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"Medicine is science of uncertainty and art of probability" said William Osler. Nowhere is this uncertainty more evident than in paediatric intensive care (PIC) because of the scarcity of evidence in this population. Knowledge gaps exist even among the most commonly used interventions such as oxygen therapy, mechanical ventilation, cardiovascular support and common scenarios such as sepsis[1]. In this article, we review progress made towards reducing these fundamental uncertainties in the last year or so.

Oxygen therapy

Continuous pulse oximetry is considered a vital part of intensive care monitoring in children and yet, no trials have compared oxygen saturation targets. Consensus guidelines on mechanical ventilation in critically ill children recommend the following: 1. Target SpO2 ≥ 95% when breathing room air for healthy lungs. 2. Keep SpO2 ≤97% where possible 3. For paediatric acute respiratory distress syndrome (pARDS): SpO2 92–97% when PEEP<10 cmH2O and 88–92% when PEEP≥10 cmH2O[2]. However, the guidelines pointed out that there are no data about the safety and necessity of liberal or restrictive oxygen therapy. Since then, Oxy-PICU investigators reported the results of a pilot multicentre randomised trial comparing conservative (88-92%) versus liberal (>94%) oxygen saturation targets in

ventilated children receiving supplemental oxygen[3]. The results showed that conservative oxygen target appeared safe and that a definitive trial was feasible. Interestingly the investigators used ‘research without prior consent’ model to randomise and initiate relevant changes in management. Yet, 90% of the families (107/119) consented subsequently and the investigators reported that the parents and legal representatives were often supportive of the consent process. A full trial is eagerly awaited.

High-Flow Nasal Cannula therapy

Due to good tolerability and ease-of-use, heated humidified high-flow nasal cannula (HFNC) therapy has emerged as a common mode of respiratory support both within PIC and in other low-intensity settings. Despite the widespread use, the exact role of HFNC is unclear. Last year, the TRAMONTANE study showed that in infants with moderate or severe bronchiolitis, HFNC had a higher failure rate than nasal continuous positive airway pressure (nCPAP)[4]. More recently, a randomised trial of HFNC versus standard oxygen therapy in infants with bronchiolitis treated outside the paediatric intensive care unit (PICU) setting, showed that HFNC was associated with a significantly lower rate of treatment failure[5]. Despite the results in favour of HFNC, it was reported that more than three-quarters of infants managed with standard oxygen therapy, did not need further escalation of care, perhaps alluding to the limited scope for HFNC.

Both these studies were conducted in infants with acute viral bronchiolitis. However, it is evident that HFNC is used more widely in the PICU setting without any supportive trial evidence. Recently published recommendations for mechanical ventilation in critically ill children conclude that although HFNC or CPAP may reduce the work of breathing, there are no outcome data showing superiority of HFNC or CPAP over any other intervention[2]. It is perhaps timely then that the UK paediatric intensive care society study group investigators have reported the feasibility of such a multicentre randomised trial comparing HFNC and nCPAP in both step-up and step-down patients in PICU[6].

Blood pressure targets

Blood pressure (BP) monitoring and interventions to restore normotension are seen as key management priorities in PICU. Significant uncertainties related to BP monitoring and treatment targets were summarised in a recent article published in the Intensive Care Medicine[7]. The key concerns were related to the use of unvalidated algorithms in oscillometric devices, lack of consensus about threshold/definition of hypotension, differences between data from mathematical modelling and observational values as well as lack of trial evidence.

Literature published recently illustrate the uncertainties well. Data from over ten thousand children with isolated severe traumatic brain injury were analysed from a national registry[8]. Investigators found that an admission BP below the 75th percentile, based on the US NIH taskforce population-based guidelines, was associated with higher risk of in-hospital mortality.

Using non-invasive BP readings in children admitted to PICU, Abdelrazeq et al, found that the 50th centile for systolic BP in young children admitted to PICU was higher than the US NIH taskforce values[9]. Using nearly 50000 readings from around 2500 children, Ray et al, reported that non-invasive BP readings provided a systematically higher systolic, lower diastolic and lower mean BP values than the invasive arterial BP readings[10]. Technological advances, big data analysis, further observational data, clinical trials and consensus are all needed to minimise some of these troubling uncertainties.

