Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Hydrocortisone in severe community-acquired pneumonia.

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Detailed inclusion criteria:

- Age ≥ 18 years
- Patients affiliated to social security scheme
- Admission to a participating ICU or intermediate care unit
- Diagnosis of Community-Acquired Pneumonia (CAP) suggested by at least two of the following: cough, purulent sputum, chest pain, dyspnea
- Focal shadowing/infiltrate on chest X-ray or CT-scan
- Diagnosis of CAP during the 48 hours post-hospital admission
- Study drug infusion initiated no longer than 24 hours post first severity criterion
- Severity defined by at least one of the following:
    - Pneumonia Severity Index (PSI) > 130 (Fine class V)[1]
    - Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more
    - Patient treated by high-flow oxygen therapy with a FiO_2 of 50% or more and a PaO_2:FiO_2 ratio lower than 300 (The PaO2:FiO2 ratio was initially set at 200 and was increased to 300 on April 4, 2017 after inclusion of 285 patients).
    - Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO2 is less than (cf. table) (This severity criterion was added on April 4, 2017, after inclusion of 285 patients).

Oxygen flow (L/min)	6	7	8	9	10 or more
PaO2 (mmHg) less than	180	210	240	270	300

- Patient already treated by antibiotics (at least one dose since admission to hospital)
- Informed consent signed by the patient, his/her legally authorized representative or emergency procedure

Detailed non-inclusion criteria:

- Patient treated by vasopressors for septic shock at the time of inclusion (See below the paragraph "prohibited treatments" for more details)
- Clinical history suggesting aspiration of gastric content
- Patient treated by invasive mechanical ventilation within 14 days before current hospital admission
- Patient treated by antibiotics for a respiratory infection for more than seven days at the time of hospital admission (except if a pathogen resisting to this antibiotic is isolated)

- History of cystic fibrosis
- Post-obstructive pneumonia
- Patients in which rapid PCR-test is positive for flu
- Active tuberculosis or fungal infection
- Active viral hepatitis or active infection with herpes viruses
- Myelosuppression
- Decision of withholding mechanical ventilation or endotracheal intubation
- Hypersensitivity to corticosteroids
- Patient needing anti-inflammatory corticosteroids or substitutive hydrocortisone for any reason
- Patients under treatment by more than 15 mg/d of prednisone (or equivalent) for more than 30 days
- Patient already enrolled in another drug trial with mortality as an end-point. If the patient is already participating in another therapeutic trial with a different endpoint, the investigator must verify that inclusion in CAPE COD cannot prejudice it.
- Pregnant or breastfeeding woman
- Patient under guardianship

Informed consent

The ethics committee (Comité de Protection des Personnes Ouest 1, Tours, France) and the French regulatory agency (Agence Nationale de Sécurité du Médicament, Saint-Denis, France) approved the protocol. Patients or their legally authorized representative provided written consent prior to inclusion. When the patient was unable to consent and no legally authorized representative could be reached, the ethics committee approved an emergency inclusion, which case a deferred written consent was obtained from the patient or a surrogate as soon as possible.

Prohibited treatments

- Hydrocortisone and other corticosteroids in any dose and by any route (except local administration, nebulization not being considered as local administration) were not allowed. If an unavoidable indication appeared during the patient's stay (e.g. biological demonstration of adrenal insufficiency) the patient had to be treated. In this case, the study treatment was stopped to avoid an unnecessarily high dose of hydrocortisone.
- Continuous infusion of neuromuscular blocking agents was to be avoided. If indicated (e.g., in severe ARDS), it should be as short as possible and an interruption of the infusion should be scheduled every 12 hours, so that treatment is not prolonged longer than necessary.
- Vasopressors administered for the treatment of septic shock were not allowed at inclusion. A patient admitted with CAP without evidence of circulatory failure whose

condition required vasopressors after initiation of invasive mechanical ventilation could be included provided that: (i) circulatory failure was related to the effects of positive pressure ventilation and sedative drugs, in the opinion of the physician in-charge; (ii) blood lactate level was less than 4 mmol/L; and (iii) epinephrine or norepinephrine dose was less than 0.25 microg/kg/min. A patient developing septic shock after inclusion could receive vasopressors at any dose. "Vasopressors" means norepinephrine or epinephrine (at any dose), or more than 5 microg/kg/min of dopamine.

Permitted Treatments

- Antibiotics were at the discretion of the responsible clinician, but had to be started before inclusion.
- All other treatments were allowed. Sedative agents were to be used within available guidelines to avoid excessive sedation.
- Rescue treatments were allowed in severe ARDS (including prone ventilation, inhaled nitric oxide, extra-corporeal venous membrane oxygenation). Rescue corticosteroids were not allowed because there was no evidence of benefit in such circumstances.

Modulation of the duration and tapering of the experimental treatment

Before the end of the fourth day, the clinician in charge decided on a short treatment regimen, if all of the following criteria were met: patient breathing spontaneously; PaO2:FiO2 ratio greater than 200; Sequential Organ Failure Assessment (SOFA)[2] score on day 4 less than or equal to SOFA score on day 1; high probability (as estimated by the clinician in charge) that the patient will be able to be discharged from the ICU by day 14. In this case, the dose was reduced to 100 mg/d for two days, then 50 mg/d for two more days. If at least one of the criteria was absent, treatment was continued at 200 mg/d until the seventh day, then decreased to 100 mg/d for four days, and to 50 mg/d for the last three days. In all cases, treatment was discontinued upon discharge from the ICU (**Fig. S1**).

