

Can a Bayesian approach clarify if corticosteroids are beneficial for severe community-acquired pneumonia?

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Despite advances in the antimicrobial treatment of sepsis and organ support in the intensive care unit (ICU), community-acquired pneumonia (CAP) remains a leading cause of mortality and disability-adjusted life years lost globally.¹ Severe CAP, where CAP becomes complicated by acute hypoxaemic respiratory failure or shock, is also the most common cause of sepsis, where complex and heterogeneous biological mechanisms underlie a dysregulated inflammatory host response that ultimately leads to major organ dysfunction and death. Along with the emerging threats of respiratory pandemics, antimicrobial resistance, ageing populations and the rise of chronic diseases, much research has been conducted to improve the treatment outcomes of CAP via host immunomodulation. These efforts have focused almost exclusively on anti-inflammatory effects of corticosteroids, which have a proven track record of improving outcomes in other forms of sepsis, such as bacterial meningitis, *Pneumocystis jirovecii* pneumonia and severe COVID-19.

Unfortunately to date, corticosteroids have been evaluated in numerous randomised controlled trials (RCTs) as a potential treatment for CAP without having reached a conclusive recommendation due to conflicting results. Early RCTs suffered from small sample sizes and heterogeneous outcome measures. This resulted in clinical practice guidelines issuing weak recommendations on the use of corticosteroids due to poor overall quality of evidence and discrepant results in higher quality studies.^{2,3} Currently, guidelines cautiously recommend corticosteroid therapy for patients with severe CAP when there is septic shock that is refractory to fluid resuscitation and vasopressor support, which is consistent with previously released sepsis guidelines for septic shock.⁴

Most recently, 2 large, high-quality and double-blind placebo-controlled RCTs were published on corticosteroid therapy in severe CAP. The Extended Steroid in Use in Community Acquired Pneumonia (ESCAPE) trial⁵ randomised patients between 2012 and 2016 across 42 hospitals in the

US who had severe CAP as defined by the 2007 American Thoracic Society/Infectious Diseases Society of America criteria⁶ for severe pneumonia, to receive intravenous methylprednisolone 40 mg per day for 7 days before tapering over a period of 20 days within 72–96 hours after admission versus (vs) placebo. Due to low recruitment, the study enrolment was stopped early at 584 patients out of an intended 1420 target sample size and the primary outcome of 60-day mortality was found to be similar in the intervention and control groups (16% vs 18%, $P=0.61$). The Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) trial⁷ was conducted in 31 French centres from 2015 to 2020 in 800 patients admitted to the ICU for severe CAP to receive either intravenous hydrocortisone of 200 mg per day by continuous infusion for 4 or 7 days that tapered over a period of 8 or 14 days within 24 hours, or placebo. Patients with influenza, septic shock at baseline, chronic corticosteroid usage or those with do-not-resuscitate orders were excluded. In contrast to the ESCAPE investigators, the CAPE COD investigators found a mortality benefit favouring the hydrocortisone group over the placebo group (6.2% vs 11.9%, $P=0.006$).

Despite the larger sample sizes, the differing results of these 2 trials have resulted in more questions than answers. Could the discrepant results be due to differences in the choice of corticosteroid drug and dosing schedule? Or was the earlier timing of initiation of corticosteroid therapy, as evidenced by the CAPE COD trial, the crux to optimising outcomes? Differences in the study cohort characteristics in terms of gender distribution (96% of patients in the ESCAPE study were men vs 69% in CAPE COD); prevalence of diabetes mellitus (more prevalent in the ESCAPE trial at 48.3% vs 22.8%); microbiological aetiology of CAP (the CAPE COD cohort had a high proportion of patients with an identified bacterial pathogen, specifically *Streptococcus pneumoniae* due to exclusion of patients with influenza); and

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biomarkers (70% of CAPE COD participants had raised C-reactive protein), also beg the question of whether there are other patient-specific criteria such as gender, comorbidity and pathogenic aetiology that may modify the efficacy and harm of corticosteroids therapy in CAP. Research on corticosteroids for severe CAP seems destined to suffer from the established track record of the many negative trials in critical care and sepsis.

