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Corticosteroids and community-acquired pneumonia: Africa deserves an explanatory trial

Daniel A. Sweeney[1*], Pedro Póvoa[2,3,4,5] and Andre C. Kalil[6]

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The African continent has historically endured a disproportionately large share of the worldwide burden of disease, from malaria to tuberculosis, to HIV. Whether this is also the case with community acquired pneumonia (CAP) is uncertain. It is estimated that 200,000 deaths due to CAP occur yearly in Sub-Saharan Africa alone [1]. What is known is that CAP in Africa, compared to North America and Europe–where countless randomized controlled trials (RCTs) have been performed–is vastly different in terms of both patient and pathogen profiles. For example, patients who die from pneumonia in Africa are younger with 55% of deaths in Sub-Saharan Africa occurring under the age of 70, whereas 90% of deaths due to severe pneumonia in the United Kingdom occur in individuals older than 70 [2]. The prevalence of HIV and tuberculosis is far more common in Africa than in high resource settings making it a particularly challenging to both identify and effectively treat African patients with CAP. In addition, vaccine preventable infections such as *H. influenza* and *S. pneumoniae*, along with *P. jirovecii* are far more common causes of CAP in Africa than in the either Europe or North America.

Corticosteroid adjunctive treatment for CAP has been studied for decades with variable results. A resurgence of interest in its use occurred with the CAPE COD trial showing a 5.6% mortality reduction with hydrocortisone therapy for the treatment of adults with severe CAP admitted to the intensive care unit [3]. However, an even more recent trial by the REMAP-CAP trialists failed to show a survival benefit of hydrocortisone for the treatment of severe CAP; in fact, hydrocortisone potentially increased mortality [4]. The uncertainty regarding the use of corticosteroid therapy for CAP is exemplified by the variable recommendations put forth by professional societies. The 2023 ERS/ ESICM/ ESCMID/ ALAT guidelines for severe CAP "suggest" the use of corticosteroids only if shock is present [5]. In contrast, The 2024 Society of Critical Care Medicine "recommend" corticosteroids for the treatment of severe CAP and explicitly make "no recommendation" regarding its use in the treatment of non-severe CAP [6]. And most recently, the 2025 ATS guidelines "suggest" corticosteroids therapy for severe CAP and "recommend" not using corticosteroids to treat non-severe CAP [7].

The SONIA trialists, acknowledging the different aspects of CAP in Africa compared to the settings in which most of the prior trials were performed, boldly set forth to answer the question of whether corticosteroid therapy would have a mortality benefit in the resource-limited setting of Africa [8]. Employing an

*Correspondence:
Daniel A. Sweeney
dasweeney@health.ucsd.edu
[1]Division of Pulmonary, Critical Care, Sleep Medicine and Physiology, Department of Medicine, University of California, San Diego, La Jolla, CA, USA
[2]NOVA Medical School, New University of Lisbon, Lisbon, Portugal
[3]Center for Clinical Epidemiology and Research Unit of Clinical Epidemiology, OUH Odense University Hospital, Odense, Denmark
[4]D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil
[5]Department of Critical Care Medicine, Hospital de São Francisco Xavier, CHLO, Estrada do Forte do Alto do Duque, Lisbon 1449-005, Portugal
[6]Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center Omaha, Omaha, NE, USA

Table 1 Biases and confounding risks associated with SONIA trial

Issue	Bias type or confounding risk	Impact
Open label design	Performance and Ascertainment bias	Inflates corticosteroid treatment effect due to lower standard of supportive care and misascertainment of control group
Definition of pneumonia without the use of radiographic or laboratory data	Misclassification bias	Defeats the principal biological premise of the trial, which was to treat pneumonia, and not other diseases
No objective measurement of baseline disease severity	Selection bias	Cannot determine the two trial arms are balanced in terms of disease severity, and can inflate corticosteroid effect due to higher severity in the control group
No testing for Influenza, *P. jirovecii* or Tuberculosis as cause of pneumonia	Confounding risk	Potential patient harm if treated with corticosteroids without antimicrobials, and inflates corticosteroid effect if higher prevalence in control group
No collection of status of HIV viral load and CD4 count	Confounding risk	Inflates corticosteroid treatment effect due to more advanced HIV disease in the control group
2/3 of patients without oxygen need were enrolled with non-severe CAP	Selection and Misclassification bias	Prior studies showing harm with corticosteroid in non-severe CAP
Timing of antibiotics not described	Confounding risk	Inflates corticosteroid effect due to faster antibiotics initiation, not due to corticosteroids
Limited safety data collected	Information bias	Undetected harm secondary to corticosteroids not identified due to the lack of data collection

