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Corticosteroids in bacterial severe community-acquired pneumonia: lessons from recent trials

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Introduction

Severe community-acquired pneumonia (SCAP) is a leading cause of intensive care unit (ICU) admission and mortality worldwide (1, 2). Bacterial SCAP, distinct from viral or fungal infections, often triggers a dysregulated host response with systemic inflammation, endothelial dysfunction, and organ injury (3), providing a rationale for adjunctive immunomodulatory therapies such as corticosteroids (3, 4).

Corticosteroids have been widely investigated in pneumonia and sepsis because of their potential to attenuate cytokine release, preserve vascular integrity, and limit lung injury (4). Although the latest guidelines suggest or conditionally recommend corticosteroids in SCAP (1, 5), evidence from randomized controlled trials (RCTs) remains inconsistent. Some studies demonstrated reductions in treatment failure or mortality (6–8), while others showed no significant clinical benefit (9, 10). These divergent findings likely reflect variability in enrolled populations, causative pathogens, corticosteroid regimens, and study designs (11, 12).

Emerging data suggest that corticosteroids effects depend on systemic inflammation and treatment protocol (13, 14), emphasizing the need for individualized rather than universal use. This paper revisits recent clinical trials of corticosteroids in SCAP, distills key lessons, examines challenges related to heterogeneous etiologies, inflammatory phenotypes, and therapeutic regimens, and outlines implications for current practice and future research.

Rationale and biological basis of corticosteroid therapy

The pathophysiology of SCAP is marked by an excessive and dysregulated host immune response that contributes substantially to lung injury and systemic complications. During the acute phase, pathogen recognition leads to activation of nuclear factor κ B (NF- κ B) and other transcriptional pathways, with subsequent release of proinflammatory cytokines such as tumor necrosis factor- α , interleukin (IL)-1 β , and IL-6 (3, 15, 16). This hyperinflammatory cascade disrupts alveolar-capillary integrity, increases vascular permeability, and amplifies the risk of acute respiratory distress syndrome (ARDS) and multiorgan dysfunction (17, 18).

Corticosteroids exert pleiotropic immunomodulatory effects that directly target these mechanisms. By binding to cytoplasmic glucocorticoid receptors, they translocate

to the nucleus and suppress transcription of proinflammatory genes while upregulating anti-inflammatory mediators (4, 15). Beyond cytokine suppression, corticosteroids stabilize endothelial and epithelial barriers, reduce leukocyte recruitment, and limit pulmonary edema (19–21). Preclinical studies suggest that corticosteroids may influence mitochondrial homeostasis and attenuate secondary tissue injury in non-infectious or *in vitro* injury models, although evidence in SCAP is lacking (22, 23). Moreover, observational and mechanistic studies have linked higher systemic inflammation (e.g., elevated IL-6, CRP) with worse outcomes in pneumonia (15–17), and randomized trials suggest that the largest clinical gains from adjunctive corticosteroids occur in patients with a pronounced inflammatory response (8, 13). These findings support the concept that modulation of the inflammatory milieu is the critical therapeutic target for corticosteroids in bacterial SCAP.

Beyond their anti-inflammatory actions, corticosteroids modulate both innate and adaptive immunity by promoting macrophage efferocytosis, enhancing clearance of apoptotic cells, and fostering a shift toward reparative immune phenotypes (24). They also upregulate anti-inflammatory mediators such as IL-10 and annexin A1, supporting resolution of inflammation and restoration of tissue homeostasis (25). In parallel, corticosteroids preserve endothelial integrity and regulate neutrophil trafficking, thereby limiting capillary leakage and alveolar injury. These actions indicate that corticosteroids not only suppress inflammation but also promote active disease resolution and tissue repair, providing a robust biological rationale for their use in bacterial SCAP characterized by severe systemic inflammation.

Taken together, these biological insights provide the rationale for investigating corticosteroids as an adjunctive therapy in bacterial SCAP. They also show that the net clinical effect is determined not only by the intensity of inflammation but also by the timing, dose, and duration of corticosteroid administration in clinical practice (11, 12).

Evidence from recent randomized controlled trials

Over the last decade, several RCTs have evaluated adjunctive corticosteroids in patients with bacterial SCAP, but the results remain inconsistent (Table 1). The trial by Torres et al. (8) demonstrated that methylprednisolone reduced treatment failure in patients with severe pneumonia and elevated C-reactive protein (CRP >150 mg/L), suggesting benefit in those with a heightened inflammatory response. More recently, the CAPE-COD trial reported a significant reduction in 28-day mortality and increased organ support-free days with hydrocortisone in ICU patients with SCAP, reinforcing the potential utility of early corticosteroid therapy (6). Similarly, a multicenter subgroup analysis of the APROCCHSS trial reported a shorter time to clinical stability

and fewer complications in patients with SCAP and septic shock who were randomized to hydrocortisone plus fludrocortisone vs. placebo (7).

