Hydrocortisone plus fludrocortisone for community acquired pneumonia-related septic shock: a subgroup analysis of the APROCCHSS phase 3 randomised trial

*Nicholas Heming, Alain Renault, Emmanuelle Kuperminc, Christian Brun-Buisson, Bruno Megarbane, Jean-Pierre Quenot, Shidasp Siami, Alain Cariou, Xavier Forceville, Carole Schwebel, Marc Leone, Jean-Francois Timsit, Benoît Misset, Mohamed Ali Benali, Gwenhael Colin, Bertrand Souweine, Karim Asehnoune, Emmanuelle Mercier, Loïc Chimot, Claire Charpentier, Bruno François, Thierry Boulain, Frank Petitpas, Jean Michel Constantin, Gilles Dhonneur, François Baudin, Alain Combes, Julien Bohé, Jean-François Loriferne, Fabrice Cook, Michel Slama, Olivier Leroy, Gilles Capellier, Auguste Dargent, Tarik Hissem, Rania Bounab, Virginie Maxime, Pierre Moine, Eric Bellissant, Djillali Annane for the APROCCHSS investigators and CRICS-TRIGGERSEP network**

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*The APROCCHSS investigators and members of the CRICS-TRIGGERSEP network are listed in the appendix (p 3–7)

Department of Intensive Care, Raymond Poincaré Hospital, APHP University Versailles Saint Quentin–University Paris Saclay, Garches, France (Prof N Heming MD, E Kuperminc MD, R Bounab MD, V Maxime MD, Prof P Moine MD, Prof D Annane MD); **Institut Hospitalo Universitaire PROMETHEUS, Garches, France** (Prof N Heming, Prof P Moine, Prof D Annane); **Laboratory of Infection & Inflammation–U1173, School of Medicine, INSERM, University Versailles Saint Quentin–University Paris Saclay, Garches, France** (Prof N Heming, Prof P Moine, Prof D Annane); **FHU SEPSIS, Garches, France** (Prof N Heming, Prof P Moine, Prof D Annane); **CIC 1414 INSERM, CHU Rennes, University of Rennes, Rennes, France** (A Renault MSc, Prof E Bellissant MD); **Service de Réanimation Médicale, Hôpital Henri-Mondor (Assistance Publique-Hôpitaux de Paris [AP-HP]), Créteil, France** (Prof C Brun-Buisson MD); **Réanimation Médicale et Toxicologique, Hôpital Lariboisière (AP-HP), Université Paris-Diderot, INSERM Unité Mixte de Recherche Scientifique (UMRS) 1144, Paris, France** (Prof B Megarbane MD); **Service de Réanimation Médicale, Hôpital Universitaire François Mitterrand, Lipness Team,**

Summary

Background Glucocorticoids probably improve outcomes in patients hospitalised for community acquired pneumonia (CAP). In this a priori planned exploratory subgroup analysis of the phase 3 randomised controlled Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial, we aimed to investigate responses to hydrocortisone plus fludrocortisone between CAP and non-CAP related septic shock.

Methods APROCCHSS was a randomised controlled trial that investigated the effects of hydrocortisone plus fludrocortisone, drotrecogin-alfa (activated), or both on mortality in septic shock in a two-by-two factorial design; after drotrecogin-alfa was withdrawn on October 2011, from the market, the trial continued on two parallel groups. It was conducted in 34 centres in France. In this subgroup study, patients with CAP were a preselected subgroup for an exploratory secondary analysis of the APROCCHSS trial of hydrocortisone plus fludrocortisone in septic shock. Adults with septic shock were randomised 1:1 to receive, in a double-blind manner, a 7-day treatment with daily administration of intravenous hydrocortisone 50 mg bolus every 6h and a tablet of 50 µg of fludrocortisone via the nasogastric tube, or their placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included all-cause mortality at intensive care unit (ICU) and hospital discharge, 28-day and 180-day mortality, the number of days alive and free of vasopressors, mechanical ventilation, or organ failure, and ICU and hospital free-days to 90-days. Analysis was done in the intention-to-treat population. The trial was registered at ClinicalTrials.gov (NCT00625209).

Findings Of 1241 patients included in the APROCCHSS trial, CAP could not be ruled in or out in 31 patients, 562 had a diagnosis of CAP (279 in the placebo group and 283 in the corticosteroid group), and 648 patients did not have CAP (329 in the placebo group and 319 in the corticosteroid group). In patients with CAP, there were 109 (39%) deaths of 283 patients at day 90 with hydrocortisone plus fludrocortisone and 143 (51%) of 279 patients receiving placebo (odds ratio [OR] 0·60, 95% CI 0·43–0·83). In patients without CAP, there were 148 (46%) deaths of 319 patients at day 90 in the hydrocortisone and fludrocortisone group and 157 (48%) of 329 patients in the placebo group (OR 0·95, 95% CI 0·70–1·29). There was significant heterogeneity in corticosteroid effects on 90-day mortality across subgroups with CAP and without CAP (p=0·046 for both multiplicative and additive interaction tests; moderate credibility). Of 1241 patients included in the APROCCHSS trial, 648 (52%) had ARDS (328 in the placebo group and 320 in the corticosteroid group). There were 155 (48%) deaths of 320 patients at day 90 in the corticosteroid group and 186 (57%) of 328 patients in the placebo group. The OR for death at day 90 was 0·72 (95% CI 0·53–0·98) in patients with ARDS and 0·85 (0·61–1·20) in patients without ARDS (p=0·45 for multiplicative interaction and p=0·42 for additive interaction). The OR for observing at least one serious adverse event (corticosteroid group *vs* placebo) within 180 days post randomisation was 0·64 (95% CI 0·46–0·89) in the CAP subgroup and 1·02 (0·75–1·39) in the non-CAP subgroup (p=0·044 for multiplicative interaction and p=0·042 for additive interaction).

