

Hydrocortisone Infusion for Severe Community-acquired Pneumonia

A Preliminary Randomized Study

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We hypothesize that hydrocortisone infusion in severe community-acquired pneumonia attenuates systemic inflammation and leads to earlier resolution of pneumonia and a reduction in sepsis-related complications. In a multicenter trial, patients admitted to the Intensive Care Unit (ICU) with severe community-acquired pneumonia received protocol-guided antibiotic treatment and were randomly assigned to hydrocortisone infusion or placebo. Hydrocortisone was given as an intravenous 200-mg bolus followed by infusion at a rate of 10 mg/hour for 7 days. Primary end-points of the study were improvement in $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$ ($\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}} > 300$ or ≥ 100 increase from study entry) and multiple organ dysfunction syndrome (MODS) score by Study Day 8 and reduction in delayed septic shock. Forty-six patients entered the study. At study entry, the hydrocortisone group had lower $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$, and higher chest radiograph score and C-reactive protein level. By Study Day 8, treated patients had, compared with control subjects, a significant improvement in $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$ ($p = 0.002$) and chest radiograph score ($p < 0.0001$), and a significant reduction in C-reactive protein levels ($p = 0.01$), MODS score ($p = 0.003$), and delayed septic shock ($p = 0.001$). Hydrocortisone treatment was associated with a significant reduction in length of hospital stay ($p = 0.03$) and mortality ($p = 0.009$).

Keywords: community-acquired pneumonia; C-reactive protein; hydrocortisone; respiratory failure; severe sepsis

Pneumonia is the leading cause of community-acquired infection requiring intensive care unit (ICU) admission (1). Despite advances in antimicrobial therapy and supportive measures, mortality for patients with severe community-acquired pneumonia admitted to the ICU remains high—22 to 54% (2). Between 58 and 87% of patients with severe community-acquired pneumonia admitted to the ICU develop respiratory failure and require mechanical ventilation, a factor associated with a higher mortality (2). Irrespective of severity of initial presentation, the development of sepsis-related complications (delayed septic shock, adult respiratory distress syndrome [ARDS], and extrapulmonary organ dysfunction) during ICU stay is associated with a significantly higher ICU mortality (57–100%) (3).

Several studies have shown increased pulmonary and circulating inflammatory cytokine levels in patients with severe community-acquired pneumonia (4–7). Among patients admitted to the

ICU, higher circulating inflammatory cytokine levels correlated with the presence of bilateral pneumonia (6), bacteremia (7), need for mechanical ventilation (7), and higher Acute Physiology and Chronic Health Evaluation (APACHE) II and multiple organ dysfunction syndrome (MODS) scores (4, 6). Among patients with severe community-acquired pneumonia, nonsurvivors, unlike survivors, exhibit persistent elevation of plasma interleukin (IL)-6 levels over time (7). Taken as a whole, the findings of these studies (4–7) indicate that, similar to patients with ARDS (8), degree and duration of the systemic inflammation have a strong effect on final outcome in patients with severe community-acquired pneumonia.

Glucocorticoids, the most important natural inhibitors of inflammation, are not always effective in suppressing life-threatening systemic inflammation. The presence of systemic inflammation-induced tissue resistance to glucocorticoids and/or inadequate adrenal output might explain why older clinical trials found no efficacy with a time-limited course of massive doses of glucocorticoids (9, 10), while recent randomized studies have shown efficacy and safety with prolonged glucocorticoid treatment in low to moderate doses in patients with catecholamine-dependent septic shock (11–16), severe pneumocystis pneumonia (12), and unresolving ARDS (13). In these studies, patients randomized to prolonged glucocorticoid treatment, in contrast to control subjects, had a significant reduction in circulating inflammatory cytokine levels over time (14–16). Little information is presently available on the effect of prolonged glucocorticoid administration in patients with severe community-acquired pneumonia presenting without septic shock. In a recent retrospective study, Monton and coworkers (17) reported that, among patients with severe community-acquired pneumonia requiring mechanical ventilation, those who received methylprednisolone for 9 ± 7 days (most for bronchodilation) had an attenuated systemic and pulmonary inflammatory response and trended toward lower mortality (36 versus 67%; $p = 0.37$).

We hypothesize that hydrocortisone administration initiated early in the course of severe community-acquired pneumonia attenuates pulmonary and systemic inflammation and leads to earlier resolution of pneumonia and a reduction in sepsis-related complications and mortality. For these reasons, we evaluated the efficacy and safety of prolonged hydrocortisone infusion in a prospective, randomized, double blind, placebo-controlled trial of patients with severe community-acquired pneumonia admitted to the ICU. Some of the results of this study have been previously reported in the form of an abstract (18).

METHODS

Patients

From July 2000 through March 2003, 46 eligible patients were enrolled in this randomized, double-blind, placebo-controlled trial, which was conducted at six hospitals in Italy. Patients were admitted to the Intensive

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Care Unit or Respiratory Intermediate Unit (RICU) of the following hospitals: Ospedale di Trieste, Ospedale Gradenigo (Torino), Ospedale Molinette (Torino), Arcispedale S. Anna (Ferrara), Ospedale di Crema, or Ospedale di Paderno Dugnano (Milano). A regional institutional review board approved the protocol, and written informed consent was obtained from all participants or their authorized representatives. The clinical coordinator was available throughout the study to answer investigators' questions regarding patients' eligibility and safety and the reporting of serious adverse events.