Interim analyses

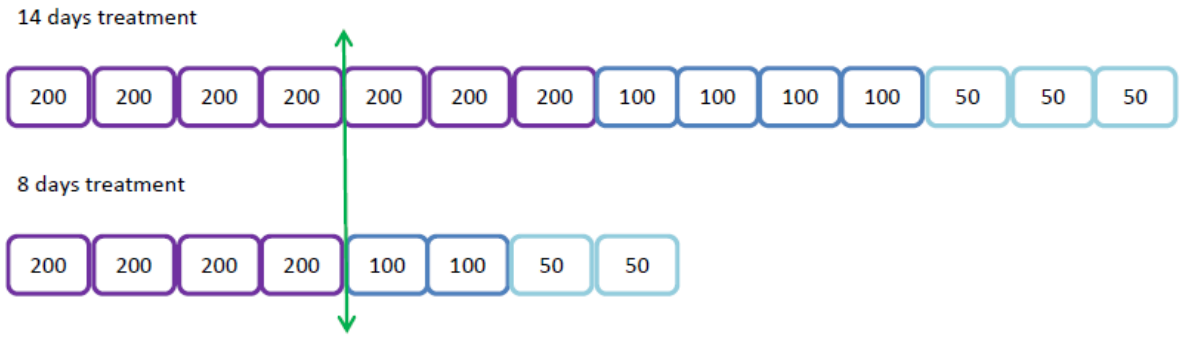
Two interim analyses were planned and were performed when the endpoints were available for the first 400 and 800 randomized patients, respectively. Using Peto's rule[3], the alpha risk was set at 0.001 for the two interim analyses and 0.049 for the final analysis.

Of the first 400 patients randomized, 196 were in the hydrocortisone group and 204 in the placebo group, of whom one patient withdrew consent and one patient was found to be under legal protection and did not receive the experimental treatment. The first interim analysis therefore included 398 patients.

On day 28, death occurred in 11 out of 196 patients (5.6%; 95% CI, 2.4 to 8.8) in the hydrocortisone group and in 27 out of 202 patients (13.4%; 95% CI, 8.7 to 18.1) in the placebo group (crude difference -7.8%; 95% CI -13.4 to -2.1; p=0.0085). Because the threshold of significance was not met for an interim analysis, the Data Safety and Managing Board recommended continued inclusion.

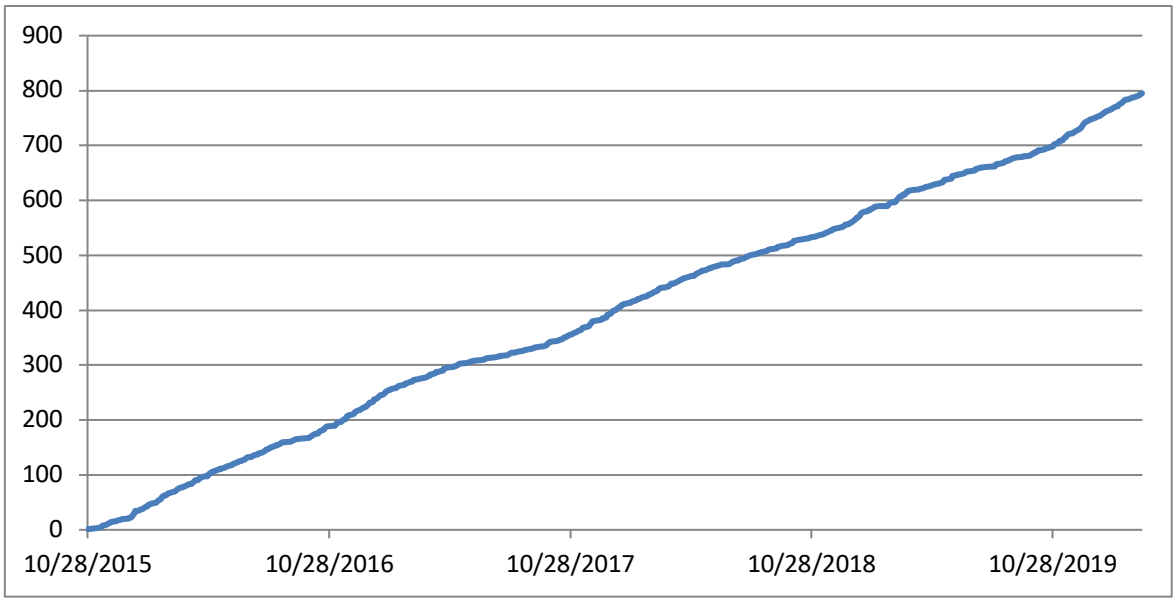
In the second interim analysis, the significance level was also not reached (p=0.0055, Table 1), but the DSMB finally recommended to definitively stop the inclusions, considering *first* that the inclusion of the last 400 planned patients would most likely not change the results, *second* that it became ethically unacceptable to continue to include in the placebo group, *third* that the prolonged suspension of the inclusions due to the COVID-19 pandemic would probably complicate the resumption of inclusions.