Interpretation In a pre-specified subgroup analysis of the APROCCHSS trial of patients with CAP and septic shock, hydrocortisone plus fludrocortisone reduced mortality as compared with placebo. Although a large proportion of patients with CAP also met criteria for ARDS, the subgroup analysis was underpowered to fully discriminate between ARDS and CAP modifying effects on mortality reduction with corticosteroids. There was no evidence of a significant treatment effect of corticosteroids in the non-CAP subgroup.

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Research in context

Evidence before this study

We systematically searched from database inception up to Dec 31, 2022 Embase, MEDLINE, Cochrane, and PubMed for randomised controlled trials (RCTs) examining corticosteroids in adults (ie, those aged 18 years or older) being treated in hospital with suspected or probable community acquired pneumonia (CAP), including severe and non-severe disease. The 2019 Official Clinical Practice Guideline of the American Thoracic Society and the Infectious Diseases Society of America did not recommend the use of corticosteroids in the management of adults with CAP. Cumulated evidence from 17 trials (3480 participants) suggested that severity of CAP variably affected patients' responses to corticosteroids (test for interaction, p=0·01) with a risk ratio of mortality of 0·55 (95% CI 0·36–0·83), in favour of corticosteroids in patients with severe pneumonia and of 1·06 (0·83–1·36) in less severe forms. These trials reported death at variable timepoints in the short-term and did not report longer outcomes. The recently published The Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) trial found a –5·6% absolute difference in 28-day mortality in adults with CAP but without septic shock.

Added value of this study

The APROCCHSS trial reported, to our knowledge, the largest subgroup of adults with CAP and septic shock. It provided evidence that the reduction in 90-day all-cause mortality with corticosteroids might be larger in patients with CAP-related septic shock than in those with non-CAP-related septic shock.

Implications of all the available evidence

Altogether previous studies, CAP COD, and this study suggest that corticosteroids might improve outcomes in adults admitted to the intensive care unit with severe CAP with or without shock. Future research should clarify the optimal corticotherapy in terms of the molecule (hydrocortisone with or without fludrocortisone, dexamethasone, or methylprednisolone), dose, and duration. The role of corticosteroids in children with CAP remains to be elucidated.

Introduction

Community acquired pneumonia (CAP) is the main form of lower respiratory tract infection and can be caused by a virus or bacteria.[1] It affects all ages and genders. It was ranked fourth in 2019 global causes of deaths and of disability-adjusted life-years.[2] Of all the patients with CAP requiring hospitalisation, 8–25% are admitted to the intensive care unit (ICU), about 8% die, and the 6-month readmission rate is up to 22% of survivors.[1,2] The total cost of hospitalised CAP has been estimated at £731 million per annum in England,[3] and adjusted mean total cost was $55 391 per hospitalisation in the USA.[4] The total health cost is almost four times greater for inpatients as compared with outpatients.[5] The 2019 American Thoracic Society and Infectious Diseases Society of America guidelines recommended standard empiric therapy with beta-lactam and macrolide combination.[6]

In CAP, severity of illness is mainly driven by exaggerated maladaptive inflammatory processes in the lung and the whole body.[1] Corticosteroids (anti-inflammatory drugs) have been investigated for the management of CAP in randomised trials as early as 1951,[7] and with a total of 17 studies of them 16 reported 313 deaths of 3480 participants with CAP.[8] Cumulated evidence from these trials[8] suggested that severity of CAP variably affected patients' responses to corticosteroids (test for interaction, p=0·01) with a risk ratio (RR) of mortality of 0·55 (95% CI 0·36–0·83), in favour of corticosteroids in patients with severe pneumonia and of 1·06 (0·83–1·36) in less severe forms (effects of treatment varied with severity of illness). The Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) trial found that in 795 adults with severe CAP but without shock, compared with placebo, intravenous hydrocortisone reduced 28-day all-cause mortality (absolute difference –5·6% (–9·6 to –1·7; p=0·0055), reduced the cumulative incidence of intubation (hazard ratio [HR] 0·59, 95% CI 0·40 to 0·86), and reduced the need for vasopressor therapy (HR 0·59, 95% CI 0·43 to 0·82).[9] The APROCCHSS trial, completed in December, 2015, and reported in January, 2018, showed that in adults with septic shock 7 days of treatment with hydrocortisone plus fludrocortisone reduced all-cause mortality by 6% compared with placebo in adults with septic shock.[10] In this trial, septic shock was secondary to CAP in almost one out of two patients. The randomisation was not stratified on the basis of a diagnosis of CAP-related septic shock. The aim of the a priori planned exploratory subgroup analysis of the APROCCHSS trial was to investigate any difference in responses to hydrocortisone plus fludrocortisone between CAP-related septic shock and non-CAP-related septic shock.

Methods

Study design

APROCCHSS was a phase 3 randomised controlled trial that investigated the effects of hydrocortisone plus fludrocortisone, drotrecogin-alfa (activated), or both on mortality in septic shock in a two-by-two factorial design. It was conducted in 34 centres in France. After drotrecogin-alfa was withdrawn from the market on October 2011, the trial continued with two parallel groups. The design and protocol of the APROCCHSS trial (NCT00625209) have been previously reported.[11] The study protocol included three a priori defined exploratory subgroup analyses, ie, according to adrenal status

