

# Intensive Care Medicine: Focus on Paediatrics

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*In 2015 in ICM and elsewhere studies are now addressing the evidence deficit in PICU: better outcome measures & consent processes should mean more, and better, RCTs.*

**WORD COUNT:** 998

**REFERENCES:** 20

**T**here is a staggeringly large gap between the number of patients admitted to the pediatric intensive care unit (PICU), and those enrolled into randomized controlled trials (RCTs) – the currency for acquiring new information for treatment in patient care. The “gap” is a ratio of 100-to-1, i.e., only one patient recruited to an RCT for every 100 patients admitted for PICU care.<sup>[1]</sup> This “focus on pediatrics” therefore explores how this gap might be closed.

### **A plea for appropriate outcomes**

The recently published unadjusted mortality rate of 26.4 per 1,000 PICU admissions<sup>[2]</sup> in contemporary United States (US) PICU practice questions the legitimacy of mortality as an endpoint for RCTs. It is not relevant to the other 973.6 per 1,000 admissions. Pollack et al.<sup>[2]</sup> addressed this problem by exploring three (or “trichotomous”) outcomes after PICU admission: significant new functional morbidity, intact survival and death.

Two articles in the *Journal* follow also question the confidence we might gain from mortality improvements alone. Aspesberro et al.<sup>[3]</sup> reviewed tools for measuring health-related quality of life (HRQL) after PICU admission and concluded that these instruments could be used to assess our 20-50% rates of morbidity, but the accompanying editorial<sup>[4]</sup> indicated that more work was needed before qualitative outcomes became the norm in our population. Second, van Zelle et al.<sup>[5]</sup> showed the expected worse performance in full-scale intelligence quotient (IQ), verbal IQ and visual memory in 47 survivors of cardiac arrest during childhood. Other, functional domains – executive functioning and

visual-motor integration – were relatively intact, and there was often a difference between parent and teacher reports. Therefore, using summary variables for complex conditions, or resorting to parent questionnaire assessments in RCTs may introduce errors in outcomes assessment.

## **Clinically usable information from observations**

Another focus in the *Journal* is large observational studies. Kanthimathinathan et al.<sup>[6]</sup> undertook a database review of 12,533 PICU admissions and reported unplanned endotracheal tube extubations at a rate of ~1 event per 2,000 intubation days, per year.

*Comparative effectiveness research* (CER) is based on prospective observations that address the question of whether a complex package of care delivery works. The approach examines effectiveness in a homogeneous population (e.g., severe traumatic brain injury) where there is a known difference in outcome and a known difference in care delivery. That is, researchers can measure the difference in outcome and relate these to the package of care and its constituent components. The *Approaches and Decisions for Acute Pediatric Traumatic Brain Injury* (ADAPT) CER study is currently recruiting patients worldwide. This same approach may be important for complex conditions such as pediatric acute respiratory distress syndrome (pARDS).<sup>[7]</sup>

## **Informative clinical experiments: RCTs in critical care**

In 2015 there were at least 12 RCTs reported in PICU patients (Table 1)

(<http://www.PICUtrials.net/>). Two studies require further comment. The *Randomized Evaluation of Sedation Titration for Respiratory Failure* (RESTORE) study in 2,449 pediatric patients found that using a sedation protocol compared with usual care did not reduce the duration of mechanical ventilation.<sup>[8]</sup> Of interest, though, 68% of cases developed “iatrogenic withdrawal”, which means that the future focus should be on this feature as an outcome measure.<sup>[9]</sup> In the *Journal*, Banupriya et al.<sup>[10]</sup> demonstrated the superiority of prophylactic probiotics in reducing the incidence of ventilator associated pneumonia (VAP from 39 to 22 per 1,000 ventilated days,  $p=0.02$ ) in an environment with a very high baseline VAP rates. The natural question now is whether this benefit translates to PICUs where the pre-test rate of VAP is closer to 4 per 1,000 ventilated days.

### **New methodologies for enhancing patient recruitment to RCTs**

The recently published *Impregnated central venous CATHeters for prevention of bloodstream infection in CHildren* (CATCH) trial compared standard with heparin or antibiotic coated central venous lines (CVL).<sup>[11]</sup> There was a small benefit of antibiotic coated CVLs with respect to blood stream infections. Of more interest, however, is the use of so-called “deferred consent” in the research report, which is worthy of further discussion.

In the United Kingdom (UK) the term “deferred consent” is referred to as “*research without prior consent*”. In US regulations, the term “waiver or alteration of informed consent” rather than the term “deferred consent” is used because the latter fails to describe the lack of opportunity to avoid or prevent a subject from receiving the intervention under investigation. To date, there have

been a number of reports about this approach and we need to gain more insight from PICU families about the potential for this practice. For example, the CATCH trial was the first pediatric critical care RCT to use this approach since UK legislation changed in 2008. In the *CONsent methods in childreN's emergEncy medicine and urgent Care Trials* (CONNECT) study a cohort of parents of children recruited into the CATCH study were interviewed.<sup>[12]</sup> The investigators found that parents supported research without prior consent and appreciated the reasons for using it as long as their child's safety was not compromised. However, these parents would be concerned about not seeking prior consent in trials involving either "new" drug interventions or other potentially significant changes in clinical practice. Last, a report from a European group of pediatric clinical researchers described a new framework for informed consent processes under different time constraints,<sup>[13]</sup> which will be applicable to PICU studies.

### **Moving the field forward and future RCTs**

There appear to be three areas that interest our authors in regard to future plans for RCTs. First, corticosteroids in pARDS may be one target,<sup>[7,14]</sup> but Yehya et al.<sup>[15]</sup> found that corticosteroid exposure for other indications was widespread in the PICU. However, recruitment to RCTs may be improved by using pulse oximetry to fractional inspired oxygen ratio as an index of severity.<sup>[16]</sup> Second, intravenous fluid resuscitation and responsiveness,<sup>[17,18]</sup> and there may soon be data from the Canadian *SQUEEZE* (septic shock reversal is quicker in pediatric patients randomized to an early goal directed fluid-sparing strategy versus usual care) and the UK *FiSh* (Fluids in Shock) studies.<sup>[19]</sup> Last, non-invasive

ventilation,<sup>[20]</sup> and their may soon be data from the *FIRST-line Support for Assistance in Breathing in Children (FIRST-ABC)* feasibility study.

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**Table 1. RCTs in Pediatric Intensive Care in 2015 by topic of care (see:**

<http://epicc.mcmaster.ca> and <http://www.PICUtrials.net/>)

<b>Topic Area</b>	<b>Subject</b>
Respiratory	<ul style="list-style-type: none"><li>• Protocolized sedation versus usual care during mechanical ventilation</li><li>• Neurally adjusted ventilator assist</li><li>• Inhaled nitric oxide</li><li>• Post-endotracheal tube extubation care</li><li>• Lung inflammation</li><li>• Ventilator associated pneumonia</li><li>• Bronchiolitis</li></ul>
Cardiovascular	<ul style="list-style-type: none"><li>• Sodium nitroprusside during prolonged infusion</li><li>• Dopamine versus epinephrine in septic shock</li></ul>
Hypothermia	<ul style="list-style-type: none"><li>• Out-of-hospital cardiac arrest</li><li>• Severe traumatic brain injury</li></ul>