Figure S1. Treatment regimen.



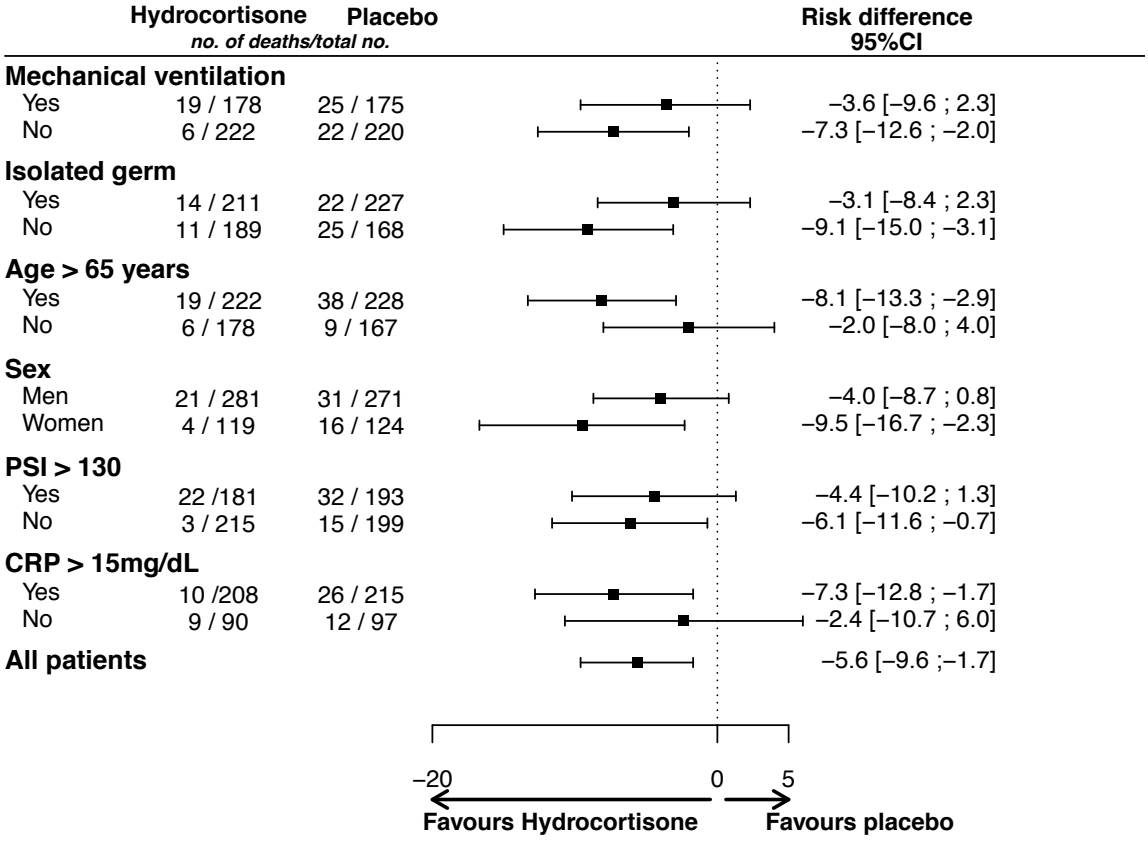
Each box represents a 24-hour period, counted from the start of the experimental treatment, and hereafter called a day. The number refers to the daily dose of hydrocortisone in mg (or an equivalent volume of placebo). The decision to shorten treatment assumed that all of the following criteria were present on day 4 (green arrow): patient breathing spontaneously; PaO2:FiO2 ratio greater than 200; Sequential Organ Failure Assessment (SOFA)[2] score on day 4 less than or equal to SOFA score on day 1; high probability (as estimated by the clinician in charge) that the patient will be able to be discharged from the ICU on day 14. In all cases, treatment was discontinued upon discharge from the ICU.

Figure S2. Randomization curve of the 800 patients



Eight hundred patients had been randomized between October 28, 2015 and March 11, 2020.