INSERM Research Center Lipids, Nutrition, Cancer-Unité Mixte de Recherche (UMR) 1231, Dijon, France (Prof J-P Quenot MD, A Dargent MD); **Laboratoire d'Excellence LipSTIC and CIC 1432, Epidémiologie Clinique, Université de Burgundy, Dijon, France** (Prof J-P Quenot, A Dargent); **Service d'Anesthésie-Réanimation, Centre Hospitalier d'Etampes, Etampes, France** (S Siami MD, T Hissem MD); **Réanimation Médicale-Hôpitaux Universitaires Paris Centre-Site Cochin (AP-HP), Paris, France** (Prof A Cariou MD); **CIC INSERM 1414, Réanimation Médico-Chirurgicale, Hôpital Saint Faron, Grand Hôpital de l'Est Francilien Site de Meaux, Meaux, France** (X Forceville MD); **Service de Réanimation Médicale, CHU de Grenoble, Grenoble, France** (Prof C Schwebel MD); **Service d'Anesthésie et de Réanimation, Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Aix Marseille Université, CIC 1409 and CIC 9502, Marseille, France** (Prof M Leone MD); **Médecine Intensive et Réanimation, Pôle 2i, Infection et Immunité, Hôpital Bichat-Claude Bernard, AP-HP, Infection, Antimicrobiens, Modélisation, Evolution (IAME) Unité 1137, Université Paris Diderot, INSERM, Paris, France** (Prof J-F Timsit MD); **Service des Soins Intensifs, CHU Liège, Liège, Belgium** (Prof B Misset MD); **Service de Réanimation Polyvalente, Centre Hospitalier de Valenciennes, Valenciennes, France** (M A Benali MD); **Service de Réanimation Médico-Chirurgicale, Centre Hospitalier Départemental de Vendée, Site de La Roche-sur-Yon, La Roche-sur-Yon, France** (G Colin MD); **Réanimation Médicale Polyvalente, CHU Gabriel Montpied, Clermont-Ferrand, France** (Prof B Souweine MD); **Laboratoire EA3826 Thérapeutiques et Expérimentales des Infections, Service d'Anesthésie, Réanimation Chirurgicale, Hôtel Dieu-Hôpital Mère-Enfant, CHU Nantes, Nantes, France** (Prof K Asehnoune MD); **Réanimation Polyvalente, Centre Hospitalier Régional Universitaire Bretonneau,**

Tours, France (E Mercier MD); Service d'Anesthésie-Réanimation, Centre Hospitalier de Périgueux, Périgueux, France (L Chimot MD); Service de Réanimation Chirurgicale, Hôpital Central, CHU de Nancy, Nancy, France (C Charpentier MD); Service de Réanimation Polyvalente, INSERM CIC 1435, CHU Dupuytren, Limoges, France (B François MD); Service Réanimation Médicale Polyvalente et Unité de Surveillance Continue, Centre Hospitalier Régional d'Orléans, Orléans, France (T Boulain MD); Réanimation Chirurgicale, Département d'Anesthésie-Réanimations-Urgences, Service d'Assistance Médicale d'Urgence (SAMU) 86, Hôpital de la Miletrie, CHU, Poitiers, France (F Petitpas MD); Department of Anaesthesiology and Critical Care, Pitié-Salpêtrière Hospital, GRC 29, DMU DREAM, AP-HP, Paris, France (Prof J M Constantin MD); Sorbonne University, Paris, France (Prof J M Constantin); Department of Anaesthesia and Intensive Care, Curie Institute, Paris, France (Prof G Dhonneur MD); Service d'Anesthésie et Réanimations Chirurgicales, Hôpitaux Universitaires Paris Centre-Site Cochin (AP-HP), Paris, France (F Baudin MD); Service de Réanimation Médicale, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France (Prof A Combes MD); INSERM, UMRS 1166-Institute of Cardiometabolism and Nutrition, Université Paris Sorbonne, Paris, France (Prof A Combes); Service de Réanimation Médicale, Centre Hospitalier Lyon-Sud (Hospices Civils de Lyon), Pierre-Bénite, France (Prof J Bohé MD); Service d'Anesthésie-Réanimation, Hôpital Saint Camille, Bry-sur-Marne, France (J-F Loriferne MD); Service d'Anesthésie et des Réanimations Chirurgicales, Hôpital Henri-Mondor (Assistance Publique-Hôpitaux de Paris [AP-HP]), Créteil, France (F Cook MD); Service de Réanimation Médicale, CHU Amiens-Picardie-Site Sud, Amiens, France (Prof M Slama MD); Service de Réanimation Médicale et Maladies Infectieuses, Centre

(responders or non-responders to a Synacthen test), patients with or without CAP, and patients with or without acute respiratory distress syndrome (ARDS); here we report on the outcomes for the CAP and ARDS subgroups. The adrenal status is reported elsewhere.[10] The trial was approved by an independent ethics committee (Comité de Protection des Personnes d'Ile de France XI, Saint-Germain-en-Laye, France).

Study participants

Adults (ie, those 18 years or older) with probable or documented septic shock[12] for less than 24 h were eligible for inclusion in the trial. Septic shock was defined by the presence of a clinically or microbiologically documented infection, a Sequential Organ Failure Assessment (SOFA)[13] score of three or four (on a scale of zero to four for each of six organ systems, with higher scores indicating more severe organ dysfunction) for at least two organs and at least 6 h, and the need for vasopressor therapy for at least 6 h to maintain a systolic blood pressure of at least 90 mm Hg or a mean blood pressure of at least 65 mm Hg. Exclusion criteria were pregnancy or lactation, underlying conditions that could affect short-term survival, or previous treatment with corticosteroids. A full list of inclusion and exclusion criteria can be found in the protocol.[11]

Community acquired pneumonia subgroup

CAP was defined as evidence for pneumonia acquired outside a health-care facility in a patient free of hospital stays for the preceding year and not living in long-term care facility. Pneumonia was defined by the presence of fever higher than 38°C, a cough, mucopurulent sputum, pleuritic chest pain, dyspnoea, new focal chest signs on examination such as crackles or bronchial breathing, and lobar consolidations, interstitial infiltrates, or cavitation.

Acute respiratory distress syndrome subgroup

ARDS was defined as symptoms occurring or worsening within 1 week of a new or known clinical insult, bilateral opacities on chest imaging—not fully explained by effusions, lobar or lung collapse, or nodules, respiratory failure not fully explained by cardiac failure or fluid overload, and PaO_2 or FiO_2 of 300 mm Hg or less with positive end-expiratory pressure or continuous positive airway pressure of 5 cm or more H_2O.[14]

Sex and gender were self-reported by study participants with as options male or female and man or woman, respectively. Written informed consent was provided by the patient or the next of kin, in which case deferred written informed consent was obtained as soon as possible.

