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Corticosteroids for community-acquired pneumonia: a critical view of the evidence

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The current evidence raises more questions than answers, and does not support routine use of corticosteroids for CAP <http://ow.ly/t01g302QDhG>

Community acquired pneumonia (CAP) remains a leading cause of morbidity and mortality, with **mortality** rates between 5% and 15% in hospitalised patients, rising to up to **30%** in patients admitted to the intensive care unit (ICU) [1–3].

There has been **little progress** in the management of CAP **since** the widespread introduction of **antibiotics** in the **1950s**, with no new classes of drugs licensed specifically for CAP and **little progress in reducing mortality**. The **focus** of international **guidelines** for CAP have been on “**doing the simple things well**”, since early antibiotic administration, appropriate fluid resuscitation, early mobilisation and guideline-concordant antibiotics have been associated with improved outcomes, albeit with low-quality evidence [3–5].

Some of the lack of progress reflects the fact that, in **many** cases, **mortality** from CAP may be **unavoidable**. A **third** of patients admitted to hospital **have** “**do not attempt resuscitation**” orders, while only a **quarter** of patients dying from CAP receive mechanical **ventilation** before death, indicating a **very high frequency of treatment restrictions** [6, 7].

Nevertheless, there is a group of patients the CAP, usually with acute **respiratory failure** and **septic shock**, who die or experience prolonged and disabling hospital admissions **despite antibiotic** treatment and appropriate quality of care. These patients have **marked** systemic and pulmonary **inflammation**, providing the **rationale** for **anti-inflammatory** therapy.

This background is essential to understanding the current debate around the use of oral or intravenous corticosteroid treatment in CAP.

Two recent randomised controlled trials (RCTs), using very different steroid preparations and studying different patient populations, reported **positive results** in 2015 [8, 9]. These were followed by a series of **meta-analyses** all suggesting positive data in **favour of corticosteroid** use [10].

In this issue of the *European Respiratory Journal*, **Wirz et al.** [8] report an important **subanalysis** of their previous RCT of prednisolone 50 mg vs placebo [11]. In the original study, 802 patients were randomised and steroid treatment was associated with a significant reduction in time to clinical **stability** (TCS) (1.4 days; hazard ratio 1.33, 95% CI 1.15–1.50) [8]. Hospital **discharge** was **1 day shorter** (6 versus 7 days, $p=0.01$) with **no difference** in ICU admission or **mortality**. There was an increase in adverse events (OR 1.77, 95% CI 1.24–2.52; $p=0.002$) largely driven by an increase in hyperglycaemia [8].

This **subanalysis** attempted to address the key question of **which** patients may **benefit** and **which** may be **harmed** by treatment. Intriguingly, they identify that patients with **pneumococcal pneumonia** did **not** derive a **benefit** from **steroids**, with no improvement in the TCS or duration of antibiotic treatment [8]. This study also addresses concern that **steroids might** be **harmful** in the context of **viral** pneumonia. Patients with **confirmed viral** infection **benefitted** with a **shortened TCS** as with the overall group.

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Nevertheless, the finding of lack of efficacy in the pneumococcal subgroup, the largest and most important microbiological subgroup in CAP, adds further question marks in an already confused picture [8].

In the other recently published RCT, TORRES *et al.* [9] performed a multicentre RCT in patients with severe CAP and a C-reactive protein (CRP) level $>150 \text{ mg}\cdot\text{L}^{-1}$ on admission. Severe CAP was defined as a Pneumonia Severity Index (PSI) of V or the Infectious Diseases Society of America/American Thoracic Society criteria [1]. The study was conducted over 8 years, and randomised 61 patients to methylprednisolone and 59 patients to placebo for 5 days. The primary outcome was treatment failure, defined as a composite of development of shock, need for mechanical ventilation, death or radiographic progression [9]. The study showed a significant reduction in treatment failure of 18%. This was driven largely by a 14% reduction in radiographic progression. Reductions in other end-points were not statistically significant. Length of stay and TCS were not affected by steroid treatment [9].

In 2011, MEIJVIS *et al.* [12] compared 4 days of intravenous dexamethasone to placebo in hospitalised CAP patients and showed a 1-day reduction in the length of stay, with no improvements in ICU admission rate or mortality. The patient population had mild-moderate CAP according to the PSI. Hyperglycaemia was increased as an adverse event.

