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Adjunctive immunomodulation in severe community-acquired pneumonia

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Community-acquired pneumonia (CAP) is common, affects economically disadvantaged people disproportionally, and is one of the leading causes of death in the world. Patients with CAP can present with a large spectrum of severity. Most patients do not require hospitalization and usually fare well. In hospitalized patients, however, this scenario is different. In Brazil, there were 392,169 admissions for pneumonia in individuals ≥ 15 years of age in hospitals monitored by the Brazilian Unified Health Care System in 2022.[1] Of these, 64,704 suffered in-hospital death, which resulted in a mortality rate of 16.5%.[1] The mortality rate numbers become even more staggering when the focus is on patients requiring ICU care, which represent approximately 20% of hospitalized patients with CAP. A study in Louisville, United States, showed that adult patients with CAP requiring ICU care have 30-day and 1-year mortality rates of 27% and 47%, respectively.[2]

Different avenues of research are being developed to combat the exceedingly high mortality of patients with severe CAP. These include new diagnostic tests, the development and testing of antimicrobials, novel medications against pathogens (e.g., monoclonal antibodies), clinical pathways, and fundamental research on the pathogenesis of the disease. The recognition that many patients with CAP develop ongoing inflammation and organ failure despite being able to eradicate the causative pathogen early in the infection has sparked interest in the host response and immunomodulation.[3]

The host immune response to CAP involves a complex interplay between innate and adaptive immune responses, pattern recognition receptors, inflammasomes, airway epithelium, and alveolar macrophages.[4] This immune response can become dysregulated in some patients, resulting in organ failure, cardiovascular complications, worsening hypoxia, and death. Systemic glucocorticoids have been tried as adjunctive therapy to immunomodulate the host response and improve outcomes in patients with CAP. Interestingly, the beneficial role of systemic glucocorticoids in the treatment of specific etiologies of CAP such as severe COVID-19 and *Pneumocystis jirovecii* infection has been established.[5,6]

What if systemic glucocorticoids also showed a mortality benefit as an adjunctive therapy for patients with severe CAP of any etiology, though? This would be a breakthrough given that systemic glucocorticoids are inexpensive and CAP (and severe CAP) is common. Recently, two large randomized controlled trials attempted to address this question but on the surface since they did not provide uniform results.[7,8] In the study by Dequin et al. (CAPE COD trial),[7] which included 795 patients, the data show that early use of hydrocortisone reduced the 28-day mortality rate (6.2%; 95% CI, 3.9-8.6 in the hydrocortisone group vs. 11.9%; 95% CI, 8.7-15.1 in the placebo group; p = 0.006), reduced the need for endotracheal intubation, and reduced the number of patients requiring vasopressors with no difference in the incidence of hospital-acquired infections. Conversely, in the study by Meduri et al. (ESCAPe trial),[8] which included 584 patients, there was no difference in 60-day mortality rate in patients with severe CAP who were treated with methylprednisolone (16% in the methylprednisolone group vs. 18% in the placebo group; OR = 0.89; 95% CI, 0.58-1.38; p = 0.61).

Although both trials were multicenter, double-blinded, randomized, and contained a placebo arm, there are important differences in the inclusion and exclusion criteria that are noteworthy. In order to be eligible for the CAPE COD trial,[7] patients had to be admitted to an ICU or intermediate care unit and satisfy one of the following criteria: Pneumonia Severity Index score > 130, initiation of mechanical ventilation, or a Pao_2:Fio_2 ratio < 300 on non-rebreather mask or high-flow nasal cannula. Subsequently, patients in the hydrocortisone arm received glucocorticoids within 24 h of fulfilling one of the aforementioned severity criteria. There were several exclusion criteria (including the presence of septic shock, influenza, and aspiration pneumonia), which resulted in ~86% of the patients who were screened being excluded from the trial.[7] This may negatively have impacted the generalizability of the study. In contrast, patients in the ESCAPe trial[8] were diagnosed with severe CAP based on one major or three minor American Thoracic Society/Infectious Disease Society of America criteria for severe pneumonia and were enrolled within 72-96 h after hospital admission. These patients were predominantly male since the study was conducted within the Veteran's Health Administration.