Randomisation and study treatments

Patients were randomly assigned (1:1) to receive hydrocortisone plus fludrocortisone, or their respective placebos. An independent statistician provided a randomisation list generated by a computer, using a permutation block of four and an online system enabling allocation concealment. At each site, trial investigators screened and enrolled patients and study nurses delivered trial medication to the patients. Randomisation was not stratified on the basis of the predefined subgroups of interest. Hydrocortisone was administered as 50 mg intravenous bolus every 6 h, and fludrocortisone was given as a 50 µg tablet through a nasogastric tube, once daily. Placebos of French commercial forms of hydrocortisone and fludrocortisone were manufactured for the requirements of the trial. Active and placebo drugs had similar aspects (checked and certified by qualified people for each batch), ie, vials of white, freeze dried powder for parenteral use of hydrocortisone hemisuccinate 100 mg or placebo, and tablets for oral fludrocortisone 50 µg or placebo in blisters of ten. Trial agents were administered for 7 days without tapering. Participants, health-care staff, investigators, pharmacists, statisticians, and the sponsor remained blinded up to the final closure of the database and final analysis.

Variables

We recorded the following variables at inclusion: age, sex and gender, McCabe classification,[15] pathogens responsible for the infection, Simplified Acute Physiology (SAPS) II,[16] SOFA score,[13] and lactate levels.

Outcomes

The primary outcome was 90-day all-cause mortality. Secondary outcomes were all-cause mortality at ICU and hospital discharge, and at day 28 and day 180, as well as the number of vasopressor-free days, ventilator-free days, organ failure-free days, ICU-free days, hospital-free days up to 90 days, and the decision to withhold or withdraw active treatment by day-90. All outcomes are reported in this Article and were all prespecified.

Safety was assessed by daily screening for serious adverse events including serious bleeding events, secondary infections, new sepsis and septic shock, hyperglycaemic episodes, and neuromuscular weakness up to 180 days. Adverse events were recorded according to the MEDDRA classification.

We assessed the credibility of effect modification analyses on all-cause 90-day mortality using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN).[17]

Statistical analysis

For the primary analysis of the primary outcome, we anticipated a 90-day mortality rate of 45% among patients with septic shock.[11] According to the 2×2 factorial design with a two-sided formulation, 320 patients were needed in each group (ie, a total of 1280 patients) to detect an absolute reduction of 10% in the 90-day mortality rate (a=0·05 and power at 95%)

with either drotrecogin alfa or corticosteroids. We did not compute specific sample sizes for the three subgroups of interest. An intention-to-treat analysis was performed. Continuous variables are presented as means and SDs. Categorical variables are presented as the number of patients in each category and the corresponding percentages. Missing data were not replaced. The frequency of fatal events (mortality at day 28, at day 90, at discharge from the ICU or hospital, and at day 180) and safety outcomes were presented with odds ratios (OR) and their 95% CIs. Interaction between subgroups, ie, CAP versus without CAP, and ARDS versus without ARDS, was assessed using logistic regression with cross-product to compare OR (multiplicative interaction) and generalised linear binomial model to compare risk difference (additive interaction). For continuous variables, interaction between subgroups was assessed using generalised linear model to compare means difference (vasopressor-free days, organ failure-free days, ventilator-free days, and number of days with hyperglycaemia). Cumulative event curves (censored endpoints) were estimated with the Kaplan–Meier method. Interaction between subgroups was assessed using the Cox model with cross-product to compare hazard ratios (overall survival up to 90 days). According to European Medical Agency guidelines, since investigations of effects of treatments across subgroups mainly serve as an indicator for the need to initiate further exploration, adjustment would be counter-intuitive and is not recommended (a p value of <0·05 will be considered significant). All analyses were conducted with SAS statistical software (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 1241 patients enrolled from Sept 2, 2008, to June 23, 2015, CAP could not be ruled in or out in 31 patients, and was the main cause of septic shock in 562 patients. The subgroup analysis therefore comprised a total of 1210 patients (562 with CAP [279 in the placebo group and 283 in the corticosteroid group] and 648 without CAP [329 in the placebo group and 319 in the corticosteroid group]; appendix p 12). The mean age was 66 years (SD 15; 65 years [14] in the hydrocortisone plus fludrocortisone group and 66 years [15] in the placebo group). There were 806 (67%) of 1210 males (395 [66%] of 602 in the hydrocortisone plus fludrocortisone group and 411 [68%] of 608 in the placebo group). There was no evidence of a clinically meaningful difference between patients with CAP (table 1) and without CAP (appendix p 14), with regard to severity of illness scores, arterial lactate levels, documented pathogens, and use of vasopressor therapy. As compared with patients without CAP, patients with CAP had a numerically lower ratio of arterial oxygen tension to fraction of inspired oxygen, a greater proportion received invasive mechanical ventilation. In the subset of patients with CAP there was no clinically relevant imbalance between treatment groups (table 1). The most frequent causal pathogens were *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Haemophilus influenzae* (table 1; appendix p 14).

In patients with CAP, death from any cause at day 90 occurred in 109 (39%) of 283 in the hydrocortisone plus fludrocortisone group and in 143 (51%) of 279 in the placebo group (OR 0·60, 95% CI 0·43–0·83; moderate credibility; table 2; figures 1, 2). In patients without CAP, death from any cause at day 90 occurred in 148 (46%) of 319 patients in the hydrocortisone and fludrocortisone group and in 157 (48%) of 329 in the placebo group (OR 0·95, 95% CI 0·70–1·29; table 2; figure 1; appendix pp 13, 16–17). There was a significant statistical heterogeneity in corticosteroids effects on 90-day mortality across subgroups with or without CAP (p=0·046, for both multiplicative and additive interaction). After adjustment for baseline covariates imbalances there were still statistically differential corticosteroids effects on mortality reduction between CAP and non-CAP subgroups by both multiplicative (p=0·042) and additive (p=0·041) interaction modelling (table 2). Excluding patients who met ARDS criteria at baseline, the OR for 90-day all-cause mortality was 0·58 (95% CI 0·33–1·03) in the CAP subgroup and 1·02 (0·66–1·57) in non-CAP subgroup, (p=0·124 for multiplicative interaction and p=0·130, for additive interaction). Effects of treatment are reported by age and sex in the appendix (p 18). ICEMAN evaluation of subgroup effects suggested moderate credibility (appendix p 19).

