Steroids in severe community-acquired pneumonia

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Early administration of hydrocortisone may be used in severe community-acquired pneumonia. Research is needed to optimise dosing regimens and evaluate long-term outcomes of steroids in pneumonia. https://bit.ly/4dZvO1Y

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Abstract

There is conflicting evidence regarding the use of steroids in severe community-acquired pneumonia (CAP), with previous randomised controlled trials limited by small sample sizes. ESCAPe and CAPE COD are two recently published large trials on steroids in severe CAP. ESCAPe assessed the initiation of methylprednisolone within 72–96 h of hospital admission, while CAPE COD studied the use of hydrocortisone within 24 h of the development of severe CAP. ESCAPe did not show any differences in all-cause 60-day mortality or any of its secondary outcomes. CAPE COD showed that hydrocortisone improved all-cause 28-day mortality and reduced the risk of intubation or vasopressor-dependent shock. Important differences between the trials included the steroid regimens used, timing of steroid administration and baseline characteristics, with more diabetic patients included in ESCAPe. The results of CAPE COD support the initiation of hydrocortisone within 24 h of developing severe CAP, but more research is needed to evaluate long-term outcomes and optimum dosing regimens for steroids in severe CAP.

Commentary on:

- Meduri GU, *et al.* Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. *Intensive Care Med* 2022; 48: 1009–1023.
- Dequin P-F, *et al.* Hydrocortisone in severe community-acquired pneumonia. *N Engl J Med* 2023; 388: 1931–1941.

Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of mortality globally, including in high-income countries, despite the widespread use of antibiotics since the 1940s [1, 2]. CAP leads to many in-hospital complications, such as septic shock, acute coronary syndrome, stroke and venous thrombosis [3–6]. Furthermore, CAP leads to long-term adverse outcomes, such as higher rates of 10-year mortality, lung function decline and overall functional decline [7–9]. The most widely accepted definition of severe CAP follows the 2007 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) criteria, in which vasopressor-dependent shock or need for mechanical ventilation are required for the classification of severe CAP [10]. Approximately 18–23% of patients admitted with pneumonia have severe CAP, which is associated with worse mortality and morbidity than non-severe CAP [11–13].

There are several global challenges in the management of severe CAP. Old age and frailty are independent risk factors for mortality, and so severe CAP will place an increasing burden on healthcare systems globally as the number of people aged ⩾65 years is expected to increase from 761 million in 2021 to 1.6 billion in 2050 [14–16]. Moreover, antibiotic resistance in pneumonia is a global crisis, with 1.5 million deaths associated with antibiotic resistance in 2019, the most out of all the infections studied [17]. This may get worse in the future with current projections of a three-fold increase in resistance to third-line antibiotics in 2035 compared with 2005 [18]. These global challenges exist despite the mainstay of CAP treatment being largely unchanged for decades [19].

New treatments are required for severe CAP to overcome these challenges, and one potential addition to the treatment paradigm is corticosteroids. The biological rationale for this is to suppress the dysregulated inflammatory response in pneumonia, which can lead to septic shock and end-organ dysfunction [20]. For this reason, steroids have already been extensively studied in sepsis. A recent meta-analysis showed modest risk reductions in short-term and long-term mortality in sepsis, with increased shock reversal by day 7, albeit with probable increases in the risk of hyperglycaemia, hypernatraemia and neuromuscular weakness [21]. However, randomised controlled trials (RCTs) of steroids in severe CAP have shown conflicting results. One RCT showed that 7 days of hydrocortisone was associated with improved mortality at days 8 and 60, as well as shorter intensive care unit (ICU) stay [22]. By contrast, several other RCTs did not show a mortality benefit, although they did show improvements in other parameters, such as need for mechanical ventilation [23–25]. Furthermore, these RCTs had small sample sizes (the largest assessed 120 patients in total), and lacked long-term follow-up data. An individual patient-data meta-analysis showed no mortality benefit for steroids in CAP, but this study included all patients with CAP, not just severe CAP [26]. International guidelines advise the use of steroids in severe pneumonia if shock is present, but warn that this is based on low-certainty evidence, does not apply to patients with viral CAP (including influenza) and uncontrolled diabetes mellitus, and recommends a larger initial dose of steroids than used in most clinical trials [27].

Recently, two large RCTs have been published on the use of steroids in severe CAP: ESCAPe (Extended Steroid Use in Community-Acquired Pneumonia) and CAPE COD (Community-Acquired Pneumonia: Evaluation of Corticosteroids) [28, 29]. In this journal club, we summarise these two trials, including the differences between them and their significance for clinical practice.