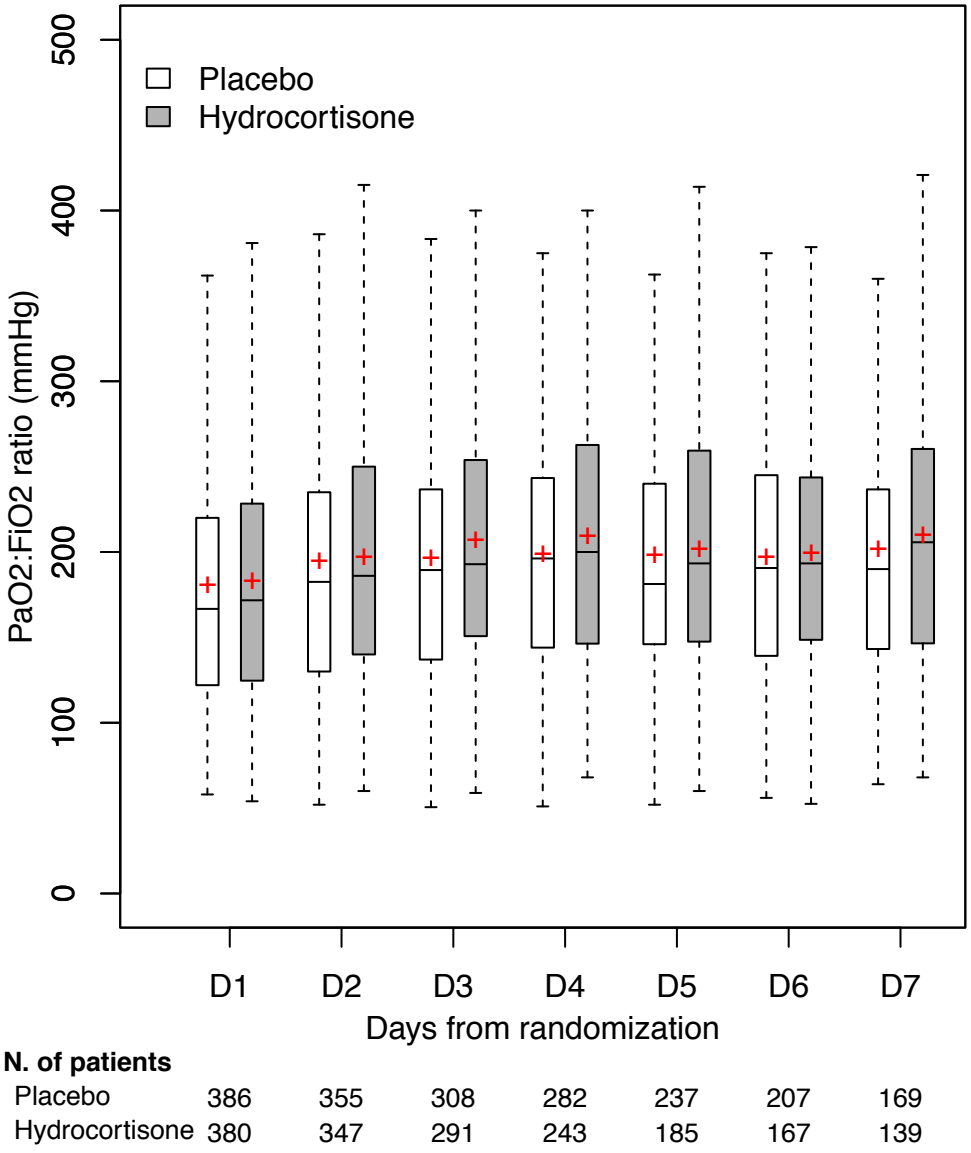
Figure S3. Mortality on day 28: Forest plot subgroup analysis.



Mortality on day 28 was analyzed in pre-specified subgroups (patients mechanically ventilated at inclusion or not; CAP with isolated germ or not) and post-hoc defined subgroups (age greater than or equal to 65 years, or not; male or female; pulmonary severity index greater than 130, or not; C-reactive protein greater than 15 mg/dL, or not). The addition of post hoc subgroups was justified: (1) for age greater than or equal to 65 years, because age is an independent prognostic factor in CAP[4], and 65 years was close to the median age of our population; (2) for gender, as recent data suggest that it may influence the response to corticosteroids in sepsis[5]; (3) for PSI, because the threshold at 130 defines a group associated with significantly higher mortality[1]; (4) for C-reactive protein and the threshold of 15 mg/dL, because some data suggest an effectiveness of corticosteroids in CAP associated with a marked inflammatory syndrome[6].

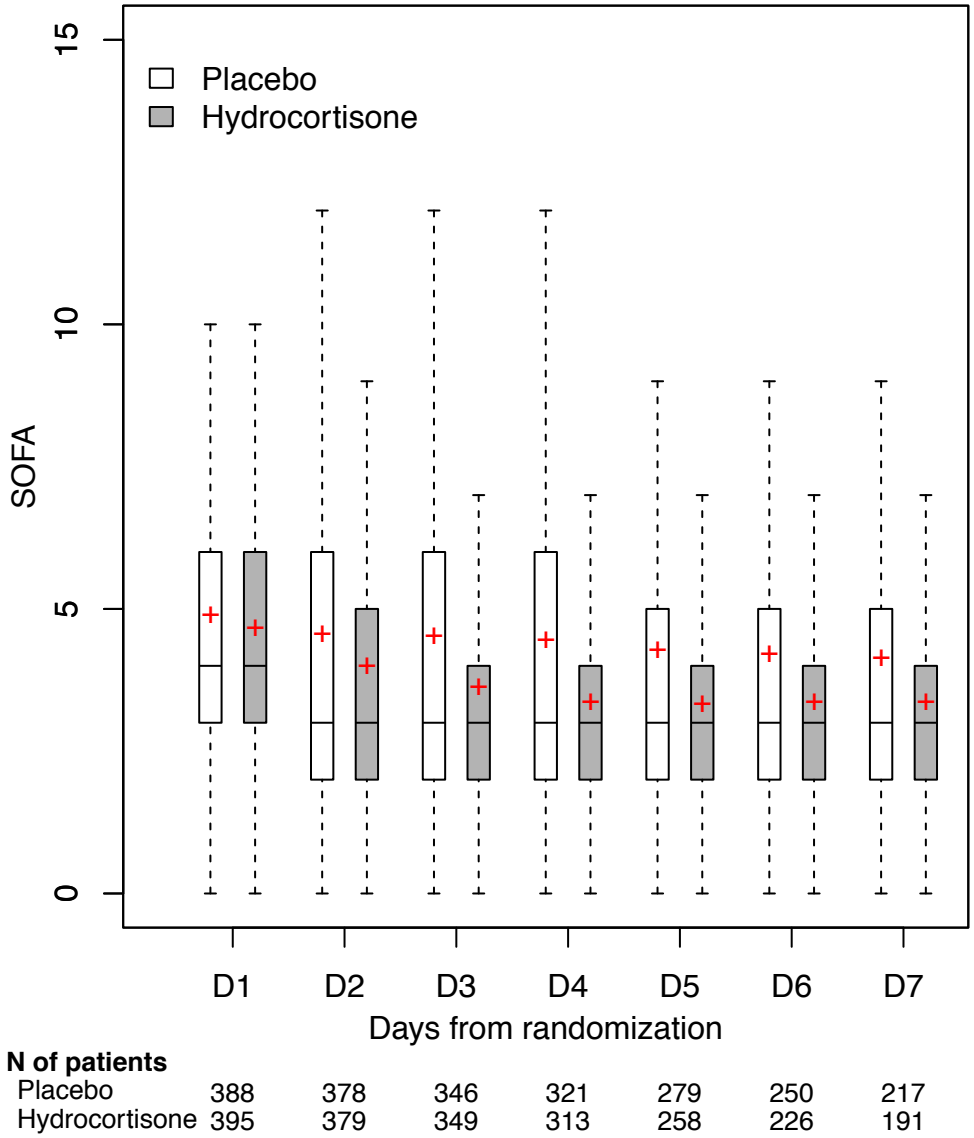
For secondary outcomes, confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Figure S4. Pa02:FiO2 ratio from day 1 to day 7.