Selection Criteria

Patients with clinical and radiographic evidence of pneumonia entered the study if they met two minor or one major 1993 American Thoracic Society criterion for severe pneumonia (19) as modified by Ewig and collaborators (20). Minor criteria included (1) respiratory rate greater than 30 breaths per minute at admission; (2) ratios of Pa_{O_2} to fraction of inspired oxygen ($\text{F}_{\text{I}_{\text{O}_2}}$) ($\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$) less than 250; (3) chest radiograph showing bilateral involvement or multilobar involvement; (4) systolic blood pressure less than 90 mm Hg; or (5) diastolic blood pressure less than 60 mm Hg. Major criteria included (1) requirement of mechanical ventilation; (2) increase in the size of opacities on chest radiograph of 50% or more at 48 hours; (3) requirement of vasopressors for more than 4 hours; or (4) serum creatinine 2 or more mg/dl.

Exclusion criteria included any of the following: (1) nosocomial pneumonia; (2) severe immunosuppression; (3) acute burn injury; (4) a preexisting medical condition with a life expectancy less than 3 months; (5) pregnancy; (6) a major gastrointestinal bleed within 3 months of the current hospitalization; or (7) a condition requiring more than 0.5 mg/kg/day of prednisone equivalent (i.e., acute asthma or chronic obstructive pulmonary disease [COPD]). Exit criteria included (1) active gastrointestinal bleeding event requiring transfusion of five units packed red blood cells (PRBC); (2) recovery of *Candida* spp. from multiple sites; or (3) development of a condition requiring prolonged glucocorticoid administration such as exacerbation of COPD or asthma.

Treatment Assignments

Patients were randomly assigned in a 1:1 manner to receive hydrocortisone infusion or placebo (sterile normal saline in a volume equal to the study drug) at each center. Randomization schemes were generated in blocks of 10 for each participating site by a central randomization center. The randomization assignment was provided to the recruiting center in sealed envelopes. The patients and the investigators were blinded to the patients' treatment assignments. Hydrocortisone was given as an intravenous 200-mg loading bolus followed by an infusion (hydrocortisone 240 mg in 500 cc 0.9% saline) at a rate of 10 mg/hour for 7 days. Initial antibiotic therapy followed the 1993 American Thoracic Society guidelines for the initial management of adults with community-acquired pneumonia (19). There was no protocol policy for the management of septic shock or unresolving ARDS with prolonged glucocorticoid treatment.

Study Aims

The primary end-points of the study were improvement in $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$ ($\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}} > 300$ or ≥ 100 increase from study entry) and multiple organ dysfunction syndrome (MODS) score by Study Day 8 and development of delayed septic shock. The secondary end-points were duration of mechanical ventilation, length of ICU/RIU and hospital stay, and survival to hospital discharge and to 60 days.

We adopted the simplified MODS score (up to 6 points) proposed by Bernard and associates (21). The number of ventilator-free days was defined as the number of days after ventilation was discontinued up to Study Day 8. Shock was defined as requirement of vasopressors. ARDS was defined by consensus criteria (22); method of BAL, laboratory processing, and diagnostic criteria followed consensus guidelines (23). The threshold for diagnosing pneumonia by quantitative bacterial culture of the BAL was 10^4 cfu/ml (23).

Statistical Analysis

This study was conducted as a group sequential clinical trial with continuation or termination determined by planned data analysis approximately every 20 patients. The sample size was not a fixed number. The variables of primary and secondary interest were (1) improvement in

$\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$ after 7 days of therapy (on Study Day 8, $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}} > 300$ or ≥ 100 increase from study entry) used to terminate the study; and (2) hospital mortality. After accrual of 46 patients, the upper stopping boundary of the triangular Whitehead test (24, 25) for improvement in $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$ was crossed, which warranted closure of the trial. A power of 0.948 for improvement in $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$ (using either criteria) was achieved with a significance of 0.002.

Data were analyzed using standard methods. In all cases, statistical significance was defined as a two-tailed test with an α of 0.05. All statistical calculations were performed using the SAS System for Windows (release 9.0; SAS Institute, Cary, NC). Additional information on the sequential design and all analyses is available in the online supplement.

RESULTS

After an interim analysis of data from 46 patients, enrollment was suspended because a significant difference was identified between the two groups for improvement in $\text{Pa}_{\text{O}_2}:\text{F}_{\text{I}_{\text{O}_2}}$ by Study Day 8 ($p = 0.002$) and hospital mortality ($p = 0.009$). Table E1 in the online supplement provides outcome data per each center. Unless specified, data are reported as placebo versus hydrocorti-

