Author's response to reviews

Title: Corticosteroid Treatment for Community-acquired Pneumonia: A Randomized, Double-blind Study - the STEP Trial

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Author's response to reviews: see over
Basel, June 4, 2014

Dear Editors,

Dear Prof. Annane and Prof. Salluh,

Thank you for the careful and detailed comments, which allowed us to considerably improve our manuscript. Please find below our point-by-point reply in which we answered to all reviewers’ comments in detail, and the changes made due to editorial request. A version of the revised manuscript including changes highlighted in yellow has been uploaded with the point-by-point reply.

Yours faithfully,

Claudine A. Blum, MD
for the co-authors

Changes due to editorial request:

1. The title has been changed to Corticosteroid Treatment for Community-acquired Pneumonia - the STEP Trial: Study protocol for a randomized controlled trial.

2. The study registration date was added to the trial registration number.

3. The list of abbreviations has been moved below the Trial Status.

4. The names of all ethical bodies that approved the study in the various centers involved have been included, and the references given, in the Methods section.

5. Each author is now mentioned individually in the Authors’ Contributions section. The initials RK have been changed to RB, it was apparently a misspelling. We apologize for this.

Reviewer: Djillali Annane
1. How will the researchers deal with viral pneumonia? The trial started in 2009, during the H1N1 pandemics. In 2010 and thereafter H1N1 influenza accounted for relatively many community-acquired pneumonia. This might be an important confounder.

Thank you for this important comment. Because the etiology of CAP is usually not known at presentation, we decided to keep patients with possible or proven viral CAP in the trial, but to do a subgroup analysis to investigate whether steroids have a different effect based on CAP etiology.

For this purpose, we have since the beginning of the study recorded whether H1N1 testing was performed and if it returned positive results. In addition, treatment with oseltamivir was documented. From 2010 on, nasopharyngeal multiplex PCR was performed routinely in all patients included in the study. Patients who had presumed or proven viral pneumonia were included in this study if they fulfilled the inclusion criteria, i.e. had an infiltrate on chest x-ray. Furthermore, participating centers were encouraged to treat patients with low procalcitonin and therefore possible viral pneumonia without antibiotics; however, the final decision if antibiotics were given to a patient was up to the discretion of the treating physician.

2. It is worth explaining why the researchers didn’t choose to start IV corticosteroids, given that all patients had to be admitted to the hospital. Even though, the treatment could be continued orally thereafter.

We decided against IV corticosteroids and for oral prednisone for practical reasons. The hospital pharmacies involved were not able to provide a blinded IV solution 24 hours/7 days per week. The bioavailability of oral prednisone is excellent, and it may be grounded and is therefore applicable in patients not able to swallow, like in patients on mechanical ventilation or in geriatric patients. Additionally, we did not want to have patients refuse informed consent in case they would not need an IV line except for study reasons, as oral antibiotics are quite often given in hospitalized patients with CAP.

We have now included this point in the discussion.

3. There is a worldwide shortage in synthetic corticotropin. Did the researchers...
secure the provision of ACTH for testing the research participants?

In Switzerland, we have not until lately been affected of the corticotrophin shortage. We have secured the provision of ACTH in case it would run out at the hospital pharmacy by keeping our own stock at the Department of Endocrinology, University Hospital Basel. Furthermore, as we are using the 1 ug test and not the 250 ug test, our and the pharmacy’s stocks will last longer.

4. At least one previous meta-analysis suggested that the more severe the CAP the more likely the benefit from corticosteroids. In particular patients with shock or ARDS may be those who will benefit at most. Why not including exploration of treatment effects in these subgroups?

We acknowledge this important comment. Outcome in ICU patients, measured by time to discharge from ICU, duration of vasopressor treatment and of mechanical ventilation, will be assessed as a secondary endpoint. However, these results will have to be interpreted with caution, as the number of ICU patients including patients with ARDS will be small. This has also been mentioned in the study limitations. However, in the paragraph about subgroup analyses we pre-specify a subgroup analysis according to severity of CAP - low risk group: PSI I-III vs. high risk group: PSI IV-V. In line with your statement we hypothesise that patients with more severe CAP and supposedly more severe inflammation will benefit more from corticosteroids.