Box height indicates IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line across and near the middle of the box is the median. The lower whisker represents the 25th percentile minus 1.5 times the IQR and the upper whisker the 75th percentile plus 1.5 times the IQR. The red cross is the mean.
The PaO2:FiO2 ratio was calculated from arterial blood gases sampled each morning. For secondary outcomes, confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

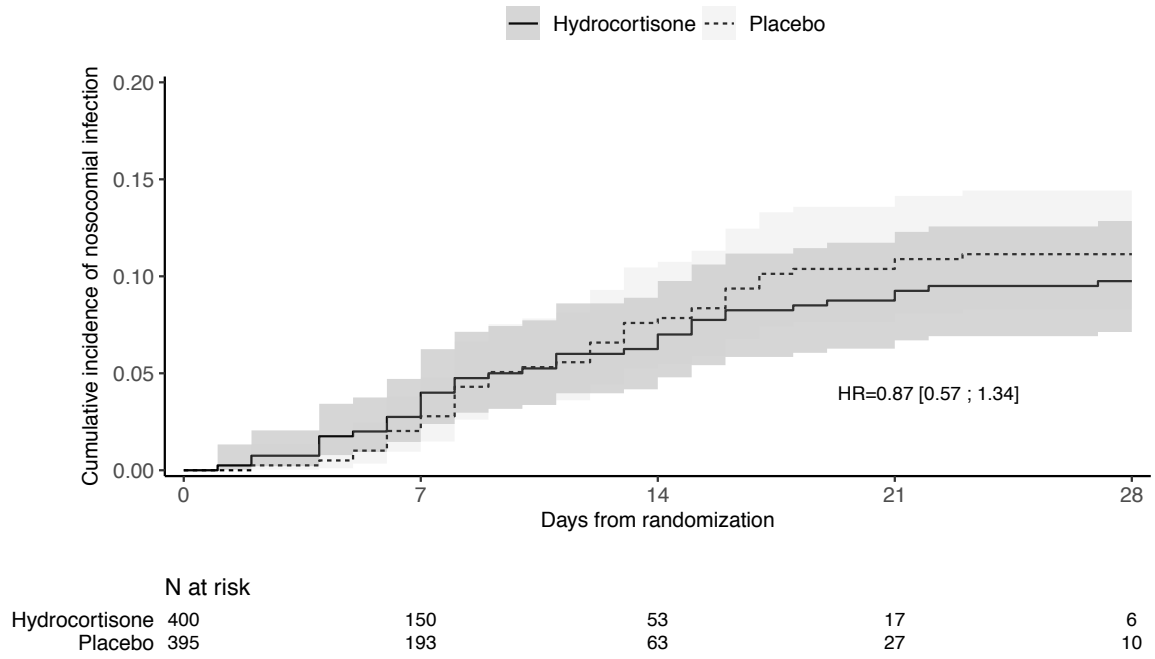
Figure S5. SOFA score from day 1 to day 7.



Box height indicates IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line across and near the middle of the box is the median. The lower whisker represents the 25th percentile minus 1.5 times the IQR and the upper whisker the 75th percentile plus 1.5 times the IQR. The red cross is the mean.

