |
|-------------------------------------------------------------|-------------------------------|-------------------|
| ALI-ARDS at randomization—no./total no. (%)                | 26/297 (9)                   | 39/285 (14)       |
| Bacteremia—no./total no. (%)                               | 49/282 (17)                  | 32/275 (12)       |
| White Blood Cell Count (×10⁶ cells/mL)                     | 15.25 ± 12.44                | 14.55 ± 7.23      |
| APACHE III Score                                           | 54.3 ± 29.4                  | 53.4 ± 28.7       |
| SAPS III Score                                              | 59.4 ± 10.7                  | 58.5 ± 9.9        |
| SOFA Score                                                  | 6.68 ± 3                     | 6.29 ± 2.85       |
| Lactate level (mmol/L)c                                    | 1.84 ± 1.25                  | 1.82 ± 1.81       |
| MV at study entry—no./total no. (%)                        | 97/297 (33)                  | 96/287 (33)       |
| Vasopressor dependent Shock at or prior to study entry—no./total no. (%) | 44/296 (15)                  | 32/285 (11)       |
| Use of anti-inflammatory medications at baseline—no./total no. (%) | 241/297 (81)                 | 221/286 (77)      |
| Use of macrolide antibiotics at baseline—no./total no. (%) | 64/297 (22)                  | 52/286 (18)       |
| Antibiotic treatment in the participants who were not admitted from other hospital—no./total no. (%) | 34/278 (12)                  | 34/271 (13)       |
| Did not receive initial antibiotics                         |                               |                   |
| Received initial antibiotics within 6 h of hospital admission | 232/278 (83)                 | 222/271 (82)      |
| Received initial antibiotics beyond 6 h of hospital admission | 11/278 (4)                   | 9/271 (3)         |
| Unknown                                                     | 1/278 (0)                    | 6/271 (2)         |
| Adequate initial antibiotic treatment based on guidelines—no./total no. (%) | 286/293 (98)                 | 265/278 (95)      |
| Tested for Influenza—no./total no. (%)                     | 182/294 (62)                 | 173/277 (62)      |
| Tested positive for influenza in participants who were tested for influenza—no./total no. (%) | 14/144 (10)                  | 11/131 (8)        |
| Tested positive for both influenza and bacteria—no./total no. (%) | 7/297 (2)                    | 6/287 (2)         |

BMI: body mass index; ACE: adult comorbidity evaluation; PSI: pneumonia severity illness; HCAP: health-care-associated pneumonia; PIRO: predisposition, insult, response, and organ dysfunction; CURB-65: confusion, uremia, respiratory rate, BP, age ≥ 65 years; ALI-ARDS: acute lung injury-acute respiratory distress syndrome; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; MV: mechanical ventilation

* 379 participants had a PaO₂/FiO₂ measurement (201 in the methylprednisolone group, 178 in the placebo group)

* 167 participants had an SpO₂/FiO₂ measurement (79 in the methylprednisolone group, 88 in the placebo group)

* 514 participants had a Lactate Level measurement (261 in the methylprednisolone group, 253 in the placebo group)

* 240 (41%) participants used aspirin at baseline (122 in the methylprednisolone group, 118 in the placebo group); and 58 (10%) participants used systemic corticosteroids (31 in methylprednisolone, 27 in placebo)

* Excludes one participant with time to initial antibiotic treatment from hospital admission longer than 700 h. This value was mostly likely due to a data entry error

* Excludes participants who did not receive antibiotics within 6 h of hospital admission
Fig. 2  Kaplan–Meier estimate of survival. Kaplan–Meier estimates of survival are shown in the overall population (A), in patients who were receiving mechanical ventilation at randomization (Patients on MV, B), and in those not receiving mechanical ventilation at randomization (Patients not on MV, C). The inset in each panel shows the same data on an enlarged y axis and up to day 60.
likely represented different pathophysiologic processes of which corticosteroids possibly have a heterogeneous effect.

For secondary and exploratory outcomes, the 1-day reduction in median hospitalization duration (95% CI −2.3 to 0.3 days) was similar to that reported in meta-analysis [27] and mainly driven by a 2.6-day reduction in the MV stratum (95% CI −6.2 to 1.1 days). Contrary to prior investigations, we did not observe significant reduction in progression to shock or ARDS [26], increased risk for re-hospitalization [27], or lower myocardial infarction incidence [33].