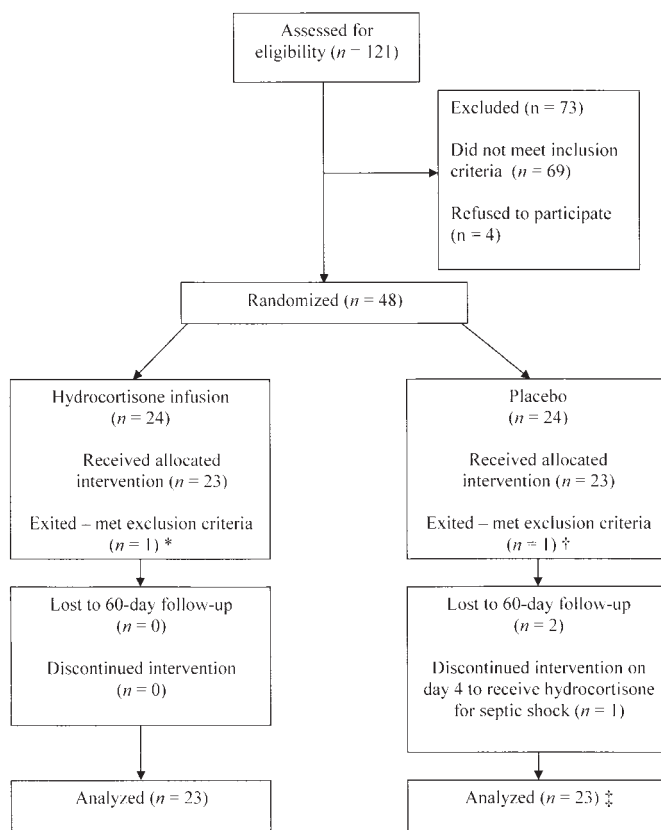


Figure 1. Flow diagram of the progress through the phases of the trial. Exited the study: *One patient with COPD blindly randomized to hydrocortisone met exclusion criteria because of a requirement for methylprednisolone treatment for an acute exacerbation of COPD. The patient did not receive hydrocortisone. †One patient blindly randomized to placebo met exclusion because he had hepatic cancer with a life expectancy less than 3 months. The patient did not receive placebo. Analyzed as randomized unless otherwise specified: ‡One patient blindly randomized to placebo exited the study on Study Day 4 to receive hydrocortisone for refractory septic shock. Two patients blindly randomized to placebo received prolonged methylprednisolone treatment for unresolving ARDS after Study Day 8.

some groups. The two groups met similar study entry criteria: requirement of mechanical ventilation (19 versus 15), requirement of vasopressors for more than 4 hours (1 versus 2), respiratory rate greater than 30 breaths per minute (18 versus 17), $Pa_{O_2}:Fi_{O_2} < 250$ (22 versus 23), chest radiograph showing multilobar involvement (23 versus 23). Nine patients (4 versus 5) met two minor criteria and no major criteria. Figure 1 shows progress through the phases of the trial. Two patients exited the study shortly after randomization when it was discovered that they met exclusion criteria. They did not receive the assigned treatment and were not included in the analysis.

Table 1 shows the clinical and physiological characteristics at study entry. Among the 34 patients requiring mechanical ventilation, noninvasive positive pressure ventilation (NPPV) was applied more frequently to those randomized to hydrocortisone (3 versus 8; $p = 0.03$). There were 33 patients with comorbidities (20 versus 13; $p = 0.08$). No significant difference was observed for type of underlying comorbidities (placebo versus hydrocortisone group): hypertension (8 versus 4), ischemic heart disease (6 versus 4), diabetes mellitus (5 versus 3), alcohol abuse (4 versus 1), chronic liver disease (3 versus 1), COPD (1 versus 2), chronic renal insufficiency (0 versus 2), and others (5 versus 1).

Information on identified pathogens and diagnostic methods is available in the online supplement. Patients received combination therapy in agreement with the 1993 ATS guidelines (19). Initial antibiotic classes and changes in antibiotics are available in the online supplement.

At study entry, serum C-reactive protein (CRP) was higher in patients randomized to hydrocortisone (Table 1). On Study Day 8, a greater than 50% reduction in CRP from study entry was observed in all but two patients in the hydrocortisone group and in only five patients in the control group ($p < 0.0001$). By Study Day 8, the 20 patients with persistent elevation in CRP levels had a higher incidence of delayed septic shock (9 versus 0; $p = 0.47$). After randomization (Figure 2, top), a progressive

reduction in CRP values was seen in the hydrocortisone group; a significant difference from the control group was seen on Study Day 8 (Table 2).

During the 7 days of treatment, the clinical response of the two groups diverged. In the control group, the single patient admitted with septic shock died by Study Day 3, whereas nine patients developed delayed septic shock that was complicated by ARDS in four. One additional control patient developed delayed septic shock after Day 8. In contrast, in the hydrocortisone group, the two patients admitted with septic shock were weaned off vasopressors by Days 3 and 5, and no other patient developed sepsis-

TABLE 1. CLINICAL AND PHYSIOLOGICAL CHARACTERISTICS AT STUDY ENTRY

Parameter	Placebo (n = 23)	Hydrocortisone (n = 23)	p Value
Male/female*	15/8	17/6	0.53
Age, yr†‡	66.6 ± 14.7	60.4 ± 17.3	0.20
APACHE II score§¶	18.2 ± 4.0	17.2 ± 4.1	0.39
MODS score‡	1.2 ± 0.4	1.2 ± 0.5	0.75
Temperature, °C‡	38.2 ± 1.2	38.3 ± 0.9	0.76
WBC count, × 10 ⁹ /L‡	13.9 ± 5.1	13.4 ± 5.5	0.73
On mechanical ventilation*	19	15	0.18
$Pa_{O_2}:Fi_{O_2}$ ‡	178 ± 58	141 ± 49	0.03
$Pa_{O_2}:Fi_{O_2} < 200$	13 (57%)	21 (91%)	0.02
Catecholamine-dependent septic shock	1 (4%)	2 (9%)	1.0
C-reactive protein, (mg/dl)***	29 (6–200)	55 (14–349)	0.04
Chest radiograph score‡	2.4 ± 0.6	2.9 ± 0.8	0.03

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; MODS = multiple organ dysfunction syndrome; WBC = white blood cell.

