

Systemic corticosteroids and community-acquired pneumonia – cautious optimism or wishful thinking?

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The potential use of oral corticosteroids in patients with community-acquired pneumonia (CAP) has become extremely topical. In the past 12 months we have had two randomized controlled trials (1,2), three meta-analysis (3-5) and a significant number of associated editorials and commentaries. While the randomized controlled trials could be described as mildly positive at best, the meta-analyses, and particularly the paper by Siemieniuk and colleagues (4), have been much more vocal in their support of steroid therapy.

That CAP is both a common and serious health problem is undisputed. CAP has also been a frequent focus of quality of care measurement with not only institutional inpatient mortality targeted, but also a host of surrogate measures selected on the basis of some association with adverse outcome (e.g., performing blood cultures and timing of antibiotic therapy). Unfortunately a large proportion of the mortality in CAP is probably not preventable as it occurs in elderly patients with multiple comorbidities in whom significant limits in the ceiling of care (e.g., not for resuscitation, not for intensive care etc.) are (almost always appropriately) in place. There remains however a significant cohort of patients who die despite all attempts to treat them, and this remains a major source of frustration and angst to clinicians and the families of those who succumb.

In the group of patients who die despite all attempts to cure them, multi-organ failure from severe sepsis is the usual scenario. Given that sepsis is generally thought to be driven by an excessive or uncontrolled pro-inflammatory response (6), suppression of the immune system with high doses of corticosteroids would seem a logical therapy to trial. Unfortunately despite a number of small trials

suggesting therapeutic benefit, large scale randomized trials have found no benefit of immunosuppressive doses of corticosteroids in either septic shock or acute lung injury and are therefore not recommended as standard therapy (7). As with many interventions it is likely that within the broad group of patients with sepsis, steroids have a net beneficial effect in some and a net harmful effect in others. Proponents of steroids have argued that it is patients with pneumonia may be in the beneficial group.

Proponents of meta-analysis argue that this methodology helps tease out whether there is a real benefit (or harm) of a therapy hidden by under powering of the clinical trials conducted so far. The problem with the approach of meta-analysis is that even one “outlier” study can significantly influence the outcome when added to a number of studies with neutral (i.e., negative) results. In the case of CAP and steroids the problematic paper is Confalonieri and colleagues (8) which demonstrated a remarkable benefit of steroids that no one has been able to repeat or even come anywhere near the efficacy demonstrated and therefore its credibility as an estimate of the likelihood of benefit of steroids is questionable particularly in the context of all the other randomized studies now published. Examining the Forrest plot in Siemieniuk and colleagues (4) it is immediately apparent that if the Confalonieri *et al.* paper is excluded as an aberrant outlier the overall analysis is minimal to no benefit (8).

The counter argument to the meta-analysis of Siemieniuk and colleagues being flawed because of the bias introduced by the Confalonieri *et al.* study is that there is no evidence of harm, so why not give steroids anyway? Personally I think this is a dangerous path to follow, driven

as it is by desperation (the need to do something) rather than clear evidence of benefit.

While I am sure that future studies will tease out subgroups of patients with CAP that will have a net positive benefit from high dose corticosteroids, I am equally sure that there are many other things with a likely much higher benefit for patients with CAP that we have evidence for but are currently not doing well. Compliance with the standard “sepsis bundle” approach outlined in the Surviving Sepsis campaign (7) is associated with better outcomes in patients with CAP (9,10), and includes rapid administration of antibiotics, fluid resuscitation and correction of electrolyte abnormalities and hyperglycemia. Inclusion of a macrolide in combination with a beta-lactam remains the optimal standard therapy in sick patients based on current evidence (11). Early mobilization improves mortality (12), but is not part of routine care in most hospitals. Acute myocardial infarction occurs in up to 10% of patients who are severely ill with pneumonia (13-15), and anti-platelet therapy appears to significantly reduce the risk (16-18), but again is not part of the standard of care. Pulmonary emboli are also a significant contributor to adverse patient outcomes (19), but thrombosis prophylaxis is also not routine in many hospitals (20,21).

In summary, the interest surrounding the use of immunosuppressant doses of corticosteroids is driven much more by clinician frustration in their inability to change patient outcomes than it is by the current strength of the data. I am sure that future research will identify patients that will benefit from steroid immunosuppressant therapy, but much greater gains are already available through careful and rigorous application of optimal treatment bundles that include rapid antibiotic therapy and fluid resuscitation, early mobilization, myocardial ischaemic and venous thrombosis prophylaxis and attention to other comorbidities such as hyperglycemia and electrolyte abnormalities. When all of these are routinely covered in all individuals then steroids may find their place.

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Footnote

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