The longer duration of methylprednisolone treatment in our trial was not associated with an increased risk of SAEs or complications within 180 days after randomization. These findings are consistent with those of updated meta-analyses of ICU patients with pneumonia [26], septic shock [34], and ARDS [30], underscoring the safety of prolonged glucocorticoid treatment in this population.

Response to glucocorticoid treatment may be affected by the severity of dysregulated systemic inflammation [31, 35, 36]. In a RCT in patients with severe CAP and C-reactive protein (CRP) levels > 150 mg/L, methylprednisolone was found to reduce treatment failure [31]. In a retrospective cohort study in patients with severe CAP admitted to ICU and receiving glucocorticoid treatment, the subgroup with CRP levels > 150 mg/L had faster recovery of hypoxemia and increased ICU- and hospital-free days [35]. These findings suggest that biomarker markers may help identify patients most likely to benefit from glucocorticoid treatment. The blood samples collected in ESCAPE will allow examination of the relationship between clinical outcomes and markers of systemic inflammation over time, which may provide the groundwork for development of personalized glucocorticoid treatment strategies [30].

Evidence of glucocorticoid benefits in severe pneumonia due to coronavirus disease 2019 (COVID-19) [37, 38] and ARDS [39] has generated greater interest in this field of research. The safety of prolonged methylprednisolone treatment has been confirmed [11, 26, 27]. However, notable treatment heterogeneity in published protocols [30], such as the specific glucocorticoid, timing of initiation, dosage, duration, mode of administration, and tapering strategy, underscore the need for a more uniform approach. Further studies are required to clarify how these treatment components impact clinical outcomes and host responses. During the pandemic, variability in response to glucocorticoid treatment was observed, leading clinicians to adjust dosage and duration based on markers of inflammation.
| Outcome | Methylprednisolone \((n = 297)\) | Placebo \((n = 287)\) | Difference\(^a\) (95% CI) | \(p\) value\(^b\) |
|---------|---------------------------------|-----------------|------------------|----------------|
| **Primary outcome** |                                |                 |                  |                |
| Died on or prior to study day 60—no./total no. (%) | 47/286 (16)      | 50/277 (18)     | 0.89 (0.58, 1.38)\(^c\) | 0.61      |
| **Secondary outcomes** |                                |                 |                  |                |
| In-hospital morbidity and mortality |                                |                 |                  |                |
| Vasopressor dependent shock during initial hospital stay among those who did not have vasopressor-dependent shock at randomization—no./total no. (%) | 13/274 (5)       | 12/271 (4)      | 1.08 (0.48, 2.4)\(^d\) | 1.00      |
| ALI-ARDS during initial hospital stay among those who did not have ALI-ARDS at randomization—no./total no. (%) | 10/265 (4)       | 8/241 (3)       | 1.14 (0.44, 2.94)\(^d\) | 1.00      |
| MODS-free days in study days 1–8—median (IQR) and no./total no. (%) | 0 (0–0)          | 0 (0–0)         | NE               | 0.38      |
| 0       | 249/288 (86)                     | 252/275 (92)    |                  |                |
| 1       | 5/288 (2)                       | 10/275 (4)      |                  |                |
| 2       | 4/288 (1)                       | 4/275 (1)       |                  |                |
| 3       | 4/288 (1)                       | 2/275 (1)       |                  |                |
| 4       | 3/288 (1)                       | 2/275 (1)       |                  |                |
| 5       | 3/288 (1)                       | 0/275 (0)       |                  |                |