In additional subgroup analysis, in patients with ARDS, mortality at day 90 occurred in 155 (48%) deaths of 320 in the corticosteroid group and 186 (57%) of 328 in the placebo group, and in patients without ARDS mortality at day 90 occurred in 105 (36%) of 290 in the corticosteroid group and in 115 (40%) of 288 in the placebo group (appendix p 18). The OR for death at day 90 was 0·72 (95% CI 0·53–0·98) for patients with ARDS and 0·85 (0·61–1·20) in patients without ARDS (p=0·45 for multiplicative interaction and 0·42 for additive interaction; appendix p 19).

In patients with CAP, as compared with placebo, there were fewer deaths in patients treated with hydrocortisone plus fludrocortisone at day 28 (85 [30%] of 283 *vs* 115 [41%] of 279; OR 0·61 [95% CI 0·43–0·87]), at ICU discharge (94 [33%] *vs* 122 [44%]; 0·64 [0·46–0·90]), at hospital discharge (100 [35%] *vs* 131 [47%]; 0·62 [0·44–0·87]), and at day 180 (117 [42%] of 281 *vs* 152 [55%] of 278; 0·59 [0·42–0·83]; table 2). There were numerically higher numbers of vasopressor-free days (mean 56 days

Hospitalier Tourcoing Gustave Dron, Tourcoing, France (O Leroy MD)**; Service de Réanimation Médicale-SAMU 25, Hôpital Jean Minjoz-CHU de Besançon, Besançon, France** (Prof G Capellier MD)

Correspondence to: Prof Djillali Annane, Department of Intensive Care, Raymond Poincaré Hospital, APHP University Versailles Saint Quentin–University Paris Saclay, Garches 92380, France
djillali.annane@aphp.fr

See **Online** for appendix

	Placebo (n=279)	Hydrocortisone plus fludrocortisone (n=283)	All patients (n=562)	p values
Sex				0·70
Female	86 (31%)	83 (29%)	169 (30%)	..
Male	193 (69%)	200 (71%)	393 (70%)	..
Age, years	65 (15)	64 (14)	65 (15)	0·29
Body weight, kg	73 (18)	73 (18)	73 (18)	0·94
Simplified Acute Physiology Score II*	56 (18)	56 (19)	56 (19)	0·85
Sequential Organ Failure Assessment score†	12 (3)	12 (3)	12 (3)	0·33
Temperature, °C	37·4 (1·7); n=278 (1)‡	37·1 (1·9); n=282 (1)‡	37·3 (1·8); n=560 (2)‡	0·024
PaO_2:FiO_2, mm Hg	176·5 (91·0); n=247 (32)‡	179·8 (97·6); n=261 (22)‡	178·2 (94·4); n=508 (54)‡	0·69
Lactate levels, mmol/L	4·33 (5·43); n=272 (7)‡	4·06 (5·52); n=277 (6)‡	4·19 (5·47); n=549 (13)‡	0·32
Time from onset of infection to hospital admission, days	0·4 (1·6); [0; 0; 1]	0·4 (0·7); [0; 0; 1]	0·4 (1·3); [0; 0; 1]	0·78
Time from onset of infection to initiation of antibiotics, days	0·1 (5·4); n=278 (1)‡ [0; 0; 0]	0·3 (1·1); n=281 (2)‡ [0; 0; 0]	0·2 (3·9); n=559 (3)‡ [0; 0; 0]	0·66
Adequate antimicrobial therapy, yes	277 (99%)	280 (99%)	557 (99%)	1·00
Positive blood cultures	92 (33%)	101 (36%)	193 (34%)	0·50
Documented pathogens	195 (70%)	208 (73%)	403 (72%)	0·34
Streptococcus pneumoniae	41 (15%)	61 (22%)	102 (18%)	0·035
Other streptococci	20 (7%)	23 (8%)	43 (8%)	0·67
Staphylococcus aureus	45 (16%)	32 (11%)	77 (14%)	0·10
Other gram positive	30 (11%)	28 (10%)	58 (10%)	0·74
Escherichia coli	36 (13%)	24 (8%)	60 (11%)	0·09
Klebsiella pneumoniae	15 (5%)	21 (7%)	36 (6%)	0·32
Haemophilus influenzae	14 (5%)	17 (6%)	31 (6%)	0·61
Pseudomonas aeruginosa	13 (5%)	15 (5%)	28 (5%)	0·73
Other gram negative	50 (18%)	50 (18%)	100 (18%)	0·94
Virus	9 (3%)	17 (6%)	26 (5%)	0·12
Crystalloids' administration	..	..	..	0·57
Yes	136/264§ (52%)	134/273§ (49%)	270/537§ (50%)	..
No	128/264§ (48%)	139/273§ (51%)	267/537§ (50%)	..
Crystalloids, mL	1594 (1277); n=136 (0); [500; 1000; 2000]	1299 (1016); n=134 (0); [500; 1000; 1500]	1448 (1162); n=270 (0); [500; 1000; 2000]	0·036
Colloids administration	..	..	..	0·30
Yes	53/263§ (20%)	45/270§ (17%)	98/533§ (18%)	..
Colloids, mL	672 (628); n=53 (0); [250; 500; 1000]	739 (723); n=45 (0); [200; 500; 1000]	703 (671); n=98 (0); [200; 500; 1000]	0·62
Vasopressors administration				
Epinephrine	..	..	..	..
Number of patients	33	29	62	..
Dose, µg/kg/min	1·30 (1·68)	1·72 (1·82)	1·50 (1·75)	0·36
Norepinephrine	..	..	..	..
Number of patients	240	244	484	..
Dose, µg/kg/min	1·14 (1·75)	1·02 (1·58)	1·08 (1·67)	0·46
Mechanical ventilation	266/277§ (96%)	273 (96%)	539/560§ (96%)	0·79
Renal replacement therapy	62/264§ (23%)	57/276§ (21%)	119/540§ (22%)	0·43

Data are n (%), n/N (%), mean (SD), [1st quartile; median; 3rd quartile]. *The Simplified Acute Physiology Score II ranges from 0 to 163, with high scores indicating greater severity of illness than low scores. †Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with high scores indicating greater severity of illness than low scores. ‡Values between brackets indicate missing values. §When the denominator is different from the column heading denominator this indicates missing data.