open-label-randomized controlled trial design, 2180 patients admitted to 18 public hospitals in Kenya with a clinical diagnosis of CAP based on signs and symptoms (radiographic imaging or laboratory data were not part of the criteria) were enrolled and randomized to either standard of care (a beta-lactam combined with a macrolide) or standard of care plus low-dose oral corticosteroids for up to 10 days. At baseline, 15.8% of participants were people with HIV without any reporting of their antiretroviral treatment status, and 1.4% had pulmonary tuberculosis; additionally, 3.2% of trial enrollees were reported to have tuberculosis during the study. A 3.4% absolute reduction in the 30-day mortality (HR for death: 0.84 [95% CI: 0.73—0.97]) was noted by the intention-to-treat analysis.

Unfortunately, there are multiple biases and confounders present within the SONIA trial that raise the question of whether corticosteroid therapy was a truly beneficial treatment for CAP among this African population (see Table 1). Compared with a blinded study design, an open-label trial design has been estimated to falsely inflate the survival benefit effect size (performance and ascertainment biases) [9]. The overly simplified definition of pneumonia based on signs and symptoms without any radiographic evidence or supporting laboratory data seriously question whether enrolled patients had true pneumonia (misclassification bias). And with only scant baseline data collected it is impossible to know whether the two arms of the trial were balanced regarding severity of disease or underlying infectious cause (selection bias). The mortality of patients in control arm (26%) was exceedingly high–even higher than predicted by the trial design (20%)--suggesting the presence of pathologies other than pneumonia, which could have falsely increased the corticosteroid treatment effect (selection bias). Among those patients who were diagnosed with pneumonia is also not known how many were infected with influenza, *P. jirovecii* or may have had undiagnosed tuberculosis—conditions for which corticosteroids are either contraindicated (influenza) or are deemed dangerous without appropriate antimicrobial treatment (*P. jirovecii*) (confounding by indication). With so much embedded bias and ambiguity even if one were to accept that corticosteroid therapy was efficacious overall, one must acknowledge the almost certain harm that occurred in unrecognized subpopulations within the treatment arm. This is unsurprising, as corticosteroid therapy for other less severe infectious conditions—such as sepsis without septic shock—has shown no benefit or harm [10].

Considering the conflicting data from resource-rich countries, how can researchers safely study corticosteroid therapy for CAP in Africa? Explanatory trials must first be conducted in Africa *before* performing pragmatic trials. To the skeptics who believe that an explanatory trial of CAP in Africa cannot be conducted one need look no further than the large African HIV experience. This was the successful strategy employed by the AIDS Clinical Trials Group (ACTG) to address the devastating African HIV epidemic. Founded in 1987 as a U.S. domestic clinical trials network, its impact has been transformative, improving HIV care globally, but especially in Sub-Saharan Africa when it later expanded to include international clinical trial sites. From its inception, the ACTG trialists recognized the importance of first conducting explanatory trials in Africa. Trials such as PEARLS and OCTANE enrolled patients from multiple African countries and compared antiretroviral regimens in terms of efficacy and safety [11, 12]. These trials were notable for rigorous protocols, strict eligibility criteria, extensive diagnostic and laboratory testing (both baseline and monitoring), comprehensive safety surveillance and centralized data oversight. As a result, these explanatory trials provided definitive therapeutic strategies for both high and low resource settings.

The role of corticosteroid therapy in severe CAP remains unclear. The specific patient population most likely to benefit is still unknown, and the optimal type, dose and duration of corticosteroids have yet to be identified. Unfortunately, the SONIA trial with its pragmatic rather than explanatory design suffers from biases and confounders that precludes the interpretation and generalizability of the results (see Table 1). Thus, changing practice based on SONIA trial results—without confirmatory explanatory trials—has the potential to have harmful consequences for Africa. Patient demographics and pathogens causing CAP in Africa differ substantially from those in North America and Europe, hence clinical trials must employ rigorous double-blind randomized designs, collect relevant clinical, radiological, and laboratory data in order to tailor treatment approaches based on African patient-centered outcomes. Only by performing an explanatory trial can the efficacy and safety of corticosteroid for the treatment of CAP in Africa be established.

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