Unless specified, data are reported as mean ± SD or n value with percentage in parentheses.

* Cochran-Mantel-Haenszel Chi Square.

† Twenty-four patients were older than 65 years of age (13 in the placebo group and 11 in the hydrocortisone group).

‡ Student's *t* test.

§ Acute Physiology and Chronic Health Evaluation (APACHE) II score on ICU admission.

|| Fisher's Exact Test.

¶ Reported as median (range). Upper normal laboratory value is 5.0 mg/L.

** Univariate analysis and Wilcoxon rank sum.

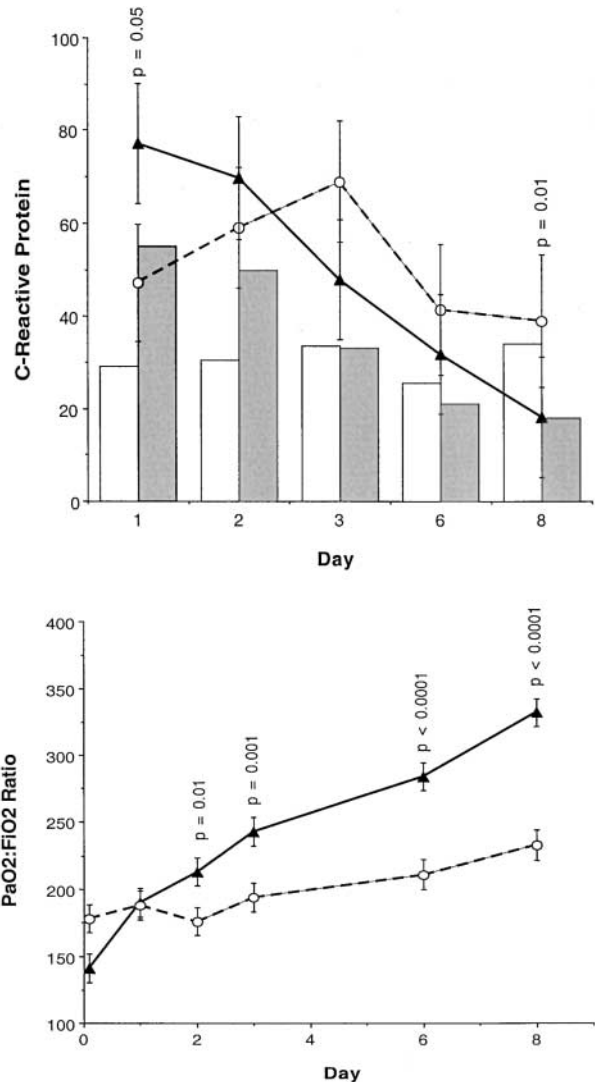


Figure 2. Values over time for serum C-reactive protein (CRP) (top) and $Pa_{O_2}:Fi_{O_2}$ (bottom) in patients randomized to hydrocortisone and placebo. Dashed lines represent the placebo group and solid lines represent the hydrocortisone-treated group. The C-reactive protein graph contains two censored outliers for Day 8 as shown in the line graph. Two placebo patients were censored because their Day 8 CRP value was beyond 3 SD of the mean Day 8 value. If the outliers were included, the difference between groups on Day 8 is more significant ($p = 0.008$). The bar graph represents median values; white bars represent the placebo group, and gray bars represent the hydrocortisone-treated group. p Values shown are median comparisons between groups. The $Pa_{O_2}:Fi_{O_2}$ graph contains censoring for Days 6 and 8 values of the placebo patient who exited to receive hydrocortisone therapy for septic shock.

TABLE 2. CLINICAL AND PHYSIOLOGICAL CHARACTERISTICS ON OR BY STUDY DAY 8

Parameter	Placebo (n = 23)	Hydrocortisone (n = 23)	p Value
On mechanical ventilation *	15 (65%)	6 (26%)	0.008
Mechanical ventilation-free days ^{††}	0 (0-6)	4 (0-7)	0.01
Pa _{O₂} :Fi _{O₂} [‡]	237 ± 92	332 ± 80	0.0008
Pa _{O₂} :Fi _{O₂} ≥ 300	5 (22%)	16 (70%)	0.003
Pa _{O₂} :Fi _{O₂} improvement ≥ 100 from study entry	8 (35%)	20 (87%)	0.0007
Chest radiograph score [§]	2.6 ± 1.3	1.1 ± 0.7	< 0.0001
Improvement in chest radiograph score from Day 1 to Day 8	5 (22%)	21 (91%)	< 0.0001
MODS score [§]	1.0 ± 0.9	0.3 ± 0.5	0.003
Patients with MODS* [¶]	16 (70%)	8 (35%)	0.02
Delayed septic shock by Day 8	9 (43%)	0 (0%)	0.001
New ARDS by Day 8	3 (13%)	0 (0%)	0.23
C-reactive protein (mg/dl) ^{††**}	34 (0-225)	18 (0-44)	0.01
Survival	21 (91%)	23 (100%)	0.49

Definition of abbreviations: ARDS = acute respiratory distress syndrome; MODS = multiple organ dysfunction syndrome.