A meta-analysis by SIMIENIUK *et al.* [10] pooled these various studies, demonstrating a reduction in mortality that did not achieve statistical significance from 12 trials (rate ratio 0.67, 95% CI 0.45–1.01), with significant reductions in mechanical ventilation and development of acute respiratory distress syndrome from five and four trials, respectively. While this might be considered encouraging, the possible mortality benefit was largely driven by a single controversial trial in which the mortality rate in the steroid arm was 0% [13]. The quality of evidence was predominantly low.

Nevertheless, in the face of a series of positive trials, leading voices advocate the routine use of corticosteroids for CAP [14]. So why should we be cautious?

First, there are well conducted RCTs showing no impact of steroid treatment. A trial conducted in the Netherlands randomised 213 patients to prednisolone 40 mg for 7 days or placebo, with a primary outcome of clinical cure at day 7 [15]. This study found no benefit of steroid treatment and, importantly, found a trend toward fewer patients with cure at day 30 ($p=0.08$) with an increase in patients meeting the criteria for late failure, defined as a worsening or increase in symptoms after 7 days (OR 2.36, 95% CI 1.05–5.31). Mortality and TCS were not different between the two groups [15].

Second, it is also important to look critically at the positive trials. The BLUM *et al.* [11] and MEIJVIS *et al.* [12] studies were criticised because the end-points may have been influenced by the antipyretic and anti-inflammatory effects of corticosteroids. Both SNIJDERS *et al.* [15] and MEIJVIS *et al.* [12] demonstrated clearly that corticosteroids have an antipyretic effect, with resolution of fever ($>37.8^\circ\text{C}$) reached approximately 1 day earlier with steroids than placebo [13, 15]. While this may be regarded as a benefit, it casts doubt on whether TCS is the right end-point to evaluate corticosteroids. TCS is a US Food and Drug Administration-approved end-point for antibiotic trials in CAP because TCS correlates well with future mortality and can therefore be used as a valid surrogate of response [16, 17]. Crucially, antibiotic treatment does not directly interfere with any of the criteria but steroids might. Fever may be artificially suppressed by corticosteroids. While studies have attempted to address this issue, the concern remains that this is a flawed end-point to test steroids [18]. Length of hospital stay is also partly dependent on defervescence and TCS. In the MEIJVIS *et al.* [12] study, consistent reduction in CRP was part of the criteria for hospital discharge [12]. Steroids have been consistently shown to accelerate decline in CRP [12].

The TORRES *et al.* [9] trial had significant methodological strengths in targeting severe CAP and using CRP to attempt to target patients with greater systemic inflammation. Nevertheless, limitations of the trial have been highlighted. The treatment failure outcome was largely driven by steroids preventing radiological progression, an outcome that is poorly characterised [9]. The study was not prospectively registered on a clinical trial database and the retrospective registration listed a different primary outcome (rate of nonresponsive to empirical therapy) to that ultimately reported in the paper (www.clinicaltrials.gov identifier number NCT00908713). In addition, although the study tried to enrich for severe CAP, 24–30% were in PSI groups I–III and the mortality rate was only 3% [9].

A further criticism of all of the steroid studies is that levels of improvement seen with steroids may be achieved with simple improvements in care. A reduction in length of stay from 7.5 to 6.5 days sounds valuable but, as in the MEIJVIS *et al.* [12] study, in a population of patients in which $>50\%$ of patients had PSI scores I–III, where inpatient care is often not required [19], this represents a surprisingly long baseline length of stay. Improvements of >1 day can be achieved with early mobilisation and good-quality inpatient care without new pharmacotherapies [4]. Likewise, reductions in duration of antibiotic therapy and intravenous antibiotic therapy can be achieved with simple clinical interventions [20, 21].

So, it is important to sound a note of caution. The quality of evidence currently available for corticosteroids would be unlikely to survive careful consideration by a clinical practice guideline panel. The recent positive trials increase the likelihood that steroids will find a role in the management of CAP but in my view, the data do not yet support routine use.

Additional RCTs will report soon and should shed additional light on the debate (NCT02517489 and NCT01743755). There is likely to be a subgroup of patients with CAP who derive significant benefit from corticosteroid treatment, but how to identify this group should be the focus of new research. Even in diseases with well-accepted roles for corticosteroids such as COPD and asthma, biomarkers can now identify groups of patients with steroid responsive and non-steroid responsive disease [22]. In a disease as heterogeneous as CAP, such studies will be difficult, but are essential.

Major improvements in length of stay, duration of antibiotic therapy and even mortality, greater than those demonstrated with corticosteroids, can be achieved through compliance with high-quality care recommendations, and yet audits show persistently poor compliance with guidelines [1–5]. Doing the simple things well should continue to take priority over the use of corticosteroids, for now.

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