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WHAT'S NEW IN INTENSIVE CARE

Adjuvant therapies in critical care: steroids to treat infectious diseases

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Introduction

Globally, clinicians have avoided prescribing corticosteroids (CS) for active infection, as they have immunosuppressive effects and therefore may impair mechanisms that fight infection. However, we, as intensivists, often see patients adequately treated with antibiotics deteriorating on the basis of progressive, localized or systemic inflammation triggered by an infection that is being treated with an adequate antibiotic regimen. Clinically, they have been proven as deleterious in some infectious diseases, such as influenza pneumonia, established for early use in a wide range of infective conditions, such as pneumococcal meningitis, and remain a matter of intense debate in several other infectious conditions, such as severe community-acquired pneumonia.

We present a synthesis of the role of corticosteroids in severe infectious situations treated in intensive care departments, discussing, as the title implies, infectious diseases and not syndromic presentations, such as sepsis or ARDS. The use of CS in HIV patients was excluded from the scope of this review.

In severe community-acquired pneumonia

In spite of improvements in mortality rates, mainly owing to early and adequate antibiotic therapy and better organ support, morbidity and mortality in patients with severe community-acquired pneumonia (SCAP) are still significant probably due to a misbalanced and disproportionate local and systemic inflammatory response, potentially exacerbated by pre-existing low-grade chronic inflammatory comorbidities, leading to several complications such multiple organ dysfunction. Based on this, the interest in the use of adjunctive anti-inflammatory drugs, such as CS and macrolides, has been increasing, particularly in the most severe cases.

Few studies evaluated the impact of adjunctive CS in SCAP. Confalonieri et al. [1] demonstrated a significant mortality reduction and improvement in several clinical endpoints such as PaO2/FiO2 ratio, multiple organ dysfunction syndrome severity scale and ICU and hospital length of stay. This beneficial effect on mortality in SCAP was confirmed in a retrospective observational study [odds ratio (OR) 0.287; 95% confidence interval (CI) 0.113–0.732] [2]. A meta-analysis [3] showed that the use of CS, namely prolonged (> 5 days) treatment, improved mortality in SCAP. More recently, Torres et al. [4] performed a randomized controlled trial (RCT) evaluating the impact of CS in SCAP patients with marked systemic inflammatory response (C-reactive protein $\geq$ 15 mg/dl) and observed a reduction in treatment failure (OR 0.34; 95% CI 0.14–0.87), mainly late treatment failure, but not in hospital mortality; and Tagami et al. [5] observed that a low dose of CS was associated with a significant reduction in 28-day mortality, but only in those patients under vasopressor support. In a systematic review [6], mortality was lower in the CS group, but this positive effect was only significant in the severe cases (OR 0.39; 95% CI 0.20–0.77). CS-associated mortality reduction was confirmed by some [7, 8] and denied by other [9, 10] recent meta-analyses. A recent individual patient data meta-analysis showed a consistent trend towards a larger benefit in the most severe CAP patients and a greater reduction in hospital length of stay (LOS) [11]. Besides reduction in LOS, also observed by other authors [6–10], CS use may positively impact on other outcomes, such as reduction in the need for mechanical ventilation [6], reduction in acute respiratory distress syndrome [6, 10] and decrease in time to clinical stability [6–8, 10]. The disparity of results observed in these meta-analyses can

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be explained by different definitions of patient populations, different types of outcomes and different selection of studies.

Although recent guidelines suggest the use of CS for 5–7 days at a daily dose below 400 mg intravenous hydrocortisone or equivalent in hospitalized patients with CAP [12], in our opinion, no clear recommendation can be made since the dosages, the type and the duration of the CS treatment were very different among all RCTs. Clearly not all SCAP patients are alike. In a recent review, based mainly on observational studies, CS use was associated with increased mortality in influenza pneumonia. However, the quality of evidence is not sufficient enough to support a definitive conclusion [13]. Until then, international guidelines suggest against their use in these cases [12]. Thereby, instead of engaging in a pro and con discussion, it is important to aim at defining the subgroup of SCAP patients that may benefit from CS adjuvant therapy.

In *Pneumocystis jirovecii* pneumonia

Data on the efficacy of CS adjunctive therapy in HIV-negative patients with moderate to severe *Pneumocystis jirovecii* pneumonia (PJP) are limited and inconsistent. No hospital mortality benefit was observed in retrospective studies. However, in a small retrospective study, CS use was associated with a shorter duration of mechanical ventilation, ICU admission and reduced supplemental oxygen use [14]. Yet, higher dose of CS (> 1 mg/kg/day) seems to be an independent predictor of ICU mortality but not of ICU-acquired infections [15]. Therefore, the use of CS in severe PJP and respiratory failure should be decided on an individual basis and not recommended by routine. An ongoing study is currently comparing CS with placebo in non-HIV immunocompromised patients with PJP, with mortality at day 28 as the main endpoint.

In severe typhoid fever

Data on CS use in severe typhoid fever are scarce. An RCT showed that dexamethasone use for 2 days accelerated defervescence, improved clinical response and reduced overall mortality [16]. However, a case control study failed to demonstrate improvement in mortality or complications [17].

In bacterial meningitis

For patients with bacterial meningitis, a recent Cochrane review [18], including 25 studies, found that dexamethasone decreased rates of severe hearing loss (6.0% versus 9.3%), any hearing loss (13.8% versus 19.0%) and neurological sequelae (17.9% versus 21.6%), although it did not significantly reduce mortality (17.8% versus 19.9%).

