

## EDITORIAL



# Focus on paediatrics

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Since a wise man or woman proportions his or her belief to the evidence [1], this focus on paediatrics discusses interesting and influential papers that have been published in important journals in 2018, related to paediatric intensive care unit (PICU) clinical research. We link the evidence in these papers to four sections of ‘interventions, setting, outcome and evaluation.’

### Interventions

#### Ultrasound for insertion of central venous access

Oulego-Eroz et al. prospectively studied central venous catheter insertions in 26 Spanish PICUs, and undertook a propensity matched analysis for 266 procedures [2]. The use of ultrasound was linked to greater first attempt success, and hence fewer complications as compared to the conventional landmark approach, by reducing the number of puncture attempts (especially in operators with less than 5 years of experience).

#### Non-invasive respiratory support

The Tramontane group of investigators, who previously published a randomised controlled trial (RCT) in infants with bronchiolitis, favouring nasal continuous positive airways pressure (CPAP) over high flow nasal cannula oxygen [3], followed this up with a further RCT. The second Tramontane RCT compared 2 L/min with 3 L/min of high flow nasal cannula oxygen, in 287 similar infants, finding that the higher flow rate conferred no benefit and may have contributed to increased patient distress [4]. The Tramontane investigators acknowledged that a further study would help to shore up the evidence supporting CPAP over high flow nasal cannula, for non-invasive respiratory support in PICU.

#### Normal saline in resuscitation

Indirect evidence against the use of normal saline in PICU resuscitation was provided by a single centre, observational study of 1935 patients by Barhight et al. which found an independent increased risk of death amongst the children who experienced the largest increases in serum chloride during the first day in PICU [5]. The Barhight findings suggest that prospective interventional studies may be needed to address outstanding questions, as to choice of resuscitation fluids in critically ill children.

#### Setting: low and middle income countries (LMIC)

Several studies were published related to paediatric intensive care in LMIC, these noting the great disparity in the distribution of resources between LMIC and high-income countries. Argent et al. stressed the importance in LMIC (even more so than elsewhere) of less costly interventions targeted towards the diseases responsible for the largest number of deaths [6]. In particular, emphasis was placed on new developments focussed on improving care pathways and better treatment for sepsis. In such an example, Urayeneza et al. reported the success of an educational initiative to increase the timeliness of evidence-based treatments such as antibiotics and fluid boluses, in a study involving 1594 children presenting with sepsis in rural Ruanda [7]. Given the increasing number and range of paediatric cardiac surgical procedures undertaken in LMIC, the Pediatric Cardiac Intensive Care Society Global Statement of 2017/2018 provided a series of management guidelines based on expert opinion, for late presenting congenital heart disease, severe malnutrition and infections with multi-resistant micro-organisms [8].

#### Outcome: longer term

In acknowledgement of temporal improvements in early survival after PICU admission, and increases in the proportion of children surviving with complex and chronic conditions, health related quality of life (HRQOL) and

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neurodevelopment (ND) have emerged as key outcomes [9]. These outcomes, though sought after, are more complicated and challenging both to measure and to interpret, than in hospital measures such as length of stay or mortality [10]. In 2018, Kyosti et al. reported HRQOL in 1109 Finnish children, 6 years after PICU admission, and found perhaps unsurprisingly, that children with chronic conditions, ND problems and greater use of health services, had poorer HRQOL [11]. A strength of this study was the identification of participants based on a national registry, and a drawback was that only 30% of survivors took part. Unresolved controversies remain as to the role of baseline HRQOL measurement in critically ill children, interpretation of HRQOL values (what represents

a normal versus a significantly low score), and the appropriate actions to be undertaken for children who have low HRQOL or ND scores at follow up [12].