In contrast, other RCTs failed to demonstrate clear survival benefit. The ESCAPE trial found no significant effect of methylprednisolone on 60-day mortality or on any of the secondary outcomes (9). This study enrolled predominantly older male veterans, raising concerns about generalizability to broader ICU populations. Likewise, the REMAP-CAP adaptive platform trial screened more than 20,000 patients with pneumonia but ultimately randomized fewer than 1,000 and reporting neutral results for hydrocortisone with respect to mortality (10).

Some analyses have underscored the considerable heterogeneity across trials (11, 12). Key sources of variability include differences in baseline mortality rates, the proportion of patients with microbiological confirmation of bacterial etiology, the timing of corticosteroid initiation, and the specific regimens used. Notably, recent analyses suggest that specific corticosteroid types and dosing regimens may confer substantial benefit in selected high-risk subgroups, particularly those with elevated systemic inflammation (13, 14). However, broad application to all patients with bacterial SCAP has not consistently translated into improved survival (10). These findings highlight the importance of careful patient selection and standardized trial designs to clarify the role of corticosteroids in bacterial SCAP, with particular attention to phenotypes most likely to benefit, such as hyperinflammation, and to the determination of optimal treatment regimens.

The challenge of heterogeneous etiologies in “bacterial” SCAP

One persistent obstacle in interpreting corticosteroid trials in SCAP is the uncertain microbiological landscape. Many studies included a substantial proportion of patients without microbiological confirmation or with mixed bacterial and viral infections (26, 27). In ESCAPE and REMAP-CAP, only slightly more than 40% of patients had an identified pathogen (with an even lower rate of confirmed bacterial infection; Table 1), while viral or mixed infections were not systematically excluded (9, 10). In contrast, the proportion of confirmed bacterial pathogens was considerably higher in CAPE-COD and in the APROCCHSS subgroup (46%–65%) (6, 7); importantly, the APROCCHSS subgroup included only patients with septic shock, 70% of participants in CAPE-COD and all patients in the trial by Torres et al. (8) had CRP >150 mg/L, collectively supporting the benefits of corticosteroids in a subgroup with a higher likelihood of bacterial infection and systemic hyperinflammation. This heterogeneity complicates treatment assessment, as corticosteroid responses may differ between purely bacterial pneumonia and mixed viral-bacterial cases. In viral pneumonias such as influenza A (H7N9) or MERS-CoV infection, corticosteroids have been associated with delayed viral clearance (28, 29), an increased risk of secondary infections, and higher mortality (30, 31), which may partly account for the inconsistent results of randomized trials, as variable inclusion of viral or mixed infections could obscure the true benefit of corticosteroids in bacterial SCAP.

Abbreviations: AP-1, activator protein-1; APACHE II, acute physiology and chronic health evaluation II; ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; NF- κ B, nuclear factor kappa B; RCT, randomized controlled trial; SCAP, severe community-acquired pneumonia; SOFA, sequential organ failure assessment.

TABLE 1 Summary of randomized controlled trials evaluating corticosteroids in patients with severe community-acquired pneumonia.

Criterion	Torres (2015) <i>n</i> = 120 (8)	Meduri 2022 (ESCAPE) <i>n</i> = 584 (9)	Dequin 2023 (CAPE-COD) <i>n</i> = 800 (1)	Heming 2024 (APROCCHSS subgroup) <i>n</i> = 562 (7)	Angus 2025 (REMAP-CAP) <i>n</i> = 658 (10)
Inclusion criteria	SCAP + CRP >150 mg/L	SCAP	SCAP + FiO ₂ ≥50% or invasive ventilation	Septic shock due to CAP	SCAP admitted to ICU (non-COVID)
Severity scores	• PSI 107 ± 38 vs. 110 ± 35	• PSI 125.6 ± 37.2 vs. 122.3 ± 34.4 • SOFA 6.68 ± 3 vs. 6.29 ± 2.85	• PSI 127 (102–153) vs. 130 (103–150) • SAPS II 37 (30–45) vs. 38 (31–47) • SOFA 4 (3–6) in both groups	• SAPS II 56 ± 19, • SOFA 12 ± 3	• APACHE II 18 (13–24) vs. 18 (13–22)
Inflammatory markers	CRP >150 mg/L	Not reported	CRP >150 mg/L in 70% participants	Not reported	Not reported
Pathogens identified	41% (26% bacteria, 15% virus)	43% (bacterial vs. viral not specified)	55% (46% bacteria, 9% virus)	72% (67% bacteria, 5% virus)	40% (30% bacteria, 10% virus/mixed)
Actual timing of steroids	Within 36 h of hospital admission	Median 40 h after hospital admission	Median 15 h after ICU admission	Within 24 h after septic shock onset	Median 8 h after ICU admission
Steroid types and doses	Methylprednisolone 0.5 mg/kg q12h × 5 days	Methylprednisolone 40 mg/day × 7 days, then taper (total 20 days)	Hydrocortisone 200 mg/day × 4 days + taper	Hydrocortisone 50 mg q6h + fludrocortisone 50 µg/day × 7 days	Hydrocortisone 50 mg q6h × 7 days
Primary outcome	↓ Treatment failure (13 vs. 31%)	No reduction in 60-day mortality (16 vs. 18%)	↓ 28-day mortality (6.2 vs. 11.9%)	↓ 90-day mortality (39 vs. 51%)	No reduction in 90-day mortality (15 vs. 9.8%)
Secondary outcomes	↓ Radiographic progression, ↓ CRP/IL-10	↓ Mechanical ventilation duration	↓ Intubation, ↓ vasopressor use, ↓ ICU stay	↓ ICU, hospital, 180-day mortality	↓ Vasopressor duration (~1 day)
Adverse events	Safe, no increase in complications	Safe, no increase in complications	↑ Hyperglycemia and insulin use	↑ Hyperglycemia	Safe, no increase in complications