Unless specified, data are reported as mean ± SD or n value with percentage in parentheses.

* Cochran-Mantel-Haenszel Chi Square.

† Reported as median (range).

‡ Univariate analysis and Wilcoxon rank sum.

§ Student's *t* test.

|| Fisher's Exact Test.

¶ Extrapulmonary organ dysfunction in four control patients and one treated patient. The control group contained one cardiac and renal failure, two renal failures alone, and one hematologic and renal failure. The treated patient had acute renal failure that was unresolved at Day 8.

** Upper normal laboratory value is 5.0 mg/L.

related complications. Hydrocortisone treatment appeared to be associated with a protective effect against delayed septic shock (odds ratio = 0.03, confidence interval 0.0015–0.51; *p* = 0.0005, relative risk = 0.05).

At baseline, the hydrocortisone-treated group had a significantly lower Pa_{O₂}:Fi_{O₂} (Table 1). As shown in Figure 2, a significant increase in Pa_{O₂}:Fi_{O₂} from study entry was observed within the hydrocortisone group by Day 1 (*p* < 0.001), and within the placebo group by Day 5 (*p* = 0.03). Additional information is available in the Web repository. On Study Day 8, a Pa_{O₂}:Fi_{O₂} ≥ 300 or improved by ≥ 100 from study entry was observed in 9 (39%) and 20 (87%) patients randomized to placebo versus hydrocortisone (*p* = 0.0018), respectively. By Study Day 8,

among survivors, the chest radiograph (placebo versus hydrocortisone) worsened in 13 (13 versus 0), did not change in 7 (5 versus 2), and improved in 26 (5 versus 21).

Major complications occurring after study entry are shown in Table 3. Four control patients developed ARDS, one died by Day 7; two of the three survivors received prolonged methylprednisolone treatment for unresolving ARDS (13). Figure 3 (*top*) shows the survival curves of patients randomized to hydrocortisone and placebo. Survival to hospital discharge was 70% in the placebo group and 100% in the hydrocortisone group (*p* = 0.009). All nonsurvivors died before Study Day 28. Deaths were reported in four of the six participating centers (Table E1). All nonsurvivors required conventional mechanical ventilation and

TABLE 3. MAJOR COMPLICATIONS AFTER STUDY ENTRY

Major Complications	Placebo	Hydrocortisone	p Value
Number of patients with major complications*	18 (78%)	6 (26%)	< 0.001
Delayed septic shock [†]	10 (52%)	0 (0%)	< 0.001
Shock not related to sepsis [†]	2 (9%)	0 (0%)	0.5
ARDS [†]	4 (17%)	0 (0%)	0.11
Patients with nosocomial infection [†]	4 (18%)	0 (0%)	0.11
Ventilator-associated pneumonia ^{††}	3 (13%)	0 (0%)	0.23
Acute renal failure ^{†§}	3 (13%)	0 (0%)	0.23
Arrhythmia [†]	3 (13%)	1 (4%)	0.61
Upper gastrointestinal bleeding [†]	1 (4%)	1 (4%)	1.0
Polyneuropathy of critical illness [†]	3 (13%)	0 (0%)	0.23
Others ^{†¶}	4 (17%)	1 (4%)	0.34

Definition of abbreviation: ARDS = acute respiratory distress syndrome.

Data are reported as n value with percentage in parenthesis.

* Cochran-Mantel-Haenszel Chi Square.

† Fisher's Exact Test.

‡ The etiologic agents of pneumonia included *P. aeruginosa* (2) and *S. aureus* (1).

§ Renal failure (serum creatinine greater than 2 mg/dl) developed on Days 2, 10, and 18.

|| The diagnosis of upper gastrointestinal bleeding was made on clinical criteria on Day 5 in the placebo patient and on Day 15 in the hydrocortisone-treated patient.

¶ Other major complications included one liver failure, two congestive heart failure, and one lung abscess in the placebo group, and one drug-induced hepatitis in the hydrocortisone-treated group.

