Mark J. Peters
Samiran Ray
Martin Kneyber

Corticosteroids for paediatric ARDS: unjustified—even unjustifiable?

Received: 30 June 2015
Accepted: 30 June 2015
Published online: 10 July 2015
© Springer-Verlag Berlin Heidelberg and ESICM 2015

M. J. Peters (✉) · S. Ray
Respiratory, Critical Care and Anaesthesia Unit, Institute of Child
Health, University College London, London WC1N 1EH, UK
e-mail: mark.peters@ucl.ac.uk

M. J. Peters
Paediatric Intensive Care Unit, Great Ormond Street Hospital
for Children NHS Trust, London WC1N 3JH, UK

M. Kneyber
Department of Paediatrics, Division of Paediatric Critical Care
Medicine, Beatrix Children's Hospital, University Medical Center
Groningen, The University of Groningen, P.O. Box 30.001,
9700 RB Groningen, The Netherlands

M. Kneyber
Critical Care, Anaesthesiology, Peri-operative and Emergency
Medicine (CAPE), The University of Groningen, Groningen,
The Netherlands

Paediatric intensivists are self-selected “do-ers”. We display a preference for action over inaction. It is possible that this may contribute to some apparently illogical behaviour in choices of therapy that are at odds with the evidence.

The recent Pediatric Acute Lung Injury Consensus Conference brought together clinicians and researchers from the main groups in the field, including the Pediatric Acute Lung Injury and Sepsis Investigators, the Canadian Critical Care Trials Group, the European Society of Paediatric and Neonatal Intensive Care, the Australian

and New Zealand Intensive Care Society and the French Speaking Pediatric Intensive Care and Emergency Group. Amongst other outputs, this august group reviewed the evidence for Specific Pulmonary Ancillary Treatments for Paediatric Acute Respiratory Distress Syndrome (PARDS).

The resultant recommendation for steroids and PARDS was unequivocal and met the standard of ‘strong agreement’: “At this time, corticosteroids cannot be recommended as routine therapy in PARDS” [1]. And of course this is the only appropriate recommendation. There are no randomised controlled trials and only very small case series supporting corticosteroid use for this indication. In contrast, adult data are plentiful but contradictory [2, 3].

In paediatric intensive care medicine, many of our potential therapies are of unproven benefit. So why do we pick on this example as important? Well, steroid use for this indication is widespread, and is the most common ancillary treatment offered to PARDS cases, at around ~35 % [4, 5]. The challenges to running a formal randomised trial are many: low incidence, subjective elements in the definition [6], an important (perhaps dominant) influence of comorbidity [7] in outcome, very wide variability in practice [8], and no consensus as to choice of steroid, dose or duration. Hence, we are unlikely to have 1A evidence anytime soon.

In this context, Yehya and colleagues’ report on the Children’s Hospital of Philadelphia’s experience of PARDS in 283 children, recently published in *Intensive Care Medicine*, is of interest [9]. This might seem an unusual paper for our journal in 2015, as a single-centre observational study with good but not compelling cohort size. However, the authors have taken great care to record all corticosteroid exposure in the PARDS cohort and not just specific PARDS treatment. They have revealed a further very significant challenge to any attempt to study corticosteroids in PARDS—the very widespread use of

Fig. 1 Variability and clinical evidence. In pARDS, case-mix and practice is highly variable between units meaning outcomes may not be comparable. However, variation between patients and treatments can both confound and contribute to clinical evidence. **a** In formal randomised trials, a subset of similar cases is selected to control patient variance (or in very large trials randomisation balances variance) while controlling variance in practice around one (or few) parameters; however, many trials are needed to build evidence. **b** Quality improvement methodology limits treatment variance and observes outcomes: this is very effective but needs evidence to recommend treatments. **c** In contrast, comparative effectiveness studies utilise variability in both patients and treatment to investigate contributions to outcome

corticosteroids for a variety of indications on the PICU. Indeed, only 65/283 (23 %) of cases did not receive corticosteroids in some form. The authors selected >24 h of corticosteroid treatment as a threshold to divide the group into higher corticosteroid exposure 169/283 (60 %) versus low/no exposure (114/283, 40 %). Given that the indication for steroids was often shock, it is no surprise that the high exposure group were significantly sicker, had fewer ventilator-free days (VFD), more hospital-acquired infections and double the observed mortality (17 vs. 8 %). What is interesting is that this mortality excess in the high steroid exposure group persisted after multiple regression analysis. But, of course, even with PRISM III, we might expect that, because our risk adjustment which we can enter into a regression model does not reflect the full bedside picture. What is intriguing in this paper is that the authors also developed a propensity score to adjust for the probability of higher corticosteroid exposure and still saw independent associations of higher exposure with worse outcomes (decreased VFD and duration of ventilation in survivors). This powerful technique is relatively new in intensive care but offers the potential of quantifying causal effects from observational studies [10]. The Yehya study does have limitations, especially the wide variety of steroid regimens employed, and the high rates of other unproven ancillary therapies that may not be used in many institutions (e.g. iNO in 37 % of cases). However, the authors should be applauded for their rigour in describing the true pattern of corticosteroid use in cases of PARDS, and adding this further challenge to the many that would be faced by a team planning a clinical trial.