| 6       | 0/288 (0)                       | 1/275 (0)       |                  |                |
| 7       | 12/288 (4)                      | 2/275 (1)       |                  |                |
| 8       | 8/288 (3)                       | 2/275 (1)       |                  |                |
| MV-free days in study days 1–8—median (IQR) | 8 (4–8)          | 8 (3–8)         | 0 (−0.4, 0.4)   | 1.00      |
| MV-free days in study days 1–28\(^f\)—median (IQR) | 28 (23–28)       | 28 (21–28)      | 0 (−0.6, 0.6)   | 1.00      |
| MV-free days in study days 1–8 in the MV stratum—median (IQR) | 4 (0–7)          | 1 (0–6)         | 3 (1.1, 4.9)    | 0.66      |
| MV-free days in study days 1–28 in the MV stratum\(^f\)—median (IQR) | 23 (13–27)       | 21 (0–26)       | 2 (−0.8, 4.8)   | 1.00      |
| Duration of initial ICU stay (from day 0)\(^f\)—median (IQR) | 3 (2–7)          | 4 (2–7)         | −1 (−1.7, −0.3) | 1.00      |
| Duration of total ICU stay up to study day 28 (from day 0)\(^f\)—median (IQR) | 3 (2–8)          | 4 (2–8)         | −1 (−1.7, −0.3) | 1.00      |
| Duration of initial hospital stay (from day 0)\(^f\)—median (IQR) | 7 (4–12)         | 8 (4–15)        | −1 (−2.3, 0.3)  | 1.00      |
| Hospital Mortality—no./total no. (%) | 34/291 (12)       | 28/281 (10)     | 1.2 (0.7, 2.03)  | 1.00      |
| Post-discharge morbidity and mortality |                                |                 |                  |                |
| Cardiovascular complications\(^h\)—no./total no. (%) |                                |                 |                  |                |
| Up to day 28 | 11/251 (4)                     | 12/234 (5)      | 0.85 (0.37–1.96) | 1.00      |
| Up to day 60 | 18/257 (7)                     | 17/250 (7)      | 1.03 (0.52–2.05) | 1.00      |
| Up to day 180 | 31/257 (12)                    | 30/253 (12)     | 1.02 (0.66–1.74) | 1.00      |
| VR-12 Physical Component Score\(^i\) |                                |                 |                  |                |
| Day 28     | 37.5 ± 14                      | 37.2 ± 13.8     | 0.2 (−2.6, 3)    | 1.00      |
| Day 60     | 38.8 ± 15.3                    | 40.3 ± 14.5     | −1.5 (−4.5, 1.5) | 1.00      |
| Day 180    | 41.2 ± 14.9                    | 40.8 ± 15.7     | 0.4 (−3.3, 3.8)  | 1.00      |
| VR-12 Mental Component Score\(^i\) |                                |                 |                  |                |
| Day 28     | 32.7 ± 9.6                     | 33.9 ± 9.3      | −1.2 (−3.2, 0.7) | 1.00      |
| Day 60     | 32.4 ± 8.9                     | 32.9 ± 9       | 0.4 (−1.4, 2.2)  | 1.00      |
| Day 180    | 31.5 ± 8.2                     | 32.8 ± 9.2      | −1.3 (−3.2, 0.6) | 1.00      |
| Katz ADL\(^l\) |                                |                 |                  |                |
| Day 28     | 4.99 ± 1.84                    | 4.74 ± 2.07     | 0.25 (−0.14, 0.64) | 1.00      |
| Day 60     | 5.11 ± 1.71                    | 5.03 ± 1.81     | 0.08 (−0.27, 0.43) | 1.00      |
| Day 180    | 5.12 ± 1.66                    | 5.02 ± 1.85     | 0.1 (−0.29, 0.48) | 1.00      |
| Lawton ADL\(^l\) |                                |                 |                  |                |
| Day 28     | 5.39 ± 2.61                    | 5.3 ± 2.72      | 0.09 (−0.45, 0.62) | 1.00      |
| Day 60     | 5.42 ± 2.62                    | 5.71 ± 2.63     | −0.29 (−0.82, 0.24) | 1.00      |
| Day 180    | 5.77 ± 2.57                    | 5.96 ± 2.6     | −0.19 (−0.76, 0.38) | 1.00      |
| Any re-hospitalization within 12 months\(^l\)—no./total no. (%) | 135/253 (53)    | 120/250 (48)    | 1.24 (0.87, 1.76)\(^l\) | 1.00      |
and oxygenation. This has called attention to an under-appreciated aspect of glucocorticoid treatment, the great interindividual variability in (i) achieved blood drug levels [40] and (ii) intracellular glucocorticoids receptor sensitivity [41], areas in need of research [30].