The SOFA score[2] was calculated for each 24-hour period, taking for each of the 6 physiological systems the worst value observed during the 24 hours, from 0 (no failure) to 4 (most severe failure). For secondary outcomes, confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

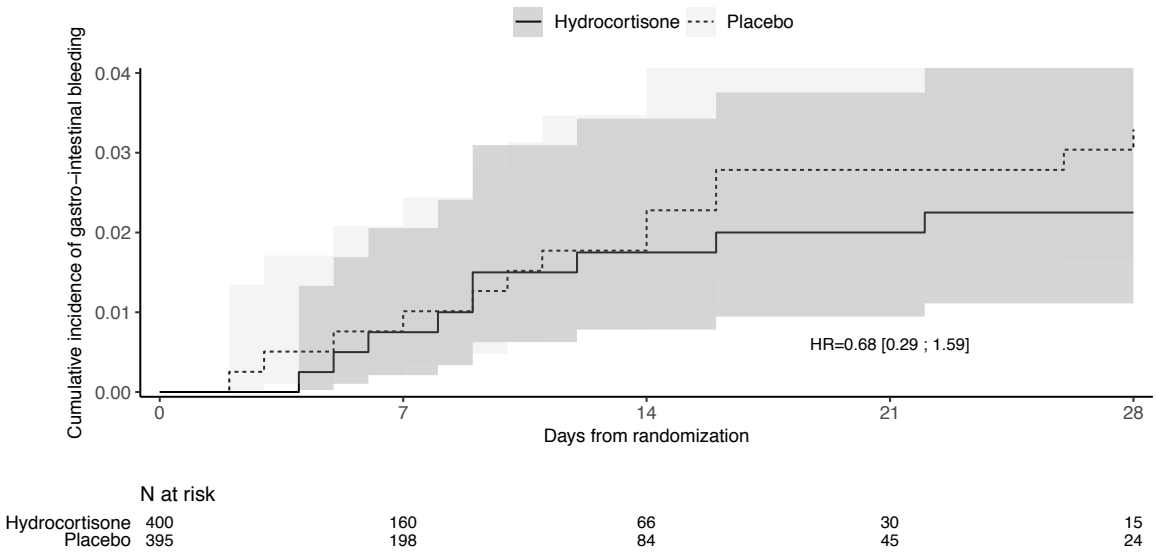
Figure S6. Cumulative incidence of hospital-acquired infections, censored on day 28.



A competing risk approach (with death and end of ICU stay as competing events) was used to compare proportions of patients experiencing ICU-acquired infection from inclusion to day 28. For secondary outcomes, confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

The diagnosis of ICU-acquired infection was based on self-reporting by the physician-in-charge and assumed that antibiotic therapy would be instituted. In particular, the diagnosis of ventilator-associated pneumonia was not adjudicated in this blinded trial.

Figure S7. Cumulative incidence of gastro-intestinal bleeding, censored on day 28.



A competing risk approach (with death and end of ICU stay as competing events) was used to compare proportions of patients experiencing gastro-intestinal bleeding from inclusion to day 28. For secondary outcomes, confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Table S1. Distribution of number of patients enrolled per site.

Centre	All	Hydrocortisone (n_1=400)	Placebo (n_2=395)
	No. death/No. (%)	No. death/No. (%)	No. death/No. (%)
AB	0/9 (0.0)	0/5 (0.0)	0/4 (0.0)
AN	1/1 (100.0)	-	1/1 (100.0)
AR	1/23 (4.3)	1/12 (8.3)	0/11 (0.0)
BB	0/8 (0.0)	0/4 (0.0)	0/4 (0.0)
BE	2/27 (7.4)	0/14 (0.0)	2/13 (15.4)
BH	3/15 (20.0)	3/7 (42.9)	0/8 (0.0)
BR	0/10 (0.0)	0/6 (0.0)	0/4 (0.0)
CA	1/7 (14.3)	0/3 (0.0)	1/4 (25.0)
CF	1/24 (4.2)	0/12 (0.0)	1/12 (8.3)
CL	3/32 (9.4)	2/17 (11.8)	1/15 (6.7)
DI	14/81 (17.3)	3/41 (7.3)	11/40 (27.5)
GA	2/24 (8.3)	1/13 (7.7)	1/11 (9.1)
GR	0/5 (0.0)	0/2 (0.0)	0/3 (0.0)
HC	13/111 (11.7)	5/55 (9.1)	8/56 (14.3)
HP	2/9 (22.2)	0/4 (0.0)	2/5 (40.0)
LG	0/17 (0.0)	0/8 (0.0)	0/9 (0.0)
LI	0/4 (0.0)	0/2 (0.0)	0/2 (0.0)
LM	1/16 (6.2)	0/9 (0.0)	1/7 (14.3)
MA	1/15 (6.7)	1/8 (12.5)	0/7 (0.0)
MO	0/11 (0.0)	0/6 (0.0)	0/5 (0.0)
MZ	0/17 (0.0)	0/9 (0.0)	0/8 (0.0)
NA	4/28 (14.3)	2/14 (14.3)	2/14 (14.3)
NY	2/17 (11.8)	0/7 (0.0)	2/10 (20.0)
OR	8/78 (10.2)	3/40 (7.5)	5/38 (13.2)
PO	0/20 (0.0)	0/11 (0.0)	0/9 (0.0)
RE	1/5 (20.0)	0/2 (0.0)	1/3 (33.3)
RY	1/23 (4.3)	0/12 (0.0)	1/11 (9.1)
SB	2/18 (11.1)	0/8 (0.0)	2/10 (20.0)
SM	0/5 (0.0)	0/3 (0.0)	0/2 (0.0)
TE	3/23 (13.0)	1/11 (9.1)	2/12 (16.7)
TO	6/93 (6.4)	3/46 (6.5)	3/47 (6.4)

Table S2. Additional characteristics of patients at baseline.