SCAP, severe community-acquired pneumonia; CRP, C-reactive protein; IL, interleukin; APACHE, acute physiology and chronic health evaluation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment score; PSI, pneumonia severity index; ICU: intensive care unit.

Another source of variability is the distribution of pathogens. Pneumococcal pneumonia remains the prototypical bacterial SCAP, but Gram-negative bacilli and multidrug-resistant organisms are increasingly represented in ICU cohorts (32, 33). Different bacterial pathogens elicit distinct host immune responses. For example, pneumococcal infection is characterized by neutrophil-driven hyperinflammation, while *Pseudomonas aeruginosa* sepsis is more often associated with features of immune paralysis, and these differences may influence the net effect of corticosteroid therapy (34).

These challenges illustrate the risk of oversimplification when all cases of “bacterial SCAP” are grouped under a single therapeutic strategy. Without robust microbiological phenotyping and stratification, clinical trials risk diluting potential benefits in specific subgroups.

The influence of inflammatory phenotypes

Accumulating evidence indicates that the host inflammatory phenotype is a critical determinant of response to corticosteroid therapy in SCAP. A recent individual patient data meta-analysis reported that adjunctive corticosteroids significantly reduced mortality only among patients with elevated systemic inflammation, defined by baseline CRP >204 mg/L, whereas those

with lower CRP values derived no benefit (13). Consistent results were observed in critically ill patients, where treatment effects were strongly dependent on baseline inflammatory markers, with reductions in treatment failure and mortality confined to those with high inflammatory activity (35). These findings suggest that the benefit of corticosteroids is likely confined to hyperinflammatory phenotypes, whereas patients with hypoinflammatory profiles may even be harmed (36, 37). This biological divergence provides a plausible explanation for the heterogeneity of trial results, as unselected cohorts inevitably included both hyper- and hypoinflammatory patients (38–40).

Recent advances in acute respiratory distress syndrome (ARDS) research reinforce the dynamic nature of the inflammatory phenotype. Pensier et al. (41) identified hyperinflammatory and hypoinflammatory phenotypes that were not static, with many patients transitioning between states during the course of illness. Notably, corticosteroid benefit was observed primarily in those with persistent hyperinflammation, whereas patients who shifted toward hypoinflammation did not derive benefit. This observation may be directly relevant to bacterial SCAP, as a substantial proportion of patients enrolled in recent RCTs of corticosteroids met ARDS criteria according to the Berlin definition (42) or the updated global definition (43). These insights emphasize the importance of repeated assessment of inflammatory status in SCAP, not only to guide the initiation of corticosteroid therapy but also to support decisions on whether to maintain or withdraw therapy.

Type, timing, dosing, tapering, and duration of corticosteroids

A major source of variability in trial outcomes is the heterogeneity of corticosteroid regimens. The five pivotal RCTs in bacterial SCAP adopted distinct approaches. Torres et al. (8) used intravenous methylprednisolone (0.5 mg/kg every 12 h for 5 days); the CAPE-COD trial administered hydrocortisone 200 mg/day by continuous infusion for 4 days, extended to a total of 8 or 14 days based on clinical improvement, with gradual tapering until ICU discharge (6); the ESCAPE trial evaluated a 20-day course of intravenous methylprednisolone, starting with a 40 mg bolus followed by 40 mg/day for 7 days, then tapered gradually to 20, 12, and 4 mg/day through day 20 (9); the APROCCHSS trial combined hydrocortisone 50 mg every 6 h for 7 days plus fludrocortisone (7); and REMAP-CAP used hydrocortisone 50 mg every 6 h for 7 days without systematic tapering (10). These differences in molecule, cumulative exposure, infusion schedule, and use of mineralocorticoid replacement highlight the lack of consensus on optimal steroid type, dose intensity, and treatment duration.