So might corticosteroids be ‘unjustifiable’ in PARDS? This word has two senses. The first—not justified—well, with these data we cannot move on from the PALICC wording: not to recommend corticosteroids as routine therapy in PARDS. But ‘unjustifiable’ can also mean ‘not possible to be justified’, in that a formal trial is not feasible. No, in our opinion, this is not the case. There are a number of options (Fig. 1): a pragmatic study that is so large that it deals with the wide variance in practice and other confounders in the randomisation; a quality improvement methodology in which—like “*Surviving Sepsis*”—we suggest our best evidence (or expert

A RCT: Random allocation balances variance in case mix and treatment between groups other than for trial intervention but only single intervention tested (multiple trials needed)

B Quality Improvement. Guidelines of best practice to limit management variability

C Comparative Effectiveness studies. Inclusive, detailed, observational study. Wide patient and management variability and standardised outcomes allow inferences to be made of treatment effects

opinion) as a tool to standardise practice and track associations with outcome, or the newer approach of a comparative effectiveness study that utilises existing

variability in both patients and practice to look for associations of outcomes within a large but detailed observational cohort study. In this last option, effectively a multiple-centre collaborative version of the work that Yehya and colleagues report appears attractive. The Respiratory Failure and Nursing Science Sections of ESPNIC are embarking on this path with their Ventilator Settings in Pediatrics European Registry (VESPER) study. Intriguingly the ‘fiddling’, the ‘desire for action

over inaction’ from which we suffer, might be put to work in generating much-needed evidence.

Acknowledgments This work was undertaken at Great Ormond Street Hospital/UCL Institute of Child Health, which received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centre’s funding scheme.

Conflicts of interest No conflicts of interest to declare.

References

1. Tamburro RF, Kneyber MCJ, Pediatric Acute Lung Injury Consensus Conference Group (2015) Pulmonary specific ancillary treatment for pediatric acute respiratory distress syndrome: proceedings from the pediatric acute lung injury consensus conference. *Pediatr Crit Care Med* 16:S61–S72. doi: [10.1097/PCC.0000000000000434](https://doi.org/10.1097/PCC.0000000000000434)
2. Tang BMP, Craig JC, Eslick GD et al (2009) Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med* 37:1594–1603. doi: [10.1097/CCM.0b013e31819fb507](https://doi.org/10.1097/CCM.0b013e31819fb507)
3. Peter JV, John P, Graham PL et al (2008) Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ* 336:1006–1009. doi: [10.1136/bmj.39537.939039.BE](https://doi.org/10.1136/bmj.39537.939039.BE)
4. Santschi M, Jouvet P, Leclerc F et al (2010) Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. *Pediatr Crit Care Med* 11:681–689. doi: [10.1097/PCC.0b013e3181d904c0](https://doi.org/10.1097/PCC.0b013e3181d904c0)
5. Santschi M, Randolph AG, Rimensberger PC et al (2013) Mechanical ventilation strategies in children with acute lung injury: a survey on stated practice pattern*. *Pediatr Crit Care Med* 14:e332–e337. doi: [10.1097/PCC.0b013e31828a89a2](https://doi.org/10.1097/PCC.0b013e31828a89a2)
6. De Luca D, Piastra M, Chidini G et al (2013) The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: multicenter evaluation and expert consensus. *Intensive Care Med* 39:2083–2091. doi: [10.1007/s00134-013-3110-x](https://doi.org/10.1007/s00134-013-3110-x)
7. Peters MJ, Tasker RC, Kiff KM et al (1998) Acute hypoxemic respiratory failure in children: case mix and the utility of respiratory severity indices. *Intensive Care Med* 24:699–705
8. Kneyber MCJ, Jouvet PA, Rimensberger PC (2014) How to manage ventilation in pediatric acute respiratory distress syndrome? *Intensive Care Med* 40:1924–1926. doi: [10.1007/s00134-014-3498-y](https://doi.org/10.1007/s00134-014-3498-y)
9. Yehya N, Servaes S, Thomas NJ, Nadkarni VM, Srinivasan V (2015) Corticosteroid exposure in pediatric acute respiratory distress syndrome. *Intensive Care Med*. doi: [10.1007/s00134-015-3953-4](https://doi.org/10.1007/s00134-015-3953-4)
10. Bailly S, Pirracchio R, Timsit JF (2015) What’s new in the quantification of causal effects from longitudinal cohort studies: a brief introduction to marginal structural models for intensivists. *Intensive Care Med*. doi: [10.1007/s00134-015-3919-6](https://doi.org/10.1007/s00134-015-3919-6)