	Hydrocortisone (n_1=400)	**Placebo (n_2=395)**
BMI, median (IQR), $kg.m^{-2}$	26.9 (23.3; 31.9)	26.3 (22.6; 31.1)
Respiratory parameters		
Mechanical ventilation, No. (%)	178 (44.5)	175 (44.3)
Invasive mechanical ventilation, No. (%)	92 (23.0)	85 (21.5)
Non-invasive mechanical ventilation, No. (%)	86 (21.5)	90 (22.8)
FiO2, median (IQR), %	50 (40; 80)	50 (40; 71)
PEEP, median (IQR), cm H2O	6 (5; 8)	6 (5; 8)
PaO2:FiO2 ratio, median (IQR)	172 (118; 226)	170 (120; 228)
High-flow nasal cannula, No. (%)	169 (42.3)	162 (41.0)
FiO2, median (IQR), %	60 (50; 80)	60 (50; 80)
Flow rate, median (IQR), L/min	50 (50; 50)	50 (50; 55)
PaO2:FiO2 ratio, median (IQR)	130 (103; 166)	118 (89; 148)
Non-rebreathing mask No. (%)	53 (13.3)	58 (14.7)
Flow rate, median (IQR), L/min	8 (4; 10)	8 (4; 13)
Estimated PaO2:FiO2 ratio, median (IQR)	113 (82; 170)	137 (81; 201)
PaO2:FiO2 ratio, regardless of the type of respiratory support, median (IQR)	143 (104; 195)	137 (96; 192)
pH_a, median (IQR)	7.4 (7.4; 7.5)	7.4 (7.3; 7.5)
P_a02, median (IQR), mmHg	79 (66; 99)	77 (66; 93)
P_aCO2, median (IQR), mmHg	37 (32; 46)	38 (32; 49)
Arterial lactate, median (IQR), mmol/L n_1=371, n_2=367	1.4 (1.0; 2.2)	1.5 (1.1; 2.3)
Pathogen		
No pathogen identified, No. (%)	189 (47.2)	168 (42.5)
At least one pathogen identified, No. (%)	211 (52.7)	227 (57.5)
Streptococcus pneumoniae, No. (%)	83 (23.8)	82 (20.8)
Legionella sp., No. (%)	22 (5.5)	29 (7.3)
Staphylococcus aureus, No. (%)	16 (4.0)	24 (6.1)
Haemophilus influenzae, No. (%)	15 (3.8)	20 (5.1)
Non-pneumoniae Streptococci	13 (3.3)	12 (3.0)
Escherichia coli, No. (%)	13 (3.3)	11 (2.8)
Klebsiella pneumoniae, No. (%)	11 (2.8)	6 (1.5)
Coagulase-negative Staphylococci	11 (2.8)	4 (1.0)
Chlamydia sp., No. (%)	4 (1.0)	6 (1.5)
Pseudomonas aeruginosa	4 (1.0)	5 (1.3)
Mycoplasma pneumoniae, No. (%)	3 (0.8)	7 (1.8)

Other bacteria, No. (%)	28 (7.1)	32 (8.1)
Myxovirus influenzae, No. (%)	12 (3.0)	12 (3.0)
Rhinovirus	9 (2.3)	6 (1.5)
Respiratory syncyticial virus	5 (1.3)	6 (1.5)
Other respiratory viruses, No. (%)	13 (3.0)	4 (1.0)
Fungi and yeasts	2 (0.5)	6 (1.5)
Antibiotics administered since admission		
Third-generation cephalosporins, No. (%)	310 (77.5)	317 (80.3)
Macrolides, No. (%)	289 (72.3)	298 (75.4)
Amoxicillin, No. (%)	90 (22.5)	72 (18.2)
Amoxicillin – Clavulanic acid, No. (%)	79 (19.8)	69 (17.5)
Fluoroquinolones, No. (%)	64 (16.0)	68 (17.2)
Other antibiotics, No. (%)	120 (30.0)	135 (34.2)

Abbreviations

IQR = Inter-Quartile Range; BMI = Body-Mass Index; FiO2 = Fraction of inspired oxygen; PEEP = Positive End-Expiratory Pressure; PaO2:FiO2 = arterial pressure of oxygen on FiO2 ratio.

Notes

The pathogens identified are those considered to cause pneumonia, regardless of when they were isolated. The total percentage of pathogens isolated is greater than 100%, as several pathogens may have been isolated from the same patient. Similarly, the total percentage of antibiotics is greater than 100%, as the same patient may have received several antibiotics. Antibiotics listed are those administered to the patient at the time of inclusion in the trial.

The relatively high proportion of patients from whom *Streptococcus pneumoniae* was isolated, compared with other studies[7], may be related to a difference in vaccination coverage between different populations.

Table S3. Representativeness of study participants.