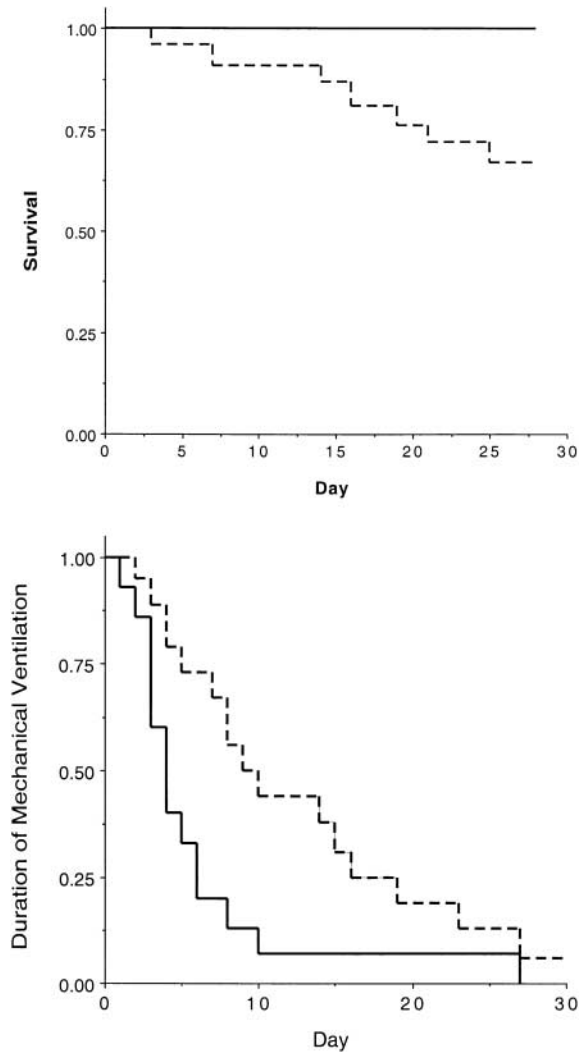


Figure 3. Survival curves (top) and time to removal of mechanical ventilation (bottom) in patients randomized to hydrocortisone and placebo. Dashed lines represent the placebo group and solid lines represent the hydrocortisone-treated group. One placebo patient who developed ARDS was extubated on Study Day 44.

all had progression of radiographic densities on chest radiograph by Day 8. All but one patients developed pressor-dependent shock. The one patient without shock had *Legionella pneumoniae* that progressed to ARDS. Causes of death included septic shock (4), ARDS (1), hypoxemic respiratory failure (1), and MODS (1).

All nonsurvivors received a macrolide antibiotic in combination with a third-generation cephalosporin (4), a quinolone (3), or an antipseudomonal penicillin (1). Three patients had a change in antibiotic for a specific laboratory finding (addition of vancomycin for *Staphylococcus aureus* in a patient with polymicrobial pneumonia and addition of rifampin in two patients with positive *Legionella* urinary antigen already receiving macrolide). Additional final outcome results are shown in Table 4. Time to removal of mechanical ventilation is shown in Figure 3 (bottom). After hospital discharge, one control patient was readmitted with recurrent pneumonia and died within 60 days of initial study entry.

DISCUSSION

This is the first randomized study evaluating the efficacy and safety of low-dose hydrocortisone infusion in patients with severe

community-acquired pneumonia, the leading cause of community-acquired sepsis. The findings of this study support our original hypothesis that modulation of systemic inflammation with early introduction of prolonged low-dose glucocorticoid administration hastens resolution of pneumonia and prevents development of life-threatening sepsis-related complications. Patients randomized to a 7-day hydrocortisone infusion had a significant reduction in CRP levels over time and by Study Day 8 had, compared with control subjects, a significant improvement in $\text{Pa}_{\text{O}_2}:\text{Fi}_{\text{O}_2}$ and chest radiograph score, and a significant reduction in median CRP levels, MODS score, and incidence of delayed septic shock. Hydrocortisone treatment was well tolerated and led to a significant reduction in duration of mechanical ventilation, length of ICU/RIU and hospital stay, and increased survival to hospital discharge and to 60 days.

The role of glucocorticoid supplementation in patients with systemic inflammation is undergoing a cyclical reassessment stirred by a new understanding of the role of glucocorticoids in modulating inflammation and immunity (26) and the consistent positive results of recent randomized studies (10). It is now appreciated that at the cellular level, transcription factor nuclear factor- κB (NF- κB)—activated by inflammatory signals—and glucocorticoid receptor α (GR α)—activated by endogenous or exogenous glucocorticoids—have diametrically opposed functions (stimulatory versus inhibitory) in regulating inflammation. Once activated, NF- κB and GR α can mutually repress each other through a protein-protein interaction that prevents their DNA binding and subsequent transcriptional activity. Activation of one transcription factor in excess of the binding (inhibitory) capacity of the other shifts cellular responses toward increased (dysregulated) or decreased (regulated) transcription of inflammatory mediators over time (16). Longitudinal studies have shown a progressive increase in NF- κB activation over time in peripheral blood mononuclear cells from nonsurvivors of septic shock and in normal peripheral blood leukocytes stimulated with serial plasma samples from nonsurvivors of sepsis-induced ARDS (27, 28).

We have recently shown that in patients with unresolving ARDS, normal PBL exposed to plasma samples collected during prolonged methylprednisolone treatment exhibited (1) a progressive increase in cytoplasmic binding of GR α to NF- κB and (2) a concomitant reduction in NF- κB binding to DNA and transcription of tumor necrosis factor- α (TNF- α) and IL-1 β (16). Similarly, one study reported a significant reduction in NF- κB activity over time in peripheral blood mononuclear cells obtained from a patient with septic shock and receiving hydrocortisone treatment (29). In the ARDS study, patients treated with methylprednisolone, compared with control subjects, had progressive and sustained reductions in circulating TNF- α , IL-1 β , and IL-6 (16). Likewise, in patients with septic shock, studies have shown that hydrocortisone infusion led to a significant reduction in circulating levels of NF- κB -transcribed proteins (phospholipase A_2 , IL-6, IL-8, and soluble E-selectin) and CRP, while after withdrawal of treatment a rebound effect was observed for all of these mediators (14, 15, 30). The latter finding underscores the short-lasting antiinflammatory action of hydrocortisone and the importance of prolonged treatment in achieving a sustained control of systemic inflammation.