### Health care evaluation

PICU researchers frequently debate the challenges of gathering evidence, given the diversity of case mix, small numbers in individual diagnostic groups and in important outcome categories such as deaths. Creative approaches to make best use of the numbers included:

### Consortia for multi-centre observational studies

Contributions, based on observational data, have been made by associations consisting of multiple PICUs

**Table 1 Overview of studies in critically ill children (search terms child, critical care OR intensive care) that are currently recruiting. Source [www.clinicaltrials.gov](http://www.clinicaltrials.gov), accessed June 25, 2019**

Study title	NCT number
Antibiotic dosing in pediatric intensive care	NCT02456974
Apneic oxygenation in the pediatric intensive care unit	NCT03374046
Assessment of pain monitoring in postoperative pediatric cardiac surgery with analgesia nociceptive index/newborn infant parasympathetic evaluation monitor program	NCT02834481
Bedside therapeutic monitoring of beta-lactam levels in newborns, children and adolescents admitted to intensive care	NCT03404089
Comparison of tidal volume between pediatric anaesthesia and paediatric intensive care patients	NCT03877354
Copeptin and arterial hypotension in critically ill paediatric and neonatal intensive care patients	NCT03320967
Double blinded randomized control trial of types of intravenous fluids in children with diabetic ketoacidosis	NCT03066440
Early rehabilitation in critically ill children-the pediatric intensive care unit liberate study	NCT03573479
Early versus late parenteral nutrition in the pediatric intensive care unit	NCT01536275
Effectiveness of a ventilator acquired pneumonia prevention bundle in the pediatric intensive care unit	NCT03763695
Efficacy and safety of dexmedetomidine during weaning from analgesia and sedation in pediatric intensive care unit	NCT03645603
Evaluation of computer decision support systems in detection of systemic inflammatory response and sepsis in pediatric patients	NCT03661450
Fast exome for diagnosis of congenital conditions in infants under 12 months of age hospitalized in intensive care unit	NCT03881035
Helmet continuous positive airway pressure support for severe bronchiolitis in pediatric intensive care units	NCT02977585
Improving family meetings in the pediatric cardiac intensive care unit	NCT03749330
Improving safety and quality of tracheal intubation practice in pediatric intensive care units	NCT02493478
Influence of techniques of chest physiotherapy in the pediatric intensive care unit	NCT03112811
Interest of high flow nasal cannula oxygen therapy in pediatric intensive care unit	NCT03505814
Long term follow up of children enrolled in the real-time effort driven ventilator management study	NCT03709199
Mortality in paediatric intensive care	NCT03969355
NEUROlogical prognosis after cardiac arrest in kids	NCT03574025
Pharmacokinetic analysis of midazolam and fentanyl in pediatric patients with long-term analgesedation	NCT02302391
Population pharmacokinetics of anti-infectives in critically ill children	NCT02539407
PROSpect: prone and oscillation pediatric clinical trial	NCT03896763
Pupillometry in pediatric intensive care unit	NCT02847195
Reducing adverse events in pediatric intensive care units in argentina	NCT03924570
SQUEEZE trial: a trial to determine whether septic shock reversal is quicker in pediatric patients randomized to an early goal directed fluid sparing strategy versus usual care	NCT03080038
Tapering of analgesedation and occurrence of withdrawal syndrome in paediatric intensive care treatment	NCT02952846
The ketogenic diet for pediatric acute brain injury	NCT02174016
Use of lung ultrasound to diagnose the etiology of respiratory failure in a pediatric intensive care unit	NCT03744169
Usefulness of protein-enriched infant formula in pediatric intensive care	NCT03901742
Ventilatory monitoring in children with respiratory distress syndrome with electrical impedance tomography	NCT03768921

joined together, for a particular purpose (consortia). Examples include data supporting the use of ultrasound during placement of paediatric central venous access (RECANVA collaborative) [2] and identifying the children most at risk of unplanned readmission to PICU (Pediatric Cardiac Critical Care Consortium, PC4) [13].

#### Analyses of high resolution data from the PICU bedside

PICU specialists are learning how to leverage the observed vital signs data collected every few seconds from groups of patients to improve care. Such analytical techniques can elucidate what vital signs are expected, for example, Abdelrazeq et al. analysed over 500,000 blood pressure measurements in order to determine the expected range for children in PICU [14]. Taking this technique further, Ross et al. used over 50,000 heart rate and blood pressure measurements in order to profile responder and non-responder patients in receipt of an adrenaline bolus [15], and Rusin et al. analysed 72,000 h of electrocardiogram data in infants with single ventricle circulation, to develop and validate an algorithm for pre detection of severe deterioration [16].