Many RCTs in critical care and almost all research studies of sepsis are beset by the major problem of having enrolment criteria that result from consensus definitions of archetypical syndromes in critically ill patients (e.g. CAP with acute hypoxaemic respiratory failure), which ignore the clinical heterogeneity of the ICU population. These definitions, while having high sensitivity and are therefore good for screening, perform poorly as diagnostic tests due to low specificity because pneumonia and sepsis involve biologically heterogeneous processes with differing pathogenic agents and inflammatory phenotypes. Additionally, corticosteroids have been shown to be beneficial in both acute respiratory distress syndrome (ARDS) for its anti-inflammatory effect and in septic shock for relative adrenal insufficiency.⁴ As a significant proportion of patients with severe CAP are expected to suffer from the complication of either ARDS or septic shock, it will likely remain an enduring challenge for investigators to fully discriminate between the effects of mortality reduction from disease-modifying effects of corticosteroids on ARDS, septic shock and CAP. Clearly, a more precision-based approach to CAP is needed where patients are phenotyped by rapid molecular pathogen diagnostics and inflammatory biomarkers to help guide the selection of various treatments such as corticosteroids.

In this issue of the *Annals*, Chua et al.⁸ proposed a different statistical approach to tackling the clinical question with Bayesian inference compared to the more traditional frequentist approach that the traditional RCT is based on and which dominates the medical literature. The frequentist approach is purely data-driven and aims to assign probabilities to a given dataset (i.e. what is the probability of obtaining another dataset at least as extreme as the one collected, thereby giving the *P* value). In contrast, the Bayesian approach that involves the incorporation of prior information into the analysis as more data become available (known as the prior, which can be assigned based on expert beliefs, historical data, or a combination of the two), attempts to assign the probabilities that a particular hypothesis is true given a particular dataset.⁹ This is the main advantage of the Bayesian approach over the frequentist approach, where the

probability that an intervention is beneficial can be updated as data accrues (the updated probability is called the posterior probability). While clinicians are more familiar with the frequentist approach, the pre-trial assumptions on plausible effect size and outcome rates in RCTs are frequently incorrect, and study designs often lack flexibility to address complex clinical questions reflective of real-world practice or to make mid-trial corrections when pre-trial assumptions are wrong.

Chua et al.'s Bayesian meta-analysis included 6 RCTs for evaluation of mortality benefit and duration of mechanical ventilation, which included both the ESCAPE⁵ and CAPE COD⁷ studies. The authors found no significant difference in hospital (risk ratio [RR] 0.70, 95% confidence interval [CI] 0.39–1.14) and all-cause mortality (RR 0.68, 95% CI 0.34–1.22), but found a high posterior probability of 94.3% and 93.1% approaching significance that corticosteroids were more likely than not to reduce both hospital and all-cause mortality, respectively. Despite not meeting the posterior probability threshold for significance, the authors should be commended for helping to inform Bayesian researchers of priors regarding the effect of corticosteroids on severe CAP. Limitations of their Bayesian meta-analysis include having a limited set of 6 RCTs where the statistical analysis risks being heavily weighted by the 2 largest studies (ESCAPE and CAPE COD), as well as significant heterogeneity owing to the differences in diagnostic inclusion criteria for severe CAP, exclusion criteria of patients with septic shock and primary outcome across the RCTs analysed.

It is with the limitations of the traditional frequentist statistical approach in mind that the results of the Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) study with recruitment currently in progress¹⁰ are eagerly awaited. REMAP-CAP adopts a Bayesian inference model with a responsive-adaptive randomisation design. Rather than testing individual interventions in a single homogeneous disease state and terminating when that task is complete, responsive-adaptive trials like REMAP-CAP aim to study a broader set of disease states where testing for multiple therapies is carried out simultaneously and sequentially without the need for a separate control group for every 2-way comparison. In this regard, REMAP-CAP is able to study the effect of 240 multiple interventions categorised across 4 treatment domains of antibiotic therapy; antiviral therapy; host immunomodulation with extended macrolide therapy; and various corticosteroid regimens in multiple patient subgroups with a randomisation design, which involves preferential assignment of subjects to interventions

that appear to be most favourable until superiority, equivalence or inferiority thresholds are met—thereby avoiding indeterminate results. With such flexibility and the promise of a single perpetual platform trial, it is hoped that we will eventually be able to answer the pernicious issue of corticosteroids in CAP with a precision-based approach.

Disclosure

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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