Category	
Condition under investigation	Adults with severe Community-Acquired Pneumonia (CAP) admitted to the Intensive Care Unit
Special considerations related to:	
Sex and gender	Severe CAP affects men more than women (approximatively 2:1)[6,8-10]
Age	Prevalence increases with age[11]. The median age is close to 65 years in both cohort studies[9,12] and randomized trials[6,11].
Race or ethnic group	In the USA, bacterial CAP affects black adults more than white adults (approximatively 2.5:1.0)[13]. French law strictly restricts the collection of racial/ethnic data, which was not collected in this trial.
Geography	In low-income countries, hospitalized CAP occurs mostly in working-age patients, and in sub-Saharan Africa, in HIV-positive patients[14]. There is little data on severe CAP.
Other considerations	Median Pulmonary Severity Index is close to 110-120[6,9,15]. Just under half of the patients are mechanically-ventilated[9]. At least one germ is isolated in slightly more than half of the patients[9].

Table S4. Actual duration of experimental treatment and reasons for premature stopping

	Hydrocortisone (n_1=400)	**Placebo** (n_2 =395)
Actual duration of experimental treatment, median [IQR], days	5 [3; 8]	6 [3; 8]
Premature stopping, No. (%)	318 (79,5)	298 (75,4)
Reasons for premature stopping		
Influenza diagnosed after randomization, No. (%)	12 (3.8)	12 (4.0)
Indication for open-label corticosteroid therapy, No. (%)	17 (5.3)	23 (7.7)
Withdrawal from the trial at the patient's request, No. (%)	4 (1.3)	1 (0.3)
Discharge alive from the intensive care unit, No. (%)	261 (82.1)	220 (73.8)
Death before the planned end of the experimental treatment, No. (%)	24 (7.5)	42 (14.1)

The experimental treatment was planned for a duration of 8 or 14 days, this duration being chosen at day 4 according to the improvement of the patient, on predefined criteria (see text and **Figure S1**). It was also planned that the treatment would be interrupted at discharge from the intensive care unit, even if this occurred before the theoretical deadline. The different indications for open-label corticosteroid therapy were not collected.

Table S5. Other Secondary Outcomes: ventilator- and vasopressor-free days, length of stay, and SF-36 Health Survey

	Hydrocortisone (n_1=400)	**Placebo** (n_2 =395)	**Median of differences** [95% CI]
Ventilator-free days at day 28, median [IQR], days	28.0 [23.0; 28.0]	28.0 [16.0; 28.0]	0 [0; 0]
Vasopressor-free days at day 28, median [IQR], days	28.0 [28.0; 28.0]	28.0 [26.0; 28.0]	0 [0; 0]
ICU length-of-stay, median (IQR), days			
In patients discharged alive from ICU	5.0 (3.0; 9.0)	6.0 (4.0; 11.0)	
In patients who died in ICU	15.0 (4.0; 26.0)	11.5 (4.0; 20.0)	
SF-36 Health Survey[16]			
Physical Component Score, median (IQR), n_1=201, n_2=174	41.0 [34.0; 49.0]	41.0 [34.0; 49.0]	0 [-2 ; 2]
Mental Component Score, median (IQR), n_1=201, n_2=174	52.0 [39.0; 57.0]	51.5 [41.0; 57.0]	0 [-2 ; 2]

Notes:

For the calculation of ventilator-free or vasopressor-free days on day 28, the following rules were applied: the period of interest began on the date of randomization; patients who died before day 28 were assigned a value of 0; days between two episodes of mechanical ventilation (or two episodes of vasopressor treatment) were considered; successful weaning from mechanical ventilation was defined as the persistence of spontaneous breathing 48 h after cessation of mechanical ventilation. The results relating to free days should be interpreted with caution, as the difference in mortality between the two groups makes these criteria of little relevance[17].

The SF-36[18] is a multidimensional, generic scale that assesses health status independent of causative pathology, gender, age, and treatment. The physical component score assesses limitation of physical activities; the psychic component score assesses discomfort due to psychic problems in daily activities; for each component, the higher the score, the better the quality of life.

For secondary outcomes, confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Additionally, blood samples were collected at baseline and at days 3 and 7 to compare the evolution of inflammation markers between the two groups, but their analysis is not yet available.

Table S6. Detailed reporting of adverse events.

	Hydrocortisone (n_1=400)	**Placebo** (n_2=395)
Serious adverse events, No.	70	99
Patients with at least one serious adverse event, No. (%)	63 (16.0)	88 (22.0)
Patients with hospital-acquired infections, No. (%)	39 (9.8)	44 (11.1)
Ventilator-associated pneumonia, No. (% of invasively-ventilated patients) n_1=152, n_2 =171	32 (21.0)	38 (22.2)
Bloodstream infections, No. (%)	5 (1.3)	9 (2.3)
Patients with gastro-intestinal bleeding, No. (%)	9 (2.2)	13 (3.2)
Patients with peptic ulcerations, No. (%)	6 (1.5)	3 (0.8)
Patients with stroke, No.	0	3
Patients with mesenteric ischemia, No.	0	2
Patients with acute pulmonary edema, No.	2	2
Patients with unanticipated cardiac arrest, No.	0	2
Patients with symptomatic hypokalemia, No.	2	0
Patients with miscellaneous serious adverse events, No. (%)	10	10

Percentages are not provided when a side effect was reported in less than 5 patients. The miscellaneous serious adverse events correspond to at most one patient in each group. Some patients experienced multiple adverse events.

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