Methods

The ESCAPe trial was a double-blind, randomised, placebo-controlled trial. Adults admitted to higher-level care with severe CAP, as defined by one major or three minor criteria of the 2007 ATS/IDSA criteria for severe pneumonia [10], were enrolled within 72–96 h of admission. Participants were randomised 1:1 to receive intravenous methylprednisolone (40 mg for days 1–7, 20 mg for days 8–14, 12 mg for days 15–17 and 4 mg for days 18–20) or placebo, in addition to standard care. The primary outcome was all-cause mortality at 60 days. Secondary outcomes focused on mortality and morbidity in-hospital (such as duration of ICU stay and hospital mortality) and post-discharge (such as quality of life at day 180 and all-cause mortality at day 365). Based on power calculations aiming for statistical power of 85% to detect a 7% absolute reduction in 60-day mortality, the aim was to recruit 1420 patients. Due to low recruitment, study enrolment was stopped early, resulting in 584 participants randomised for primary outcome analysis.

The CAPE COD trial was also a double-blind, randomised, placebo-controlled trial of adults admitted to intensive care, employing a superiority design. The diagnosis of CAP was defined according to symptoms and imaging features within 48 h of admission to hospital, with severity graded according to the Pneumonia Severity Index, need for mechanical ventilation, and high supplemental oxygen requirement delivered either *via* high-flow nasal cannula (inspiratory oxygen fraction (F_{IO_2}) >50% and partial pressure of arterial oxygen:F_{IO_2} ratio <300 mmHg) or a non-rebreather mask. Patients with treatment limitations (a do-not-intubate decision), influenza and septic shock were excluded. Participants were randomly assigned to receive either intravenous hydrocortisone (200 mg per day for days 1–4, up to either 8- or 14-days total duration of tapered treatment based on clinical response) or placebo. The primary outcome was 28-day all-cause mortality, with multiple domains of secondary outcomes, such as length of ICU stay, respiratory support, organ failure scores, quality of life and relevant safety outcomes. Based on an absolute risk reduction of 6.75% in mortality from 27% in the placebo group, the group aimed to enrol 1200 participants. Due to the coronavirus disease 2019 (COVID-19) pandemic, however, recruitment was shifted to a dedicated embedded trial, with 800 participants having undergone randomisation up to the point of the second interim analysis.

Results

Tables 1 and 2 summarise the main characteristics and outcomes of the two clinical trials, respectively. Participants in ESCAPe were randomised to methylprednisolone (n=297) and placebo (n=287) for an intention-to-treat analysis. The two groups had balanced baseline characteristics; 96.4% of participants were male and 83.1% were white. There was no significant difference in the primary outcome of 60-day mortality between methylprednisolone and placebo, including when baseline characteristics were adjusted (16% *versus* 18%; adjusted OR 0.89 (95% CI 0.58 to 1.38); p=0.61). There were no significant differences in the secondary outcomes, including duration of ICU stay (median 3 *versus* 4 days) and 1-year mortality (30% *versus* 33%; OR 0.88 (95% CI 0.61 to 1.27); p=1.00). There were similar rates of adverse effects and complications in-hospital and at 180 days post-discharge.

TABLE 1 Baseline characteristics in the two studies

Study	ESCAPe [28]	CAPE COD [29]
Design	Double-blind, randomised, placebo-controlled trial	Double-blind, randomised, placebo-controlled trial
Inclusion criteria	Adults with CAP admitted to ICU or intermediate care with one major or three minor criteria of the ATS/IDSA criteria for severe pneumonia [10]	Adults with CAP admitted to ICU or intermediate care, and at least one of: 1) On mechanical ventilation (noninvasive or invasive) with PEEP $\geqslant$5 cmH_2O 2) Use of high-flow nasal oxygen with P_{aO_2}:F_{IO_2} <300 and F_{IO_2} >50% 3) Use of non-rebreather mask and estimated P_{aO_2}:F_{IO_2} <300 4) Pulmonary Severity Index score >130
Intervention	Intravenous methylprednisolone: Days 1–7: 40 mg·day^{-1} Days 8–14: 20 mg·day^{-1} Days 15–17: 12 mg·day^{-1} Days 18–20: 4 mg·day^{-1}	Intravenous hydrocortisone: Days 1–4: 200 mg·day^{-1} Then treatment based on whether there was a high chance of being discharged from ICU before day 14 (adaptive scheme) or not (full treatment) Adaptive scheme: Days 5–6: 100 mg·day^{-1} Days 7–8: 50 mg·day^{-1} Full treatment: Days 5–7: 200 mg·day^{-1} Days 8–11: 100 mg·day^{-1} Days 12–14: 50 mg·day^{-1}
Primary outcome	All-cause mortality at day 60	All-cause mortality at day 28
Follow-up	365 days	90 days
Patients (n)	584 (required 1406 for power of 85% to detect a 7% absolute reduction in 60-day mortality)	795 (required 1165 for power of 80% to detect a 25% relative reduction in 28-day mortality)
Age (years)	Mean: 68.8	Median: 67.0
Male (%)	96.4	69.4
Diabetes mellitus (%)	48.3	22.8
Treatment initiation	Within 72–96 h of hospital admission Median time from hospital admission to randomisation: 37 h	Within 24 h of the development of severe CAP Median time from hospital admission to ICU admission (treatment arm): 5.5 h Median interval from ICU admission to initiation of treatment: 15.3 h
Mechanical ventilation (%)[#]	33	44.4
SOFA score	Mean: 6.5	Median: 4
P_{aO_2}:F_{IO_2}	Mean for intervention arm: 181	Median for intervention arm: 143
Vasopressor-dependent shock (%)	13.1	11.6