Reviewer: Jorge Salluh

Major revisions:

1. Is the study adequately powered for harm? How was this calculated (if so)?

All statistical tests in the analysis of this trial will be two-sided. Therefore, apart from the known side effects of corticosteroid therapy, the statistical power to detect a harmful effect will be the same as for a beneficial effect. The power calculation for the primary outcome is reported in the manuscript – 85% power with 800 randomised patients and 80% with 700 randomised patients. Our trial is not powered for
designated secondary outcomes but we estimated that we have about 60% power to detect a 33% relative risk increase or decrease in a most patient-relevant combined outcome of mortality and need for ICU admission (two-sided type I error of 5%). In addition, we are currently planning an individual patient data meta-analysis of all randomised controlled trials that investigate adjunct corticosteroids for patients with CAP. This will maximize the statistical power for all patient-relevant outcomes. Apart from typical corticosteroid-related side effects, there was only one harmful effect detected in a previous trial by Snijders et al. [1] that randomized a total of 213 patients; late failure (defined as „a recurrence of signs and symptoms of pneumonia after 72 hours of admission after an initially beneficial response to treatment“) was more common in the prednisolone group (20 patients, 19.2%) than in the placebo group (10 patients, 6.4%; P=0.04). In order to comprehensively examine potential harms from corticosteroid therapy in CAP we will add “late failure” to our list of secondary outcomes (see methods section, secondary endpoints, page 11). With our planned sample size of 800 patients we will have a statistical power of practically 100% to detect the harm signal of late failure found by Snijders et al. (two-sided type I error of 5%). Our power calculation for the endpoint late failure is based on 19.2% vs 6.4% events (alpha: 0.05).

2- In the study by Meijvis et al. (Lancet 2011) a statistically significant reduction in time to clinical stability was observed as reflected by a reduction of 1 day in length of stay. However is this clinically significant? (especially in the face of potential harm to some patients as observed by longer ICU LOS in the dexamethasone group in the same study, as well as higher rates of hyperglycemia, and also other - though not statistically significant, albeit underpowered- endpoints as empyema). Please comment how you will overcome these limitations in the STEP trial.

By reducing the time to clinical stability and potentially also length of stay (LOS), nosocomial complications like infections, thrombembolic events, worsening of pre-existing frailty or delirium may be prevented. This arguably leads to better allocation of resources at the hospital and to a marked reduction of costs [2]. However, we will also investigate a number of other secondary endpoints especially including mortality, and complications to make sure that no increase in harm associated with corticosteroid use is observed.
Of note, while Meijvis et al. looked at length of stay (LOS) [3], our primary endpoint will be time to clinical stability, as defined by IDSA/ATS Guidelines [4]. As we have previously observed, LOS itself in community-acquired pneumonia may be confounded and prolonged by medical or organisational problems unrelated to CAP [2, 5, 6]. We believe that by measuring time to clinical stability and not LOS as our primary endpoint, we will be looking at a clinically significant parameter, as patients are feasible for switching to oral antibiotics and for discharge once they reach stability.

We have added this important point to the discussion on page 15.

1-please provide the number of IRB approval (Institutional Review Board)

We have now inserted the according reference numbers of the IRB approvals.

2-The study is almost finished...so how could potential suggested changes in the revision modify it?

We agree with the reviewer that changes in study design are no longer possible. Yet, as we have not yet started our statistical analysis, the reviewers’ inputs are still very much appreciated and will influence our final analysis plan.

Additional comment by the autors:

We made some additional editing changes to the methods section in order to improve the clarity and consistency of our report (see page 12, intention-to-treat and per-protocol population and page 14, planned subprojects).

References