Paediatric Early Warning Scores (PEWS)

Tools to identify deteriorating children, clinical pathways that trigger appropriate escalation in care and timely access to the intensive care support are all required for a safe and effective system of care. PEWS-based assessment is thought to reduce some of the variability in recognition and response process. The EPOCH cluster randomised clinical trial compared the introduction of the ‘bedside PEWS’ to usual care in hospitalised children [11]. This large

and impressive study showed that ‘bedside PEWS’ was not associated with a reduction in mortality. However, the overall mortality rate was less than 0.2%.

During the last decade, many health systems across the world have embedded some form of PEWS system. What implications do the results of the EPOCH trial have for the future of such severity scoring systems? As Chapman et al, argue in their editorial, mortality is perhaps, not the answer[12]. Given the complexities of why children die and the relatively small proportion of preventable deaths in children, this study was probably under-powered, despite the massive numbers studied, to detect a mortality difference. By contrast, this study provides robust evidence that PEWS is not harmful. PEWS or similar systems are here to stay.

Sepsis

A feasibility study that compared a practice of administering restricted fluid bolus (10 ml/kg) compared to current standard practice (20ml/kg) concluded that a large trial in the UK was not feasible due to the very low mortality[13]. While it is heartening to note that the mortality rate in children presenting to emergency department with septic shock is extremely low, mortality related to paediatric sepsis remains a key issue in the ICU setting. Schlapbach et al., analysed data from a cohort of children admitted to PICU with sepsis or septic shock to accurately predict mortality from variables available within 1-hour of admission. They observed a mortality rate of 8.5% with nearly half the deaths occurring within first 48-hour of PICU admission[14].

Revised definitions for sepsis based on SOFA score (sequential organ failure assessment) as marker of organ dysfunction were recently published in adults. While efforts are ongoing for a similar revision in paediatrics, these have been hampered by lack of a universally agreed paediatric version of SOFA score in children. Schlapbach et al derived an age-adapted SOFA score[15]. They reported that the prognostic accuracy of the age-adapted SOFA and PELOD-2 scores performed better than SIRS and qSOFA scores for in-hospital

mortality among children with suspected infection admitted to PICU. Two other proposals for a paediatric SOFA score have also been published[16, 17]. Given the significance of a new universally applicable paediatric SOFA score, Kawasaki et al suggest that the way forward requires worldwide collaboration of paediatric intensivists to agree on the most relevant and useful paediatric SOFA score[18].

A renewed focus on re-evaluating sepsis epidemiology with novel and generalisable sepsis stratification tools are necessary to designing efficient trials to improve care for paediatric sepsis[19]. We share the authors' optimism about the possibility of large-scale collaborative trials made possible by international paediatric research networks.

Mechanical Ventilation

There is limited evidence for appropriate level of positive end-expiratory pressure (PEEP) in severe lung injury in children. Also, it is unclear how to assess optimal PEEP and whether markers of oxygenation or compliance predict best PEEP[2]. Using retrospective data from over a thousand children with pARDS, Khemani et al, observed that children managed with lower PEEP relative to FiO2 than recommended by the 'ARDSNet model' had higher mortality than those who had PEEP in-line with or higher than 'ARDSNet model'[20]. The need for a clinical trial is evident.

However, pARDS is a heterogeneous entity and the most appropriate study design should be adopted. Yehya et al observed that children with direct and indirect ARDS had distinct clinical characteristics, but similar outcomes[21]. In contrast, they observed that infectious and non-infectious ARDS demonstrated heterogeneity of clinical characteristics, mortality, and predictors of mortality. Identification of different phenotypes of pARDS has significant implications for future study design. In their article published in Intensive Care Medicine, De Luca et al., point out the pros and cons of 'lumping' (pragmatic, more inclusive) and 'splitting' (explanatory, less inclusive) patients of different phenotypes in a clinical trial[22]. Clearly, as the authors argue both types of clinical trial evidence may be required in pARDS.

Summary

Recent efforts to establish large scale collaborative paediatric critical care research networks across the world has meant that several clinical trials are in progress or planned. It is noteworthy however, that the significant disparity between geographical regions where clinical trials are ongoing and where a large number of childhood deaths occur (Figure). North America, Europe and China, despite the relatively low childhood mortality continue to initiate majority of clinical trials. However, it is heartening that trials are being performed in other parts of the world where evidence is most needed and there is the most to gain from improving outcomes: the Indian sub-continent, Africa, Latin America and the Middle-East.