Table 1: **Baseline characteristics of the patients with community acquired pneumonia**

[SD 39] *vs* 45 days [40]), organ failure-free days (53 days [39] *vs* 42 days [39]), ventilator-free days (46 days [38] *vs* 38 days [38]), and more ICU-free days (44 days [37] *vs* 35 days [37]), and hospital-free days (34 days [33] *vs* 27 days [32]) with hydrocortisone plus fludrocortisone compared with placebo but differences were not

	Patients with community acquired pneumonia			Patients without community acquired pneumonia			p value for multiplicative interaction	p value for additive interaction
	Placebo (n=279)	Hydrocortisone plus fludrocortisone (n=283)	Odds ratio (95% CI)	Placebo (n=329)	Hydrocortisone plus fludrocortisone (n=319)	Odds ratio (95% CI)		
Primary outcome: deaths from any cause at day 90								
Primary analysis	143 (51%)	109 (39%)	0·60 (0·43–0·83)	157 (48%)	148 (46%)	0·95 (0·70–1·29)	0·046	0·046
Adjusted analysis on covariates imbalances	..	..	..	..	..	..	0·042	0·041
Sensitivity analysis, excluding ARDS	43/106 (41%)	31/109 (28%)	0·58 (0·33–1·03)	68/174 (39%)	68/172 (40%)	1·02 (0·66–1·57)	0·124	0·130
Secondary outcomes								
Death from any cause	..	..	..	..	..	..	..	..
At day 28	115 (41%)	85 (30%)	0·61 (0·43–0·87)	122 (37%)	116 (36%)	0·97 (0·70–1·34)	0·057	0·058
At day 180	152/278 (55%)	117/281 (42%)	0·59 (0·42–0·83)	167/328 (51%)	161/318 (51%)	0·99 (0·73–1·35)	0·027	0·027
At intensive care unit discharge	122 (44%)	94 (33%)	0·64 (0·46–0·90)	128 (39%)	117/318 (37%)	0·91 (0·67–1·26)	0·135	0·133
At hospital discharge	131 (47%)	100 (35%)	0·62 (0·44–0·87)	145 (44%)	133/318 (42%)	0·91 (0·67–1·25)	0·096	0·098
Decision to withhold or withdraw active treatment by day 90	30 (11%)	21 (7%)	0·67 (0·37–1·19)	28 (9%)	42 (13%)	1·63 (0·98–2·70)	0·023	0·020
Vasopressor-free days to day 90,† n=; mean (SD); median (IQR)	n=272 (7);* 45 (40); 42 (1–87)	n=276 (7);* 56 (39); 84 (7–88)	..	n=326 (3);* 49 (40); 73 (1–88)	n=315 (4);* 52 (40); 81 (5–88)	..	..	0·088
Ventilator-free days to day 90,† n=; mean (SD); median (IQR)	n=274 (5);* 38 (38); 23 (0–80)	n=278 (5);* 46 (38); 67 (0–83)	..	n=327 (2);* 43 (40); 49 (0–84)	n=317 (2);* 45 (39); 53 (0–84)	..	..	0·108
Organ failure-free days to day 90,† n=; mean (SD); median (IQR)	n=272 (7);* 42 (39); 27 (0–84)	n=278 (5);* 53 (39); 77 (1–87)	..	n=325 (4);* 47 (40); 64 (0–86)	n=317 (2);* 49 (40); 77 (0–86)	..	..	0·057
Intensive care unit-free days to day 90,† n=; mean (SD); median (IQR)	n=278 (1);* 35 (37); 17 (0–76)	n=283 (0);* 44 (37); 61 (0–79)	..	n=329 (0);* 41 (38); 45 (0–81)	n=318 (1);* 41 (38); 52 (0–80)	..	..	0·073
Hospital-free days to day 90,† n=; mean (SD); median (IQR)	n=278 (1);* 27 (32); 0 (0–61)	n=283 (0);* 34 (33); 32 (0–68)	..	n=329 (0);* 31 (34); 10 (0–68)	n=318 (1);* 29 (32); 5 (0–63)	..	..	0·010

Data are n (%) or n/N (%) unless otherwise stated. *Values in brackets indicate missing values. †Patients who died before day-90 were assigned zero free days.

Table 2: **Primary and secondary outcomes in patients with and without community acquired pneumonia-related sepsis**

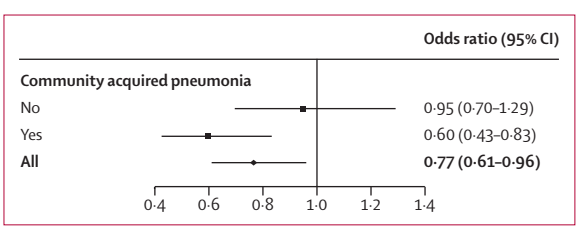

Figure 1: **Forest plot of corticosteroid effects across subgroups with or without community acquired pneumonia**
Odds ratio and 95% CI for 90-day all-cause mortality in the whole population and in the subgroups with or without community acquired pneumonia. There was a significant statistical heterogeneity in corticosteroid effects on 90-day mortality across subgroups with or without community acquired pneumonia (multiplicative interaction p=0·046 and additive interaction p=0·046).