#### Pilot trial to multi centre RCT

The pilot trial enables methods of randomisation, recruitment, delivery of the intervention and data collection to be tested ahead of the future full scale version multi-centre RCT. The outcome of a pilot RCT is the feasibility of undertaking the multi-centre RCT at scale, including necessary sample size data. The pilot trials for conservative versus liberal oxygenation targets in critically ill children (oxy-PICU) [17] and high flow nasal cannula oxygen versus CPAP (first ABC) [18], represent 'for runners' to multi centre RCT starting in 2019.

#### Multi centre trials with serial and multi-dimensional outputs ('get the most out of your RCT')

The Pediatric Early vs Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) and Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) RCTs continue to produce new evidence. These are high quality multi centre RCTs, with serial multi-dimensional outputs including, importantly, ND outcome. PEPaNIC found that withholding TPN for 1 week in PICU improved aspects of ND outcome at 2 years [19] and THAPCA found that across both study groups there were important declines in ND outcome at 1 year amongst the highest risk patients [20].

#### Summary and future directions

Although PICU researchers debate the paucity of evidence in almost all areas, our focus paper demonstrates

that progress is being made. Moreover, when we undertook a search of the clinicaltrials.gov database provided by the US National Library of Medicine, as an exemplar international clinical trials registry, we found an exciting range of RCTs planned or being conducted (Table 1). These span interventions from low to the high technology areas, promising to take the speciality forwards.

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#### Compliance with ethical standards

#### Conflicts of interest

Katherine Brown is an associate editor of Intensive Care Medicine. Martin Kneyber is the scientific co-chair of the European Society for Paediatric and Neonatal Intensive Care (ESPNIC).

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#### References

- Hume D (1748) An enquiry concerning human understanding. University of Adelaide, Scotland
- Oulego-Erroz I, Gonzalez-Cortes R, Garcia-Soler P, Balaguer-Gargallo M, Frias-Perez M, Mayordomo-Colunga J, Llorente-de-la-Fuente A, Santos-Herraiz P, Menendez-Suso JJ, Sanchez-Porras M, Palanca-Arias D, Clavero-Rubio C, Holanda-Pena MS, Renter-Valdovinos L, Fernandez-De-Miguel S, Rodriguez-Nunez A, Rc study (2018) Ultrasound-guided or landmark techniques for central venous catheter placement in critically ill children. *Intensive Care Med* 44:61–72
- Milesi C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A, Baleine J, Durand S, Combes C, Douillard A, Cambonie G, Groupe Francophone de Reanimation et d'Urgences P (2017) High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Med* 43:209–216
- Milesi C, Pierre AF, Deho A, Pouyau R, Liet JM, Guillot C, Guilbert AS, Rambaud J, Millet A, Afanetti M, Guichoux J, Genuini M, Mansir T, Bergounioux J, Michel F, Marcoux MO, Baleine J, Durand S, Durand P, Dauter S, Javouhey E, Leteurtre S, Brissaud O, Renolleau S, Portefaix A, Douillard A, Cambonie G, GRS Group (2018) A multicenter randomized controlled trial of a 3-L/kg/min versus 2-L/kg/min high-flow nasal cannula flow rate in young infants with severe viral bronchiolitis (TRAMONTANE 2). *Intensive Care Med* 44:1870–1878
- Barhight MF, Brinton J, Stidham T, Soranno DE, Faubel S, Griffin BR, Goebel J, Mourani PM, Gist KM (2018) Increase in chloride from baseline is