Data presented as the mean, unless stated otherwise. CAP: community-acquired pneumonia; ICU: intensive care unit; ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America; PEEP: positive end-expiratory pressure; P_{aO_2}: partial pressure of arterial oxygen; F_{IO_2}: inspiratory oxygen fraction; SOFA: Sequential Organ Failure Assessment. [#]: includes invasive and noninvasive ventilation.

CAPE COD randomised participants to hydrocortisone (n=400) or placebo (n=395) with balanced baseline characteristics between groups. 28-day all-cause mortality was significantly lower in the hydrocortisone group when compared to placebo (6.2% *versus* 11.9%; absolute difference −5.6%; 95% CI −9.6 to −1.7; p=0.006). The difference in mortality was also observed at 90 days (9.3% *versus* 14.7% for hydrocortisone and placebo, respectively). Participants allocated to hydrocortisone were more likely to be discharged from ICU by day 28 (HR 1.33 (95% CI 1.16 to 1.52)), avoid invasive mechanical ventilation (19.5% *versus* 27.7%; HR 0.69 (95% CI 0.50 to 0.94)), and less likely to require vasopressor treatment (15.3% *versus* 25.0%; HR 0.59 (95% CI 0.43 to 0.82)) when compared to participants allocated to placebo. There was no significant difference in the rate of adverse events. There was a trend towards lower 28-day mortality in patients with an isolated organism (risk difference −9.1% (95% CI −15.0 to −3.1)) but not in those without an isolated organism (risk difference −3.1% (95% CI −8.4 to 2.3)).

Commentary

ESCAPe and CAPE COD are two of the largest RCTs on the use of systemic corticosteroids in severe bacterial pneumonia. ESCAPe showed no statistically significant differences between hydrocortisone and

TABLE 2 Differences in the results between the two studies

Study	ESCAPe [28]	CAPE COD [29]
Primary outcome	60-day all-cause mortality: 16% *versus* 18%; adjusted OR 0.89 (95% CI 0.58 to 1.38); p=0.61	28-day all-cause mortality: 6.2% *versus* 11.9%; absolute difference −5.6% (95% CI −9.6 to −1.7); p=0.006
Secondary outcomes		
Median ICU length of stay, days	3.0 *versus* 4.0; difference in medians −1 (95% CI −1.7 to −0.3); p=1.00	In-patients discharged alive from ICU: 5.0 *versus* 6.0
Median mechanical ventilation-free days by day 28	28 *versus* 28; difference in medians 0 (95% CI −0.6 to 0.6); p=1.00	28 *versus* 28; difference in medians 0 (95% CI 0 to 0)
Vasopressor use in those not on vasopressors at baseline, %	5 *versus* 4; difference in means 1.14 (95% CI 0.47 to 2.73); p=1.00	15.3 *versus* 25.0; HR 0.59 (95% CI 0.43 to 0.82)
Incidence of gastrointestinal bleeding, %	By day 180: 1.7 *versus* 1.4	By day 28: 2.2 *versus* 3.3; HR 0.68 (95% CI 0.29 to 1.59); p=0.38

Results are presented as treatment *versus* placebo. ICU: intensive care unit.

placebo in its primary or secondary outcomes. By comparison, CAPE COD showed a lower risk of 28-day mortality and need for mechanical intubation and vasopressors in participants treated with methylprednisolone.