The response to glucocorticoid treatment observed in our study and in recent randomized trials of patients with catecholamine-dependent septic shock (11, 15, 31–34) and severe pneumocystis pneumonia (12) contrasts with the negative findings of older trials. A careful assessment of the literature indicates that failure to detect a beneficial effect in older randomized studies evaluating a time-limited course of massive doses of glucocorticoids in sepsis and early ARDS was most likely related to the short

TABLE 4. OUTCOME

Outcome Variable	Placebo	Hydrocortisone	p Value
ICU mortality*	7 (30%)	0 (0%)	0.009
Hospital mortality*	7 (30%)	0 (0%)	0.009
60-d mortality*†	8 (38%)	0 (0%)	0.001
Length of ICU or RICU stay, d‡	18 (3–45)	10 (4–33)	0.01
Length of hospital stay, d‡	21 (3–72)	13 (10–53)	0.03
Duration of mechanical ventilation, d‡	10 (2–44)	4 (1–27)	0.007

Definition of abbreviations: ICU = intensive care unit; RICU = respiratory intermediate unit.

Data are reported as n value with percentage in parenthesis or median with range in parentheses.

* Fisher's Exact Test.

† Two patients were lost to follow-up.

‡ Univariate analysis and Wilcoxon rank sum.

duration of treatment (9, 10). Among a number of studies in support of this hypothesis (9), a randomized trial of patients with severe community-acquired pneumonia found that a single dose of hydrocortisone (10 mg/kg) before antibiotic administration had no effect on plasma TNF- α levels (35).

Although dosage and duration of hydrocortisone in our study are similar to the one used in recent randomized studies in patients with septic shock, treatment was initiated much earlier in the course of sepsis in an attempt to hasten resolution of pneumonia and to prevent the development of sepsis-related complications. In this regard, treated patients improved gas exchange and radiologic findings more rapidly than control subjects, and none developed delayed septic shock or ARDS. The relationship between reduction in CRP values and absence of sepsis-related complications and death supports the notion that containment of systemic inflammation is an important priority in the management of patients with severe community-acquired pneumonia.

The small number of patients in our study may have biased the estimate of the treatment effect on mortality, and a larger randomized trial is necessary to support the mortality findings of this trial. Study limitations are attributed primarily to the small sample size that resulted in a few imbalances among prognostic factors among treatment groups. These imbalances included unplanned differences in the number of patients receiving NPPV, and with co-morbidities (a trend), as well as an imbalance of treatment allocation at the various sites. Although there were an equal number of subject randomized to each treatment group, this distribution was not reflected at each center. The small sample limits our ability to control for these imbalances. Moreover, our study was designed in 1999 and did not include recent advancements made in the management of patients with severe sepsis or septic shock (36), including patients with severe pneumonia (37). In the recent study by Annane and collaborators (34), the 28-day mortality among patients with severe community-acquired pneumonia and septic shock was 45% and 65% for patients randomized to hydrocortisone (n = 47) and placebo (n = 54), respectively (odds ratio 0.44; 95% confidence interval 0.20–0.98; p = 0.044) (data graciously provided by Dr. D. Annane). In our study, however, only 1 of 11 control patients with septic shock received hydrocortisone.

In a future randomized study, we recommend using a smaller block size to assure balanced treatment assignment among participation centers. In addition, it would be beneficial to use a dynamic allocation scheme that allows stratification among key prognostic factors such as initial mode of mechanical ventilation. The new trial should incorporate recent guidelines for the management of patients with severe sepsis and septic shock (36), evaluate adrenal reserve in patients with septic shock (34), record timing to initial antibiotic administration (37), and obtain serial

measurements of circulating inflammatory cytokine levels over time.

In conclusion, the finding of this small randomized study of a patients with severe community-acquired pneumonia support the original hypothesis that control of inflammation with prolonged low-dose hydrocortisone infusion hastens resolution of pneumonia and prevents the development of sepsis-related complications. In this study, a 7-day course of low-dose hydrocortisone infusion was associated with a significant reduction in duration of mechanical ventilation, hospital length of stay, and hospital mortality.

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References

1. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, Moreno R, Boulme R. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002;28:108–121.
2. Leeper KV, Torres A. Community-acquired pneumonia in the intensive care unit. *Clin Chest Med* 1995;16:155–172.
3. Leroy O, Devos P, Guery B, Georges H, Vandebussche C, Coffinier C, Thevenin D, Beaucaire G. Simplified prediction rule for prognosis of patients with severe community-acquired pneumonia in ICUs. *Chest* 1999;116:157–165.
4. Puren AJ, Feldman C, Savage N, Becker PJ, Smith C. Patterns of cytokine expression in community-acquired pneumonia. *Chest* 1995;107:1342–1349.
5. Schutte H, Lohmeyer J, Rosseau S, Ziegler S, Siebert C, Kielisch H, Pralle H, Grimminger F, Morr H, Seeger W. Bronchoalveolar and systemic cytokine profiles in patients with ARDS, severe pneumonia and cardiogenic pulmonary oedema. *Eur Respir J* 1996;9:1858–1867.
6. Monton C, Torres A, El-Ebiary M, Filella X, Xaubet A, de la Bellacasa JP. Cytokine expression in severe pneumonia: a bronchoalveolar lavage study. *Crit Care Med* 1999;27:1745–1753.
7. Fernandez-Serrano S, Dorca J, Coromines M, Carratala J, Gudiol F, Manresa F. Molecular inflammatory responses measured in blood of