This trial has several limitations. First, enrollment was stopped before reaching the target sample size 1420 because of low recruitment. The main contributing factor to low recruitment was that the proportion of the patient population meeting study eligibility criteria was lower than anticipated (26% versus anticipated 70%), even though the consent rate for eligible patients was higher than anticipated (57% versus anticipated 30%). Another contributing factor was 2 years of relatively low influenza activity during the recruitment period. Second, the certainty of our overall study findings may be limited given that the sample size was lower than target and the analyses may be underpowered. Third, delayed initiation of anti-inflammatory therapy may have attenuated the differences between the treatment groups [29]. Fourth, the VA population is predominantly older, male, and with multiple comorbidities compared to the general population [27]; therefore, the trial’s results may not be generalizable to non-Veterans. Fifth, the high proportion

### Table 2 (continued)

| Outcome | Methylprednisolone (n = 287) | Placebo (n = 287) | Differencea (95% CI) | p valueb |
|---------|-----------------------------|------------------|---------------------|---------|
| Number of re-hospitalizations within 12 months k—median (IQR) | 1 (1–3) | 2 (1–3) | −1 (−1.4, −0.6) | 1.00 |
| Died by study day 180—no./total no. (%) | 59/279 (21) | 65/274 (24) | 0.86 (0.58, 1.29)c | 1.00 |
| Restricted mean survival time up to day 180—RMST (SE) | 151.5 (3.6) | 149 (3.7) | 2.5 (−7.7, 12.6)d | 1.00 |
| Died by 1 year—no./total no. (%) | 79/260 (30) | 84/253 (33) | 0.88 (0.61, 1.27)e | 1.00 |
| Time to death (days)—no./total no. (%) | 79/297 (27) | 84/287 (29) | 0.9 (0.66, 1.22)f | 1.00 |

### Exploratory outcome

| Duration of MV up to day 28 in the participants who were on MV at randomization—median (IQR) | 4 (1–9) | 7 (2–27) | 1.4 (1, 2) | 0.21 |

**Note:**
- ALI-ARDS: acute lung injury—acute respiratory distress syndrome; MODS: multiple organ dysfunction syndrome; IQR: inter quartile range; VR-12 Veterans RAND-12; ADL: Activities of Daily Living; IADL: instrumental activities of daily living; RMST: Restricted mean survival time.
- The p values for secondary and exploratory outcomes are adjusted for multiplicity by Bonferroni correction (for 12 in-hospital outcomes and 21 post-discharge outcomes). The widths of the confidence intervals for the treatment differences in secondary and exploratory outcomes have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects.
- The adjusted odds ratio for 60-day mortality is 0.90 (95% CI 0.57–1.40; p = 0.63) when adjusted for site and mechanical ventilation status at randomization, and is 0.87 (95% CI 0.53–1.42; p = 0.58) when adjusted for site, mechanical ventilation status at randomization, age, APACHE III score,CCI, bacteremia, use of anti-inflammatory medications at baseline, and use of macrolide at baseline. The unadjusted absolute risk difference in the 60-day mortality is −2% (95% CI −8 to 5%)
- The unadjusted absolute risk difference is 0% (95% CI −3 to 4%) for vasopressor-dependent shock, and 0% (95% CI −3 to 4%) for ALI-ARDS.
- MV-free days from days 1 to 28 was calculated in 558 participants (287 in the methylprednisolone group and 271 in the placebo group). In the MV stratum, MV-free days from days 1 to 28 was calculated in 181 participants (92 in the methylprednisolone group, 89 in the placebo group).
- The number of participants for whom the outcome was calculated in the methylprednisolone and placebo groups was, respectively, duration of initial ICU stay: 295 and 281; duration of total ICU stay up to day 28: 291 and 280; duration of initial hospital stay: 291 and 281.
- The unadjusted methylprednisolone versus placebo absolute risk difference is 2% (95% CI −3 to 7%) for hospital mortality, 5% (95% CI −3 to 14%) for re-hospitalization within 12 months, −3% (95% CI −10 to 4%) for 180-day mortality, −3% (95% CI −11 to 5%) for 1-year mortality, and −3% (95% CI −10 to 5%) for mortality over the study period.
- Cardiovascular complications included acute myocardial infarction, serious arrhythmias, new congestive heart failure or acute worsening of long-term congestive heart failure, and cardio-respiratory arrest.
- The number of participants for whom the VR-12 Physical Component Score (PCS) and Mental Component Score (MCS) was calculated at day 28, 60, and 180 was: 197, 201, and 166 in the methylprednisolone group and 184, 177, and 148 in the placebo group. The number of participants for whom the Katz Activities of Daily Living (ADL) score was calculated at day 28, 60, and 180 was: 203, 203, and 172 in the methylprednisolone group and 187, 180, and 150 in the placebo group. The number of participants for whom the Lawton Instrumental Activities of Daily Living (IADL) score was calculated at day 28, 60, and 180 was: 202, 201, and 169 in the methylprednisolone group and 187, 180, and 149 in the placebo group.
- Among the 510 participants (257 in methylprednisolone group, 253 in placebo group) who were discharged alive from initial hospitalization. Seven of the 510 participants had missing re-hospitalization data (4 in methylprednisolone group, 3 in placebo group) and were excluded from analysis.
- Among the 255 patients (135 in methylprednisolone group, 120 in placebo group) who had at least one re-hospitalization within 12 months.
- The estimated difference in RMST up to study day 180, adjusted for MV status at randomization in an RMST regression using pseudovalue method, is 2.3 (95% CI −7.8 to 12.4), and p value adjusted for multiplicity = 1.00.
- Participants who died on MV on or prior to day 28 were censored on day 29. 185 participants were included in this analysis (91 in the methylprednisolone group and 94 in the placebo group).
of patients excluded due to physician opinion of not being a viable candidate might indicate a potential risk of selection bias. Sixth, this study excluded patients with recent or concurrent use of glucocorticoids; thus, it cannot determine if patients with severe CAP who require a short course of glucocorticoids for co-morbid diseases (such as COPD) would benefit from prolonged glucocorticoid treatment.