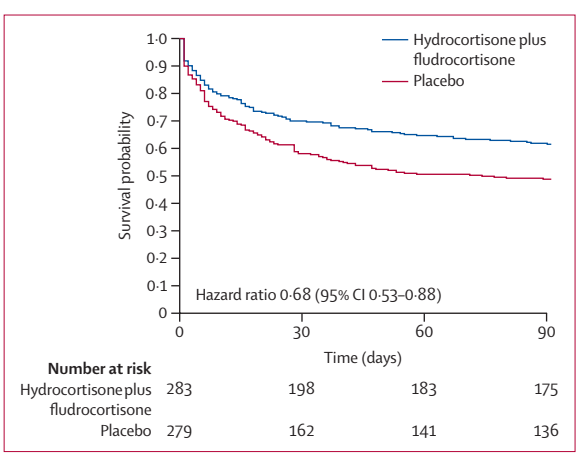

Figure 2: **90-day survival distributions**
In patients with community acquired pneumonia. Survival curves from randomisation up to 90 days. Hydrocortisone and fludrocortisone therapy (blue line) versus placebo (red line). Interaction test, p=0·061. Only interaction tests are presented in this Article.

statistically significant (table 2). Differential corticosteroids effects on secondary outcomes in CAP and non-CAP subgroups are reported in table 2. The OR for observing at least one serious adverse event (corticosteroid group *vs* placebo group) within 180 days post randomisation was 0·64 (95% CI 0·46–0·89) in the CAP subgroup and 1·02 (0·75–1·39) in the non-CAP subgroup (p=0·044 for multiplicative interaction and p=0·042 for additive interaction; table 3). A description of serious adverse events in the CAP subgroup and non-CAP subgroup as per MEDDRA classification is provided in the appendix (pp 24–42).

	Patients with community acquired pneumonia			Patients without community acquired pneumonia			p for multiplicative interaction	p for additive interaction
	Placebo (n=279)	Hydrocortisone plus fludrocortisone (n=283)	Odds ratio (95% CI)	Placebo (n=329)	Hydrocortisone plus fludrocortisone (n=319)	Odds ratio (95% CI)		
≥1 serious adverse event by day 180	167 (60%)	138 (49%)	0·64 (0·46–0·89)	185 (56%)	181 (57%)	1·02 (0·75–1·39)	0·044	0·042
≥1 serious bleeding event by day 28	54 (19%)	54 (19%)	0·98 (0·65–1·50)	58 (18%)	71 (22%)	1·34 (0·91–1·97)	0·290	0·284
Gastroduodenal bleeding	20 (7%)	12 (4%)	0·57 (0·28–1·20)	21 (6%)	25 (8%)	1·25 (0·68–2·28)	0·109	0·119
≥1 episode of superinfection by day 180	94 (34%)	101 (36%)	1·09 (0·77–1·55)	77 (23%)	88 (28%)	1·25 (0·88–1·78)	0·602	0·679
Site of superinfection								
Lung	68 (24%)	69 (24%)	1·00 (0·68–1·47)	44 (13%)	57 (18%)	1·41 (0·92–2·16)	0·243	0·330
Blood	28 (10%)	24 (8%)	0·83 (0·47–1·47)	18 (5%)	25 (8%)	1·47 (0·79–2·75)	0·188	0·211
Catheter-related	18 (6%)	23 (8%)	1·28 (0·68–2·43)	17 (5%)	17 (5%)	1·03 (0·52–2·06)	0·653	0·590
Urinary tract	15 (5%)	21 (7%)	1·41 (0·71–2·80)	16 (5%)	19 (6%)	1·24 (0·63–2·45)	0·793	0·727
Other	24 (9%)	42 (15%)	1·85 (1·09–3·15)	29 (9%)	27 (8%)	0·96 (0·55–1·66)	0·090	0·059
New sepsis	64 (23%)	71 (25%)	1·13 (0·76–1·66)	52 (16%)	61 (19%)	1·26 (0·84–1·89)	0·695	0·803
New septic shock	55 (20%)	55 (19%)	0·98 (0·65–1·49)	44 (13%)	53 (17%)	1·29 (0·84–1·99)	0·374	0·420
Hyperglycaemia								
≥1 episode of blood glucose levels of ≥150 mg/dl by day 7	234 (84%)	260 (92%)	2·17 (1·28–3·70)	272 (83%)	280 (88%)	1·51 (0·97–2·34)	0·296	0·457
Number of days with ≥1 episode of blood glucose levels of ≥150 mg/dl by day 7, mean (SD); median (IQR)	3·6 (2·5); 4 (1–6)	4·6 (2·4); 6 (3–7)	..	3·2 (2·5); 3 (1–6)	4·1 (2·5); 4 (2–6)	..	..	0·529
Neurologic sequelae by day 28*								
Last Muscular Disability Rating Scale score of >1	58 (21%)	78 (28%)	1·45 (0·98–2·14)	70 (21%)	75 (24%)	1·14 (0·79–1·65)	0·375	0·351
Last Muscular Disability Rating Scale score of >3	43 (15%)	58 (20%)	1·42 (0·92–2·19)	49 (15%)	50 (16%)	1·06 (0·69–1·63)	0·357	0·316
Last Muscular Disability Rating Scale score of 5	35 (13%)	38 (13%)	1·08 (0·66–1·77)	30 (9%)	35 (11%)	1·23 (0·74–2·05)	0·726	0·793

Data are n (%) unless otherwise stated. *Neurologic sequelae were assessed according to the score on the Muscular Disability Rating Scale (MDRS), with a score of 1 indicating no deficit, 2 minor deficits with no functional disability, 3 distal motor deficit, 4 mild-to-moderate proximal motor deficit, and 5 severe proximal motor deficits.

Table 3: **Adverse events**

Discussion

This exploratory subgroup analysis of the APROCCHSS trial found a statistically significant interaction between corticosteroids effect on 90-day all-cause mortality and CAP as the main cause of septic shock. In CAP-related septic shock, hydrocortisone plus fludrocortisone reduced 90-day all-cause mortality, ICU and in-hospital mortality, and mortality at day 28 and day 180. With hydrocortisone plus fludrocortisone there were numerically higher numbers of days alive and off vasopressors and mechanical ventilation, and free of organ dysfunctions, and out of the ICU and out of hospital. These corticosteroid treatments were not associated with serious adverse events, relative to placebo, except increased risk of hyperglycaemic episodes (table 3). In patients with non-CAP-related septic shock, the possible protective effects of corticosteroids might be less pronounced.