The baseline Pao_2:Fio_2 ratio was 137-143 in patients in the CAPE COD trial[7] and 181-188 in the ESCAPe trial.[8] In both trials, the distribution of patients in each Pneumonia Severity Index class was approximately similar. A critical difference was the time from patient presentation to glucocorticoid administration. The median time from hospital admission to study treatment initiation was 40 h in the ESCAPe trial.[8] The median time from hospital admission to ICU admission was 5.5 h and from ICU admission to study treatment initiation was 15.3 h in the CAPE COD trial.[7] It is, therefore, apparent that glucocorticoids were initiated earlier in the CAPE COD trial.[7] This difference is important since earlier treatment is more likely to modulate the host inflammatory response and consequently lead to better outcomes. An extreme

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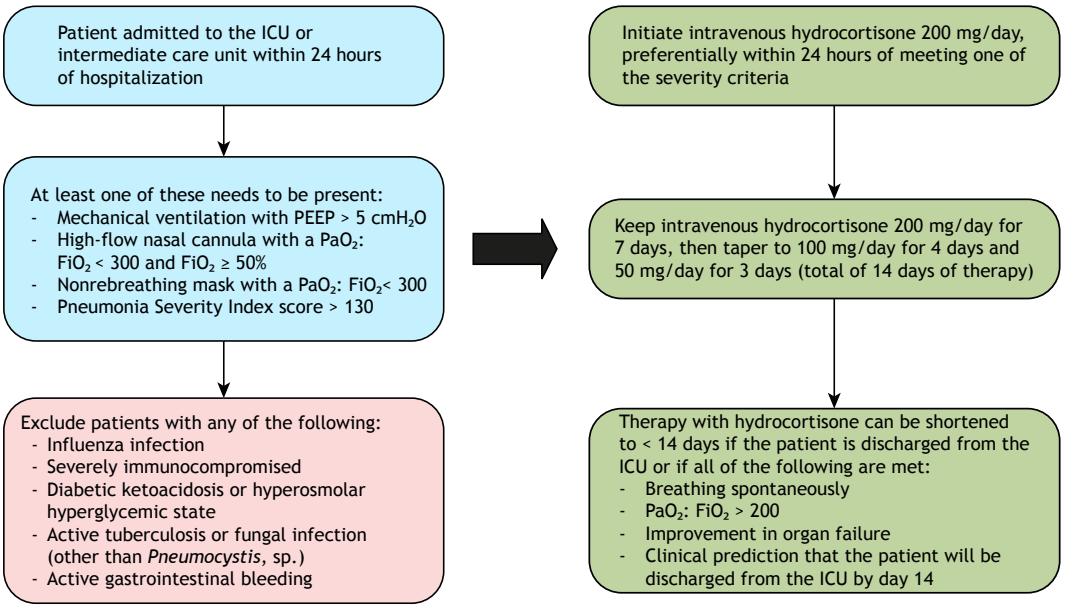

Figure 1. Strategy for initiating adjunctive immunomodulatory therapy with hydrocortisone in patients with severe CAP. Figure adapted from the trial by Dequin et al.[7]

analogy to this is the response seen with the early use of dexamethasone in bacterial meningitis, which has been shown to decrease cerebrospinal fluid levels of inflammatory cytokines and reduce cerebral edema.[9]

Overall, despite some degree of uncertainty, we believe that it is more likely that there is a benefit in the use of systemic glucocorticoids for the treatment of severe CAP (Figure 1). The mortality benefit may be more evident when systemic glucocorticoids are started earlier in the course of infection. Clinicians should be aware of clinical features, such as hypoxia, which may be an indicator of a better response to systemic glucocorticoids, and hydrocortisone should be the systemic glucocorticoid of choice in the absence of comparative data among the different glucocorticoid formulations.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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