In summary, significant in-roads have been made towards reducing fundamental uncertainties for paediatric intensivists in many fronts over the last few years.

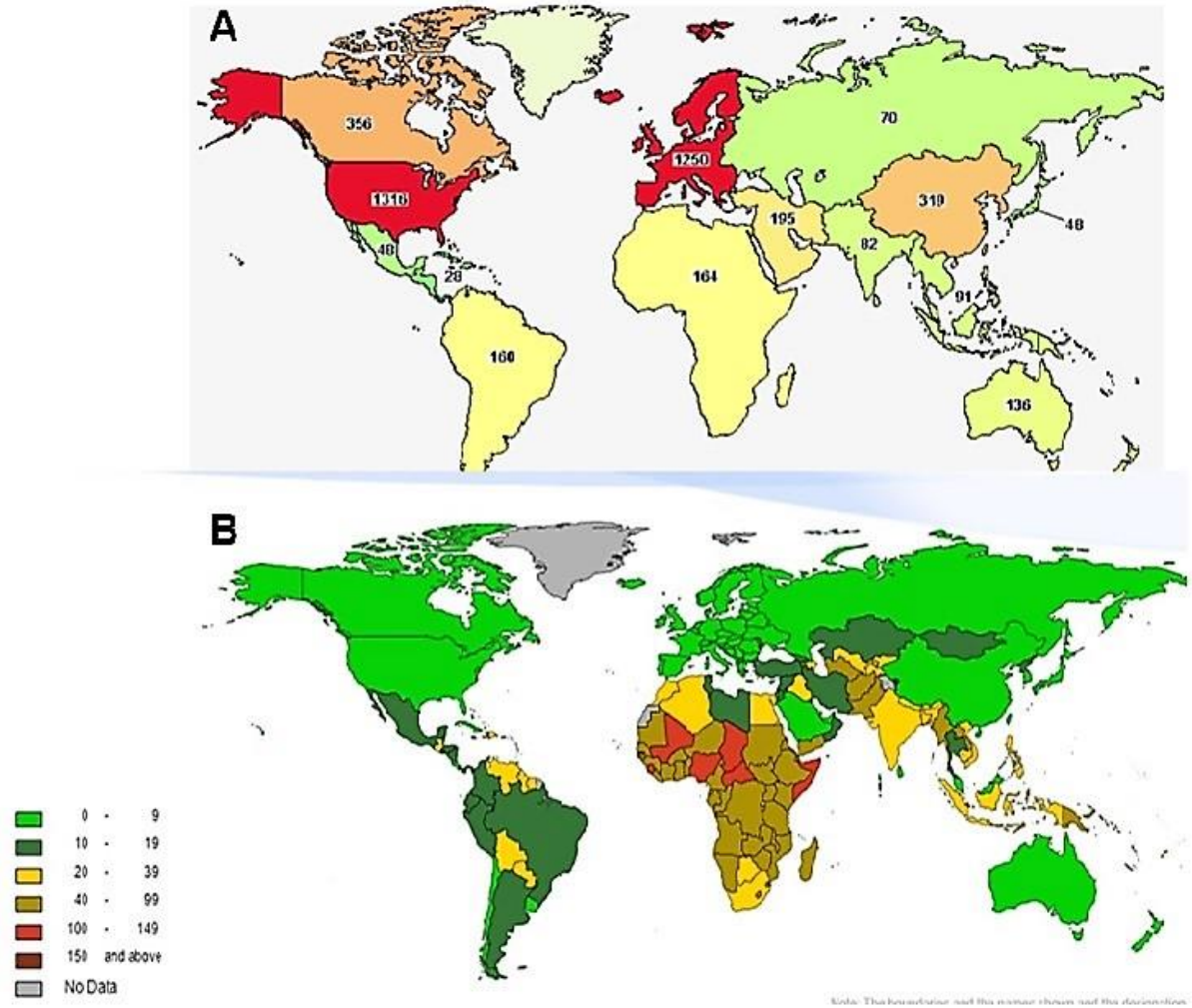

Figure: A: Map from http://www.clinicaltrials.gov showing ongoing/planned clinical trials related to children, critical care or intensive care. [accessed 27 September 2018]. B: Map of under-5 mortality rate from http://www.childmortality.org/ [accessed 27 September 2018]

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