- patients with severe community-acquired pneumonia. *Clin Diagn Lab Immunol* 2003;10:813–820.
8. Meduri GU, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, Leeper K. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest* 1995;107:1062–1073.
 9. Meduri GU. An historical review of glucocorticoid treatment in sepsis. Disease pathophysiology and the design of treatment investigation. *Sepsis* 1999;3:21–38.
 10. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med* 2004;141:47–56.
 11. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998;26:645–650.
 12. Jantz MA, Sahn SA. Corticosteroids in acute respiratory failure. *Am J Respir Crit Care Med* 1999;160:1079–1100.
 13. Meduri GU, Headley S, Carson S, Umberger R, Kelso T, Tolley E. Prolonged methylprednisolone treatment improves lung function and outcome of unresolving ARDS: a randomized, double-blind, placebo-controlled trial. *JAMA* 1998;280:159–165.
 14. Briegel J, Jochum M, Gippner-Steppert C, Thiel M. Immunomodulation in septic shock: hydrocortisone differentially regulates cytokine responses. *J Am Soc Nephrol* 2001;12:S70–S74.
 15. Keh DBT, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, Volk HD, Doecke WD, Falke KJ, Gerlach H. Immunologic and hemodynamic effects of “low-dose” hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003;167:512–520.
 16. Meduri GU, Tolley EA, Chrousos GP, Stentz F. Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome: evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. *Am J Respir Crit Care Med* 2002;165:983–991.
 17. Monton C, Ewig S, Torres A, El-Ebiary M, Filella X, Rano A, Xaubet A. Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. *Eur Respir J* 1999;14:218–220.
 18. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Umberger R, Meduri GU. Hydrocortisone infusion in patients with severe community-acquired pneumonia: results of a randomized clinical trial. *Am J Respir Crit Care Med* 2004;169:A782.
 19. Niederman MS, Bass JB Jr, Campbell GD, Fein AM, Grossman RF, Mandell LA, Marrie TJ, Sarosi GA, Torres A, Yu VL. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. American Thoracic Society. Medical Section of the American Lung Association. *Am Rev Respir Dis* 1993;148:1418–1426.
 20. Ewig S, Ruiz M, Mensa J, Marcos MA, Martinez JA, Arancibia F, Niederman MS, Torres A. Severe community-acquired pneumonia: assessment of severity criteria. *Am J Respir Crit Care Med* 1998;158:1102–1108.
 21. Bernard GR, Doig G, Hudson LD, et al. Quantification of organ failure for clinical trials. *Am J Respir Crit Care Med* 1995;151:A323.
 22. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–24.
 23. Meduri GU, Chastre J. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. *Chest* 1992;102:557S–564S.
 24. Whitehead J. The design and analysis of sequential clinical trials. New York: J. Wiley and Sons; 1983.
 25. Whitehead J. The design and analysis of sequential clinical trials, 2nd ed. New York: J. Wiley and Sons; 1992.
 26. Franchimont D, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and Inflammation Revisited: The State of the Art. NIH Clinical Staff Conference. *Neuroimmunomodulation* 2003; 10:247–60.
 27. Bohrer H, Qiu F, Zimmermann T, Zhang Y, Jllmer T, Mannel D, Bottiger BW, Stern DM, Waldherr R, Saeger HD, et al. Role of NF kappa B in the mortality of sepsis. *J Clin Invest* 1997;100:972–985.
 28. Stentz F, Tolley EA, Headley AS, Chrousos GP, Meduri GU. Mechanisms of NF-kB and glucocorticoid receptor (GRa) in activation and regulation of systemic inflammation (SI) in ARDS [abstract]. *Am J Respir Crit Care Med* 2001;163:A450.
 29. van Leeuwen HJ, van der Bruggen T, van Asbeck BS, Boereboom FT. Effect of corticosteroids on nuclear factor-kappaB activation and hemodynamics in late septic shock. *Crit Care Med* 2001;29:1074–1077.
 30. Briegel J, Kellermann W, Forst H, Haller M, Bittl M, Hoffmann GE, Buchler M, Uhl W, Peter K. Low-dose hydrocortisone infusion attenuates the systemic inflammatory response syndrome: the Phospholipase A2 Study Group. *Clin Investig* 1994;72:782–787.
 31. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999;27:723–732.
 32. Chawla K, Kupfer Y, Goldman I, Tessler S. Hydrocortisone reverses refractory septic shock. *Crit Care Med* 1999;27:A33.
 33. Yildiz O, Doganay M, Aygen B, Guven M, Keleutimur F, Tutuu A. Physiological-dose steroid therapy in sepsis. *Crit Care* 2002;6:251–259.
 34. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862–871.
 35. Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia: a randomized controlled study. *Chest* 1993;104:389–392.
 36. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, et al. Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–873.
 37. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004;164:637–644.