**Conclusion**

In patients with severe CAP, prolonged low-dose methylprednisolone treatment did not significantly reduce 60-day mortality. The risk for complications was similar to the control group.

**Data sharing statement**

See Supplement Appendix.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06684-3.

**Author details**

1 Pulmonary, Critical Care and Sleep Medicine Services, Memphis VA Medical Center, Memphis, USA. 2 University of Tennessee Health Science Center, Memphis, USA. 3 VA Cooperative Studies Program Coordinating Center, Palo Alto, USA. 4 Department of Biomedical Data Sciences, Stanford University, Stanford, USA. 5 Salem VA Health Care System, Salem, USA. 6 Virginia Tech Carilion School of Medicine, Roanoke, USA. 7 Edward Via Virginia College of Osteopathic Medicine, Blacksburg, USA. 8 VA Western New York Health Care System, Buffalo, USA. 9 University at Buffalo, Buffalo, USA. 10 National Institutes of Health Clinical Center, Bethesda, USA. 11 VA Cooperative Studies Program Pharmacy Coordinating Center, Albuquerque, USA. 12 South Texas Veterans Health San Antonio, San Antonio, USA. 13 University of Texas Health Science Center, Houston, USA. 14 Malcom Randall VA Medical Center, Gainesville, USA. 15 Michael E DeBakey VA Medical Center, Houston, USA. 16 Robley Rex VA Medical Center, Louisville, USA. 17 University of Louisville, Louisville, USA. 18 Bay Pines VA Healthcare Center, Bay Pines, USA. 19 Renown Health, Reno, NV, USA. 20 Office of Research and Development, Department of Veterans Affairs, Baltimore, USA.

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ESCAPE study group members: Khalid Bashir, Octavian Ioachimescu, Theresa Buck, David Johnson, Ali El Solh, Michael Frye, Ralph Panos, Mohammad Shatat, Enoch Gray, Brian Smith, Myron Kung, James Cутrell, Roger Bedimo, Peruvemba Siriam, Charlie Lan, Padmasri Rastogi, John Callaghan, Chadi Hage, Mark Plautz, Takako Schaninger, Richard Greenberg, Lennard Specht, Catherine Sassoon, Jian Guardiola, Julio Ramirez, Muthiah P Muthiah, Roland Schein, Andrea Antonesu-Turcu, Kathryn Rice, Houssein Youness, Lee Morrow, Ware Kuscher, Lilibeth Pineda, Richard Allen Robbins, Sharon Cambi, Matthew Jankowich, Waseem Ahmad, Thomas Martin, Mitchell Horowitz, John Nord, Mark Elstad, Marcos I. Restrepo, Antonio Anzueto, Timothy Bigby, William Rodriguez-Cintron, Vincent Fan, Pratibha Kaul, Michael Habib, Nitin Seem, Guy Soo Hoo.