- independently associated with mortality in critically ill children. *Intensive Care Med* 44:2183–2191
6. Argent AC, Chisti MJ, Ranjit S (2018) What's new in PICU in resource limited settings? *Intensive Care Med* 44:467–469
  7. Urayeneza O, Mujoyarugamba P, Rukemba Z, Nyiringabo V, Ntihinurwa P, Baelani JI, Kwizera A, Bagenda D, Mer M, Musa N, Hoffman JT, Mudgapalli A, Porter AM, Kisoona N, Ulmer H, Harmon LA, Farmer JC, Dunser MW, Patterson AJ, Sepsis in Resource-Limited Nations Workgroup of the Surviving Sepsis C (2018) Increasing evidence-based interventions in patients with acute infections in a resource-limited setting: a before-and-after feasibility trial in Gitwe, Rwanda. *Intensive Care Med* 44:1436–1446
  8. Brown KL, Beke DM, Cooper DS, MacLaren G (2017) Pediatric Cardiac Intensive Care Society statement: caring for children with critical cardiac disease across the globe. *Cardiol Young* 27:S1–S2
  9. Verstraete S, Van den Berghe G, Vanhorebeek I (2018) What's new in the long-term neurodevelopmental outcome of critically ill children. *Intensive Care Med* 44:649–651
  10. Brown KL, Utens E, Marino BS (2018) The ten things you need to know about long-term outcomes following paediatric cardiac surgery. *Intensive Care Med* 44:918–921
  11. Kyosti E, Ala-Kokko TI, Ohtonen P, Peltoniemi O, Rautiainen P, Kataja J, Ebeling H, Liisanantti JH (2018) Factors associated with health-related quality of life 6 years after ICU discharge in a Finnish paediatric population: a cohort study. *Intensive Care Med* 44:1378–1387
  12. Killien EY, Watson RS, Zimmerman JJ (2018) Inherent value of baseline measures when assessing the trajectory of health-related quality of life among children surviving critical illness. *Intensive Care Med* 44:1979–1981
  13. Smith AH, Anand V, Banerjee M, Bates KE, Brunetti MA, Cooper DS, Lehrich J, Mistry KP, Pasquali SK, Shin AY, Tabbutt S, Gaies M (2018) Variation in case-mix adjusted unplanned pediatric cardiac ICU readmission rates. *Crit Care Med* 46:e1175–e1182
  14. Abdelrazeq S, Ray S, Rogers L, Noren DP, Peters MJ, Inwald DP (2018) Age-associated blood pressure distributions in paediatric intensive care units differ from healthy children. *Intensive Care Med* 44:384–386
  15. Ross CE, Asaro LA, Wypij D, Holland CC, Donnino MW, Kleinman ME (2018) Physiologic response to pre-arrest bolus dilute epinephrine in the pediatric intensive care unit. *Resuscitation* 126:137–142
  16. Rusin CG, Acosta SI, Shekerdemian LS, Vu EL, Bavare AC, Myers RB, Patterson LW, Brady KM, Penny DJ (2016) Prediction of imminent, severe deterioration of children with parallel circulations using real-time processing of physiologic data. *J Thorac Cardiovasc Surg* 152:171–177
  17. Peters MJ, Jones GAL, Wiley D, Wulff J, Ramnarayan P, Ray S, Inwald D, Grocott M, Griksaitis M, Pappachan J, O'Neill L, Eaton S, Mouncey PR, Harrison DA, Rowan KM, Oxy PIfPICSSG (2018) Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. *Intensive Care Med* 44:1240–1248
  18. Ramnarayan P, Lister P, Dominguez T, Habibi P, Edmonds N, Canter RR, Wulff J, Harrison DA, Mouncey PM, Peters MJ, United Kingdom Paediatric Intensive Care Society Study G (2018) FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): a multicentre pilot randomised controlled trial of high-flow nasal cannula therapy versus continuous positive airway pressure in paediatric critical care. *Crit Care* 22:144
  19. Verstraete S, Verbruggen SC, Hordijk JA, Vanhorebeek I, Dulfer K, Guiza F, van Puffelen E, Jacobs A, Leys S, Durt A, Van Cleemput H, Eveleens RD, Garcia Guerra G, Wouters PJ, Joosten KF, Van den Berghe G (2019) Long-term developmental effects of withholding parenteral nutrition for 1 week in the paediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomised, controlled trial. *Lancet Respir Med* 7:141–153
  20. Slomine BS, Silverstein FS, Christensen JR, Holubkov R, Telford R, Dean JM, Moler FW, Therapeutic Hypothermia after Paediatric Cardiac Arrest Trial I (2018) Neurobehavioural outcomes in children after in-hospital cardiac arrest. *Resuscitation* 124:80–89