Regarding meningitis aetiology, mortality was lower (29.9% versus 36.0%) in those patients with *Streptococcus pneumoniae* treated with CS, while no effect on mortality was seen in *Haemophilus influenzae* and *Neisseria meningitidis* meningitis. The rate of hearing loss in children with meningitis due to *H. influenzae*, but not due to other bacteria, was lower in the CS group (4% versus 12%). In some studies, CS therapy decreased mortality, seizures prevalence and accelerated recovery from stupor and coma [18]. Although a greater risk reduction occurs when steroid is given with or before the start of antibiotics, some experts suggest they may be administered up to 4 h after start of antibiotics [19]. Therefore, a regimen of dexamethasone 0.6 mg/kg daily for 4 days, started preferably before antibiotic therapy, is indicated [20] and this recommendation is supported by the most recent guidelines [12]. CS should be discontinued in all cases other than pneumococcal and *H. influenzae* infection [19].

In tuberculosis

A review of 1337 patients with mild to severe tuberculous meningitis showed a quarter mortality reduction with steroids [RR 0.75 (CI 0.65 to 0.87)] [21], at least in the short term. The survival benefit was mostly seen in patients with mild disease and CS have little or no effect if advanced neurologic symptoms are present. In addition, no increased risk of adverse effects was observed. Therefore, adjunctive CS, such as dexamethasone tapering over 4 weeks from 0.3 to 0.4 mg/kg, is recommended for tuberculous meningitis.

In patients with other presentations of severe tuberculosis, such as pericarditis, CS may reduce complications, need for pericardiectomy/repeated pericardiocentesis and death from all causes, and probably deaths caused by pericarditis [22]. Nevertheless, the impact of CS on constriction or cancer is not known. Therefore, we advise the use of prednisolone tapering from 60 mg daily over 11 weeks in constrictive or at high risk of constrictive tuberculous pericarditis.

Regarding tuberculous pleurisy, CS may reduce time to symptoms or pleural effusion resolution and the risk of pleural scaring on chest X-ray after cure. However, the impact on long-term respiratory function is not known. So, further studies are needed to clarify the use of CS in this setting [23]. Data on the role of CS in patients with miliary tuberculosis are limited, with conflicting results coming from case reports and small clinical series [24].

Conclusion

CS administration benefits a variety of infections and the greatest benefit seems to occur in severe infections with high morbidity and high baseline mortality, namely bacterial and tuberculous meningitis, tuberculous

Table 1 Corticosteroids use in infectious diseases: authors' personal point of view

Infectious disease	Potential benefits	CS use	Type and dose	Duration	Remarks
SCAP	Reduction in the need for MV Reduction in ARDS Reduction in hospital and ICU length of stay Reduction in treatment failure (mainly late) Mortality reduction?	Individualized (probably in patients with high degree of systemic inflammation)	Not defined (e.g. methylprednisolone 0.5 mg/kg IV q12 h)	5–7 days	Rule out influenza pneumonia
PJP	HIV patients Mortality reduction Reduction in the need for MV Non-HIV patients Reduction duration of MV Reduction in ICU admission Reduced supplemental oxygen use	HIV patients: strongly recommended in patients with moderate to severe disease Non-HIV patients: if $paO_2 \leq 70$ mmHg or alveolar-arterial gradient > 35 mmHg on room air or hypoxemia (< 92%) in pulse oximetry)	Prednisone[a]	21 days	
Typhoid fever	Accelerates defervescence Improve clinical response Mortality reduction?	In patients with severe systemic disease (shock, delirium, obtundation, stupor or coma)	Dexamethasone (3 mg/kg bolus followed by 1 mg/kg q6 h)	2 days	
Bacterial meningitis	Reduction of hearing loss Reduction of neurologic sequelae Mortality reduction only in *S. pneumoniae* meningitis	Strongly recommended	Dexamethasone (0.15 mg/kg q6 h)	4 days	Should ideally be started 15–20 min before antibiotic therapy 1st dose
Tuberculous meningitis	Mortality reduction	Recommended mainly in patients progressing from one stage to the next, patients with acute encephalitis, intracerebral tuberculoma, spinal block or incipient block, patients with head CT scan evidence of moderate or advancing hydrocephalus or marked basilar enhancement	Dexamethasone (0.3–0.4 mg/kg/day)[b]	8 weeks	
Tuberculous pericarditis	Reduction in constrictive pericarditis Reduction in the need for pericardiotomy Reduction in the time to clinical resolution	Recommended in constrictive or at high risk of constrictive tuberculous pericarditis	Prednisone[c]	11 weeks	Do not use if pericarditis is not constrictive, particularly among HIV patients

SCAP severe community-acquired pneumonia, *MV* mechanical ventilation, *ARDS* acute respiratory distress syndrome, *PJP Pneumocystis jirovecii* pneumonia, *id* Once daily

[a] Regimen: 40 mg bid for 5 days followed by 40 mg id for 5 days and then 20 mg id for 11 days

[b] On week 3: 0.2 mg/kg/day; week 4: 0.1 mg/kg/day; week 5: 4 mg/day and then taper 1 mg off daily dose each week. Prednisone 60 mg/day for 2 weeks and then taper 10 mg/week is an alternative regimen

[c] 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks and 5 mg/day for 1 week

pericarditis and, perhaps, in severe typhoid fever and severe non-HIV PJP. Further studies are needed to define which SCAP patients benefit from this therapy. Table 1 summarizes our personal point of view in terms of CS use for treatment of infectious disease, although there is an obvious need for more adequately powered trials to provide definitive evidence of benefit or harm and a better understanding of how steroids modulate disease processes.

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Compliance with ethical standards

Conflicts of interest
José Manuel Pereira: received honoraria for lectures from MSD, Astellas, Pfizer and Novartis. Thiago Lisboa: no conflicts of interest. José Artur Paiva: no conflicts of interest.

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