Mechanistic pharmacology provides a rationale for these divergent strategies. Hydrocortisone, with mineralocorticoid activity, supports vascular tone in septic shock and may be particularly advantageous when SCAP is complicated by vasodilatory collapse (6, 7, 44). In contrast, methylprednisolone achieves higher pulmonary tissue penetration (45), theoretically favoring alveolar inflammation. However, this pharmacologic advantage has not consistently translated into survival benefit in RCTs (8, 9), whereas hydrocortisone emerged as the only corticosteroid associated with mortality reduction in network meta-analysis (14).

As discussed in the section on inflammatory phenotypes, hyperinflammatory and hypoinflammatory states are not fixed and may evolve during the course of illness (41). This dynamic trajectory has important implications for corticosteroid tapering and timing. Tapering serves not only to prevent hypothalamic-pituitary-adrenal axis suppression and rebound cytokine release after abrupt discontinuation (46), but also to provide a planned reassessment point. In practice, tapering has two purposes including (1) to continue modulating a persistent hyperinflammatory state while avoiding abrupt withdrawal, and (2) to allow discontinuation if the patient has transitioned into a hypoinflammatory phenotype where further immunosuppression may be harmful (13, 41). Regarding timing, early initiation (often ≤ 24 h in trials) in patients with hyperinflammation may intercept the cytokine surge at its peak, whereas late initiation risks missing this window, potentially diminishing efficacy.

Importantly, a recent meta-analysis reported that adjunctive corticosteroids did not significantly increase serious adverse events such as gastrointestinal bleeding or secondary infections, although mild hyperglycemia and hyponatremia were more common (47). These metabolic disturbances are generally transient and manageable, but they underscore the need for close monitoring in critically ill patients. Corticosteroid exposure may increase the risk of neuromuscular weakness in critically ill patients with sepsis; however, this complication appears minimal and is outweighed by the survival benefits observed in bacterial SCAP (47, 48). When

given at appropriate doses and with tapering, corticosteroids are safe but require close monitoring for metabolic and neuromuscular effects to balance benefit and harm.

Clinical implications and future directions

The cumulative evidence from recent trials shows both the promise and the limitations of corticosteroid therapy in bacterial SCAP. Clinical translation requires moving beyond a “one-size-fits-all” paradigm toward approaches that account for heterogeneity in both inflammatory phenotype and therapeutic regimens.

First, stratification is essential. Microbiological distinctions and inflammatory phenotypes shape both the magnitude and the direction of steroid effects. Systematic pathogen identification and advanced diagnostics may help clarify which patients benefit or are harmed by corticosteroids. Evidence from sepsis and ARDS studies have integrated clinical features with biomarkers to define inflammatory profiles that identify patient subgroups most likely to benefit from corticosteroids (35, 37–41, 49–52). Similar investigations are warranted in patients with bacterial SCAP.

Second, regimen optimization remains a priority. Current data suggest that hydrocortisone, particularly when initiated early in hyperinflammatory states and tapered according to dynamic inflammatory phenotype, may provide the best balance of systemic and pulmonary effects (6, 7, 14). However, variation in dosing, duration, and tapering strategies across pivotal RCTs underscores the urgent need for standardized and adaptive protocols (6–10).

Finally, future research should embrace adaptive trial designs that integrate repeated inflammatory assessments, biomarker thresholds, and flexible treatment algorithms. Such designs could reconcile the conflicting results of past trials by targeting corticosteroid therapy to the right patients, at the right time, with the right dose. Ultimately, tailoring corticosteroid therapy according to host inflammatory status and pathogen profile may transform inconsistent trial results into consistent survival benefits for patients with severe bacterial pneumonia.

In conclusion, adjunctive corticosteroids hold promise in bacterial severe community-acquired pneumonia, but their effectiveness depends on underlying etiology, host inflammatory phenotype, and the treatment regimen applied. Future research should prioritize biomarker-guided strategies and standardized protocols to ensure corticosteroids are targeted to the right patients at the right time.

Author contributions

TN: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. HD: Methodology, Visualization, Writing – review & editing. CT: Conceptualization, Supervision, Writing – review & editing. PP: Conceptualization, Visualization, Writing – review & editing. VH: Conceptualization, Methodology, Writing – review & editing. VD: Conceptualization, Methodology, Visualization, Writing – review & editing.

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