Of the three a priori planned subgroups, ie, responders or non-responders to ACTH test,[10] with or without CAP, and with or without ARDS, a significant interaction was found only for the CAP subgroup with evidence that the effects of corticosteroids on 90-day mortality were significantly different in patients with CAP-related septic shock versus without CAP-related septic shock in analyses for both multiplicative and additive interactions. There was no qualitative interaction suggesting that corticosteroids had protective effects in both groups. In patients with ARDS, corticosteroids could reduce 90-day mortality. Even though, the magnitude of corticosteroid effects on 90-day mortality was numerically greater in patients with ARDS than in those without ARDS, there was no significant interaction.

The credibility of the CAP subgroup analysis was judged moderate according to ICEMAN.[17] This effect modification analysis was a priori defined and reported.[12] We limited the number of subgroup analyses to three effect modifiers, namely CAP, ARDS, and non-responders to the Synacthen test. There was previous evidence for a potential clinical benefit from corticosteroids in hospitalised patients with CAP.[18–20]

The biological plausibility of a larger corticosteroid protective effect in CAP-related septic shock versus non-CAP-related septic shock could be supported by clinical, pharmacological, and mechanistic considerations. These findings align with recent meta-analyses examining the effects of corticosteroids in CAP.[8,21] They are also

consistent with the 5·6% fewer deaths at day 28 with hydrocortisone than compared with placebo recently reported in adults with severe CAP without septic shock.[9] In this trial, hydrocortisone therapy reduced the requirement of vasopressors and of invasive mechanical ventilation. A recent individual patient data meta-analysis of hydrocortisone effects in adults with septic shock did not include separate data for CAP.[22] CORTICUS[23] and ADRENAL[24] are the largest trials that did not find survival benefits from hydrocortisone therapy in adults with septic shock. The proportion of pneumonia-related septic shock was about 34% in both trials, as compared with 45% in APROCCHSS.[10] ADRENAL[24] and CORTICUS[23] did not report separate data for CAP and health-care associated lung infection. Hence, the discrepancy in survival benefit from corticosteroids between these trials could be explained by a larger proportion of CAP-related septic shock in APROCCHSS. Altogether these studies suggest that mortality reduction with corticosteroids might be greater in patients with CAP-related septic shock. Patients in the APROCCHSS trial, with CAP versus without CAP did not differ with regard to age, gender, severity of illness as assessed by SAPS 2 and SOFA scores, lactate levels, or the need for vasopressor therapy. Patients with CAP had lower PaO_2:FiO_2 ratio, were more likely to be ventilator-dependent, and more likely to meet ARDS criteria. Subgroup analysis, excluding patients with ARDS, suggested a numerically greater magnitude of corticosteroid effects in patients with CAP versus those without CAP, but was underpowered to reach statistical significance. After adjustment for baseline covariates imbalances (including ARDS) there was still a significant multiplicative and additive interaction in mortality reduction by corticosteroids. In the placebo group, all-cause mortality at day 90 was 51% versus 48% in patients with CAP compared with the non-CAP group. From a pharmacological and mechanistic point of view, downstream consequences of glucocorticoid receptor activation are cell and tissue specific, particularly in fine tuning the balance between pathogen elimination and protection against excessive inflammation and immunopathology.[25] Immune cell infiltration of the lung is a hallmark of severe CAP.[26] Glucocorticoid receptors are abundant in immune cells.[27] Following intravenous infusion, glucocorticoids rapidly and massively diffuse to the lung.[28] Finally, the additive effect of corticosteroids across CAP and non-CAP subgroups might also provide strong evidence for an underlying biological interaction.[29]

The strengths of this study include a large cohort of adults with CAP-related septic shock, using multiplicative and additive interaction modelling, a moderate credibility of the subgroup analysis, and consistency in treatment effects across primary and secondary outcomes. A limitation of this study could be the delay since the publication in 2018 of the main analysis of the APROCCHSS. There were two main reasons for this delay. First, the 2 years of the pandemic that diverted all our time toward caring for patients with COVID-19 and concentrating research efforts on critical COVID-19, in early 2020. Second, we planned to align the report of this prespecified subgroup analysis to our group-led CAPE COD trial on hydrocortisone for severe CAP without shock. This delay has no effect on the validity of the subgroup analysis. The randomisation was not stratified based on CAP diagnosis at baseline. However, there were no clinically relevant differences in baseline characteristics between the two treatment groups, and modelling interaction after including important baseline factors in the model did not modify the results qualitatively or quantitatively. Finally, as a large proportion of patients with CAP also met criteria for ARDS, the subgroup analysis was underpowered to fully discriminate between ARDS and CAP modifying effects on mortality reduction with corticosteroids.

In conclusion, in this prespecified exploratory secondary analysis of the APROCCHSS trial of patients with CAP and septic shock, hydrocortisone plus fludrocortisone reduced mortality as compared with placebo. However, the subgroup analysis was underpowered to fully discriminate between ARDS and CAP modifying effects on mortality reduction with corticosteroids. There was no evidence of a significant treatment effect of corticosteroids in the non-CAP subgroup.

Contributors

DA designed the study and obtained the funding for the study. AR and EB wrote the statistical analysis plan and did the statistical analyses. All authors contributed to the conduct of the study, participant recruitment and follow-up, and to the interpretation of study data. DA wrote the first draft of the paper with the input of NH, EK, and AR. All authors read and approved the final manuscript. DA and AR had full access to all data in the study, vouched for the integrity of the study and had final responsibility for the decision to submit for publication. All authors had access to the data.

Declaration of interests

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Data sharing

Individual participant data and a data dictionary defining each field in the set, will be made available within 3 months from publication, by email request to DA and after signed data sharing agreements are signed.

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