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Corticosteroids in pediatric ARDS: all cards on the table



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## Authors
Schwingshackl, Andreas
Meduri, Gianfranco Umberto
Kimura, Dai
et al.

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**Andreas Schwingshackl**
**Gianfranco Umberto Meduri**
**Dai Kimura**
**Stephania A. Cormier**
**Kanwaljeet J. S. Anand**

# Corticosteroids in pediatric ARDS: all cards on the table

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Dear Editor,

Hardly any topic in modern critical care medicine remains as controversial as steroid administration in acute respiratory distress syndrome (ARDS), despite multiple adult randomized controlled trials (RCTs) and recent pediatric data. The article by Yehya et al. [1] and the editorial commentary by Peters et al. [2] are vital, since few, if any, therapeutic approaches are simultaneously associated with such profound potential benefits and risks as steroid therapy in critically ill patients.

Marked contradiction, however, exists between the Yehya et al. data and the findings of well-designed and protocol-driven RCTs in adult ARDS patients. These studies consistently reported significant improvements in markers of systemic inflammation, ventilator-free days, ICU-free days, no changes or actually improved survival, and either no increase or decreases in infection rate [3, 4]. The findings of Yehya et al. cannot be interpreted because the specific indications for corticosteroid use were not reported. To imply that any type of steroid, at any concentration, and used for more than 24 h represents a protocol-driven treatment for pediatric ARDS (PARDS) is simply not justifiable.

Further, grouping short-term (less than 24 h) and non-corticosteroid exposed patients together is an improper control for evaluating steroid therapy. Corticosteroids can exert important, non-genomic effects within minutes, including decreased cell adhesion, phosphokinase activation, MCP-1 and $H_2O_2$ release, CD63 translocation, TNF-$\alpha$ and IL-6 expression. Possible corticosteroid effects cannot be assessed unless exposed and non-exposed patients are categorically separated. Thus, proposing that this single-center, observational study "has relevance for clinical practice", a conclusion unsupported by data, will likely mislead and confound many bedside physicians. Undoubtedly, the most likely explanation for Yehya et al.'s findings are (1) selection of steroid therapy for the sickest patients (confounding by indication) and (2) rebound effects resulting from abrupt discontinuation of corticosteroids, as is well documented by worsening $PaO_2/FiO_2$ ratios and increasing CRP levels.

Owing to the wide-ranging implications and inherent responsibility of publishing patient data, it is imperative that we treat this topic with the utmost equipoise until clear evidence for or against steroid use in ARDS/PARDS is gained. Whether comparative effectiveness research (CER) can provide such evidence is questionable, since the US Food and Drug Administration, European Medicines Agency, or other labeling agencies do not consider this research methodology Level 1 evidence. CER studies can "adjust" the outcomes for measured confounders, and bootstrapping techniques like propensity scoring can reduce the margin of inferential errors, but only large, well-designed RCTs can control for unmeasured and non-measurable confounders. We recommend caution in drawing conclusions from a data set with multiple confounding variables and improper controls. Statistical approaches such as propensity score matching can only take into account measured confounding factors, whereas randomized trials allow for controlling of both measured and unmeasured confounders. The beneficial or no-harm results reported in adult RCTs cannot be disregarded unless systematically investigated in pediatric patients. We recently published a feasibility RCT investigating prolonged low-dose methylprednisolone in pediatric ARDS [5] and, undoubtedly, there is an urgent need to conduct a large-scale, well-designed RCT in PARDS.

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A. Schwingshackl (✉) · G. U. Meduri · D. Kimura · S. A. Cormier · K. J. S. Anand
Department of Pediatrics, University of California Los Angeles David Geffen School of Medicine, 10833 Le Conte Ave, Los Angeles, CA 90095, USA
e-mail: aschwingshackl@gmail.com