There are several potential reasons for these differences. Steroids were administered within 24 h of the development of severe CAP in CAPE COD, compared to within 72–96 h of hospital admission in ESCAPe. Studies of steroids in sepsis have shown better outcomes with earlier administration of steroids (although some did not demonstrate a mortality benefit) [30, 31]. Diabetes mellitus was more prevalent in the ESCAPe trial (48.3% *versus* 22.8%), which is pertinent since diabetes is a risk factor for CAP mortality and poorer ICU outcomes, as well as long-term mortality [32–34]. Moreover, CAPE COD used an adaptive treatment scheme with lower steroid doses (equivalent to 220 mg hydrocortisone over 8 days) for patients who recovered more quickly, whereas ESCAPe did not, so patients could potentially receive up to 468 mg over 20 days. An adaptive treatment approach may have led to a mortality benefit by avoiding excess immunosuppression in patients with less severe disease. However, it should be noted that it is unclear how many participants in CAPE COD were on the adaptive treatment scheme. CAPE COD also reached closer to its target recruitment number compared with ESCAPe (68.2% *versus* 41.5% of target), and therefore may have been more powered to detect differences in the treatment arm.

The authors of the CAPE COD study and its accompanying editorial highlight that ESCAPe featured more males (96.4% *versus* 69.4%) [35]. However, the importance of this is unclear. *Post hoc* analysis of a RCT of steroids in septic shock showed that hydrocortisone increased the risk of shock recurrence in women but not men, while it decreased time on mechanical ventilation in men but not women [36]. Furthermore, a study of young patients with inflammatory bowel disease showed that women were more likely to develop steroid resistance when commencing treatment, possibly due to reduced activity of the glucocorticoid receptor [37].

There are several potential reasons why CAPE COD showed a mortality benefit with the use of steroids in severe CAP while many of the previous RCTs did not [23–25]. Importantly, previous studies had much smaller sample sizes and therefore may not have been adequately powered to detect a mortality benefit. One trial was specifically powered to detect differences in treatment failure rather than in-hospital mortality [23]. Another trial used a single dose of steroids in their treatment arm, which may have been insufficient to provide the necessary level of immune modulation [25]. Furthermore, one RCT reported on mortality at day 8, which may have been too early to detect meaningful mortality differences between steroids and placebo [24].

A recent meta-analysis of steroids in severe CAP, which included ESCAPe and CAPE COD, showed that when trial results were stratified based on different steroids, hydrocortisone was the only steroid with a significant mortality benefit (52% reduced risk of all-cause mortality) [38]. The authors suggested that this may be due to hydrocortisone being shorter-acting and less potent than the other steroids, and thus less likely to induce excessive immunosuppression, in addition to having more mineralocorticoid activity, thus improving fluid balance and blood pressure control [38, 39]. By comparison, dexamethasone and methylprednisolone reduce mortality in severe COVID-19 [40, 41]. This difference likely reflects the differing pathophysiologies of COVID-19 pneumonitis and severe CAP.

Implications for practice and research

The results of CAPE COD support the use of intravenous hydrocortisone within 24 h of the development of severe CAP. However, it is important to note the key exclusion criteria of CAPE COD, which limit its external validity to some extent. These include vasopressor-dependent septic shock, influenza detected by rapid PCR, patients with cystic fibrosis and those on maintenance prednisolone of 15 mg per day. In these cases, there is limited evidence for the use of steroids in CAP and so clinical discretion may be needed on a case-by-case basis. Also, subgroup analysis in CAPE COD showed that there was no 28-day mortality benefit in participants with isolated pathogens, which were mostly bacterial. A significant proportion of the remaining cases were likely to be viral, since procalcitonin was $<0.5\ ng{\cdot}mL^{-1}$ in ∼25% of participants. This suggests that steroids are effective in viral pneumonias, consistent with data on viral pneumonia except influenza [41, 42], but the benefit in bacterial pneumonia remains unclear.

Furthermore, long-term follow-up data on the efficacy of hydrocortisone in severe CAP are needed since CAPE COD only followed participants up for 90 days. Moreover, the two trials reported on mostly different outcomes (including differing primary outcomes), which limits comparison between them and reflects the heterogeneity of outcomes reported by clinical trials of pneumonia management [43]; a core outcome set for trials evaluating pneumonia management is being developed by the European Respiratory Society. Finally, adaptive platform trial designs, such as the one used in REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia), could be deployed to evaluate different steroids and dosing regimens in severe CAP [44].

Conflict of interest: A.G. Mathioudakis is a member of the *Breathe* editorial board; the authors have no further conflicts to disclose.

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