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## **DAD in nonresolving ARDS provides support for prolonged glucocorticoid treatment: a rebuttal**

Accepted: 7 April 2015  
Published online: 25 April 2015  
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Dear Editor,

We appreciate the comments of our esteemed colleague, Dr. Meduri, on our paper reporting results of open lung biopsy (OLB) performed in nonresolving ARDS patients [1]. In this paper part of the discussion section was dedicated to clinical implications, and proposed to make the decision of starting steroids in nonresolving ARDS on the basis of the results of OLB. Given that the frequency of diffuse alveolar damage (DAD) on OLB performed 9 days after completion of ARDS criteria was 58 %, we suggested that the choice of steroids could not be made systematically in this setting. Dr. Meduri argues in his letter [2] that this finding is, by contrast, an indication for steroids. First of all, it should be clarified that DAD as defined in our paper included either the exudative or fibroproliferative stage of ARDS. We also made the point that DAD at the fibroproliferative stage may be difficult to mark off as different from organizing pneumonia, an expected steroid-sensitive pattern.

Dr. Meduri notably based his debate on data from a meta-analysis that showed significant benefit on mortality, ventilator-free days, and oxygenation by using steroids for more

than 8 days in ARDS, which was ongoing for less than 14 days [3]. This meta-analysis included three trials, two of them led by Dr. Meduri and the third by the ARDS Network, in which various steroid regimens were used. It is worth noting that none of these trials showed a benefit on mortality and, hence the American College of Chest Physicians (ACCP) recommendation to use steroids in nonresolving ARDS was graded 2B [2]. It should also be noted that other meta-analyses did not reach the same conclusions with no effect of steroids on mortality in ARDS patients. In a review article by Sessler and Gay [4] the conclusions were more balanced. Whilst the authors acknowledged benefits on ventilator-free days and oxygenation from using steroids, the effect on mortality was qualified as neutral (see their Table 1 [4]). At this point, it would be argued that survival should be the main end-point in ARDS. Indeed, cohort studies have emphasized the long-term quality of life in ARDS patients who survived the acute stage. Five years after they had been discharged alive from the ICU, more than 75 % of the patients were still alive and had normal mental status, though their physical condition was impaired. From these findings it turns out that the management in the acute stage of ARDS should take into account the impact on long-term outcomes. However, for a better quality of life in the long term, maintaining the short-term survival is mandatory. This is, however, controversial as other authors consider that ventilator-free days and physiology, which are intermediate end-points, are as important. One should question the real benefit for an ARDS patient who will be off the ventilator for 4 days and eventually die the day after.

In the “Discussion” section of our paper, we pointed out the potential role of OLB to better select patients who may benefit from steroids on a

histologically based and patient-centered approach. We agree that nonresolving ARDS is still a selected population. However, OLB may further refine this subset. Importance of testing interventions in selected subgroups of ARDS has recently been demonstrated, as neuromuscular blocking agents and prone positioning were able to afford a significant benefit on survival. There are other ways to disclose ARDS subsets, like using latent class statistical analysis performed over a large cohort of patients. So, looking at specific subsets is an attractive approach to reduce the heterogeneity in ARDS and hence to anticipate significant benefits from specific and targeted interventions. OLB has been used in ARDS patients by other groups. Laurent Papazian’s group found that contributive OLB was associated with better survival in ARDS patients. The use of biomarkers of ARDS is another method that can be applied in this setting. In the context of the present debate biomarkers can be seen as surrogates of OLB. In the ARDSNet trial on steroids already mentioned, a subgroup analysis found that survival was dependent on procollagen III lung concentration, a marker of fibroproliferation, with a better survival in the steroids group in those patients with greater alveolar concentration. Very recently, Forel et al. [5] found that alveolar concentration of NT-procollagen III had an excellent accuracy to predict OLB-defined fibroproliferation in ARDS patients. Finally, the impact of steroids should also be considered in relation to the etiology of ARDS. In cohort studies on influenza-related ARDS the risk of death was increased by 2.45-fold with the use of steroids [6]. In conclusion, it would be desirable to better define nonresolving ARDS in order to target the indication of steroids in better selected subgroups of patients.

**Conflicts of interest** The author declares no conflict of interest.

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