Veterans affairs medical centers participating in the ESCAPE trial: Participating VAMCs in alphabetical order (ESCAPE site personnel in parenthesis): Asheville, (Khalid Bashir, Whitney Sprinkle, Webster Bazemore, Sujatha Goli, John Luke, Valerie Allen); Atlanta, (Octavian Ioachimescu, Tiffany Elliott, Amy Anderson, Joanne Allam, Ashish Mehta, Patricia Noren, Vidisha Tanakonda); Bay Pines, (Theresa Buck, David Johnson, Caitlin Butler, James Blankenship, Patricia Ellis, Minha Siddiqui, Lynn Anderson); Buffalo, (Ali El-Solh, Lynne Fdrych, Karin Pro沃st, Rachel LaPorta, Philippe Jaoude, Leah Vermont); Charleston, (Michael Frye, Leslie Harrell); Cincinnati, (Michael Frye, Leslie Harrel); Indianapolis, (Ralph Panos, Laura Lach, Dennis McGraw, Nishant Gupta, William Eschenbacher); Cleveland, (Mohammad Shatat, Kimberley Byrne, Frank Jacono, Puja Van Epps); Columbia, (Enoch Gray, Brian Smith, Myron Kung, Joanna Snead, Justin Reynolds, Mohammed Wallam, Shilpa Patel, Stuart Smith, Kathryn Mason, Heather Roth, Rebecca Warnier, Dallas, (James Cutrell, Roger Bedimo, John Battaile, Teagan Lampkin, Joyce Gormley, David Albright, Cyenthia Willis); Gainesville, (Peruvemba Siriam, Omera Herring, Daniel Urbine, James Wynne, Ramanjeet Singh, Alice Boyette, Rose Kizza, Eloise Harman, Michelle Ginsburg); Houston, (Charlie Lan, Sarah Perusich, Daniel Musher, Farrah Kherad-
mand, Lavannya Pandit, Roberto Casal, Rolando Rumbaut, Amir Sharaefkhaneh, Sunnyakanta Velamuri, Pamela Smithwick, Sheryllyn Pillack, Nazanin Zarnikar, Emily Broussard, Cynthia Boudreaux; Indianapolis, (John Callaghan, Sharon Henson, Casey Stahlheber, Vu Patel, Aliya Noor); Kansas City, (Mark Plautz, Cheryl Perkins, Trenton Nauser, Justine Unruh); Lexington, (Takako Schaninger, Edward Hirshowitz, Hannah Ferrell, Sabrina Broden); Loma Linda, (Lennard Specht, Laura Weaver-Carahan, James Anholm, Hemed Parekh, Nagamani Dandamuri, Kathleen Ellstrom, Jamie Portillo, Sara Rubio); Long Beach, (Cath- erine Sasoun, Romana Helal, Yih‑Xing Chi, Farhad Mazdizinian, Aliya Asghar, David Stansbury, Gelincik Orcaklar, Lei Zhu); Louisville, (Juan Guardiola, Bellica Graf, Rafael Perez, Bogdan Moldoveanu, Julio Ramirez, Jesse Roman, Umar Guahar, Angela Klein, Jiness Mehta, Ginny Scipriortino); Memphis, (Muthiah P. 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Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Felipe Fernandez, Pamela Foltz, Tim Antonio, (Marcos I. Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Felipe Fernandez, Pamela Foltz, Tim Antonio, (Marcos I. Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Felipe Fernandez, Pamela Foltz, Tim Antonio, (Marcos I. Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Felipe Fernandez, Pamela Foltz, Tim Antonio, (Marcos I. Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Felipe Fernandez, Pamela Foltz, Tim Antonio, (Marcos I. Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Felipe Fernandez, Pamela Foltz, Tim Antonio, (Marcos I. 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Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Felipe Fernandez, Pamela Foltz, Tim Antonio, (Marcos I. Restrepo, Luis Reyes, Antonio Anzueto, Alejandro Arango, Sandra Adams, Anisha Arora, Karla Diaz, Filip...
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