Focus on Paediatrics: 2017

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Introduction

"*It is a capital mistake to theorize before one has data. Insensibly, one begins to twist facts to suit theories, instead of theories to suit facts"* observed Sir Arthur Conan Doyle. For Sherlock Holmes, this was insightful wisdom, but data voids mean that the pediatric intensivist currently has to diagnose and treat on the basis of what is both known and unknown. The need to improve our empirical evidence-base and be clear when we are defaulting to precedent, assumption, or plausibility is increasingly acknowledged.[1] This "Focus on Paediatrics" reviews what has been and what remains to be learned in several key topics.

Tight Glycemic Control

Following the initial remarkable benefits demonstrated for critically ill adults treated with insulin to limit even mild hyperglycemia,[2-4] there was widespread uptake of tight glycemic control in both critically ill adults and children. With additional data,[5] the pendulum soon swung back towards more moderate glucose control for critically ill adults. Earlier this year, Agus and colleagues reported no difference in ICU-free days, organ dysfunction, or mortality for children receiving vasoactive support for hypotension and/or invasive mechanical ventilation randomized to glycemic targets of 4.4 to 6.1 mmol/L versus 8.3 to 10.0 mmol/L.[6] This latest glucose trial minimized hypoglycemia using a computer-assisted algorithm but failed to reproduce earlier enthusiastic results reported for tight glycemic control in children,[2] similar to the SPECS [7] and CHiP studies.[8] Following these studies, Yamada et al. published in *Intensive Care Medicine* a network meta-analysis demonstrating that, over time, cumulative results stabilized across multiple trials and trended toward the null hypothesis.[9] The totality of

data for paediatric patients now shows that mild glycemic control achieves similar clinical outcomes as tight control, with less risk of hypoglycemia.

Acute Kidney Injury

In ICM in 2015, Ronco and Ricci reviewed the remarkable advances in experience and technology over the last 20 years that have led to the development of a new field of critical care nephrology for infants and children.[10] This review was largely based on small, predominantly retrospective studies from a few centers. In 2017, the AWARE investigators prospectively evaluated 4,683 pediatric patients admitted to 32 ICUs by KDIGO criteria for acute kidney injury (AKI).[11] In total 26.9% developed AKI, including 11.6% with severe (KDIGO stage 2 or 3) AKI, with a strong independent association with use of mechanical ventilation and death. This large, multicenter, prospective study allowed unique insight, independent from a large number of confounding variables, as to the incidence and association of AKI in pediatric critical illness.

Sepsis

In 2017, the latest update to the American College of Critical Care Medicine (ACCM) Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock was published.[12, 13] Although the literature review ended in year 2014—several years prior to ultimate publication—seven years had elapsed since the prior version was published. Even so, the taskforce itself noted, “the changes recommended were few.” Most of the interim data available had focused on improving implementation of prior guidelines. Although this led to the inclusion of four bundles to address sepsis recognition, resuscitation, stabilization, and

performance review, new data was scarce. However, several recent studies have already begun to push the field of pediatric sepsis forward. First, in ICM, paediatric investigators from ANZICS derived a pediatric sepsis score using PaO2:FiO2 ratio, need for invasive mechanical ventilation, systolic blood pressure, lactate, and pupillary response that predicted mortality with reasonable accuracy in the first hour of ICU admission.[14] Such early prediction is vital, as the authors showed that about half of sepsis-associated deaths occurred within 48 hours of admission, a finding similarly reported in the United Kingdom and United States.[15, 16] Second, Matics and Sanchez-Pinto also used a large observational database to develop a pediatric version of the Sequential Organ Failure Assessment (SOFA) score, which was previously used by Sepsis-3 to operationalize organ dysfunction in adult sepsis.[17] The new pSOFA score performed better than other organ dysfunction scores, and nearly two-thirds of deaths met the Sepsis-3 definition for septic shock.

A common theme across Sepsis-3, the ANZICS study, and the Matics et al study is reliance on blood pressure measurements. But what cut-points are most optimal for pediatric hypotension? Ray et al. compared concurrently recorded invasive and non-invasive blood pressure measurements across 50,000 pairs and found that non-invasive measurements gave systematically lower readings for mean and diastolic values.[18] How is one to determine *which* blood pressure targets are optimal in septic shock when it is not even clear *how* to best to measure? Another troublesome topic is the role for low-dose corticosteroids in septic shock. Despite controversial results in adults for which the totality of data provide for a reasonable recommendation, there are is no high-level evidence for pediatric septic shock.[19] Clearly a clinical trial is necessary. Menon et al. tested the feasibility of randomizing children with septic shock to hydrocortisone versus placebo and found that a pragmatic study design enhanced

enrollment but lack of equipoise among intensivists, as evidenced by frequent overall use of corticosteroids, was noted to be an important potential barrier.[20] It seems that, even in the absence of strong data, strong opinions may be difficult to overcome. Finally, although not sepsis, James and colleagues studied use of nitric oxide (NO) during cardiopulmonary bypass—another systemic inflammatory insult—and found that patients randomized to NO had a lower incidence of cardiogenic shock and reduced length of stay, especially in neonates and complex heart disease.[21] Perhaps ameliorating reperfusion injury is as important as reperfusion itself.

Mechanical Ventilation

In ICM in 2017, the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC) developed and voted on 152 recommendations about paediatric mechanical ventilation.[22] In keeping with the theme of scarce evidence, randomised clinical trial data were available for only *three* topic areas and most recommendations were either deferred or based on low-to-moderate evidence. Still, the synthesis of available data—and the areas devoid of data—is of monumental benefit to clinicians and investigators. Moreover, the Oxy-PICU investigators described current practice of oxygenation targets in a PICU and showed, with high-fidelity SpO2 data, that liberal oxygenation targets <95% are the general rule irrespective of the FiO2 or mean airway pressure used.[23] These data pave the way for a trial of oxygenation targets in critically ill children. The TRAMONTANE study randomized infants <6 months with moderate/severe bronchiolitis to either high-flow nasal cannula (HFNC) or continuous positive airway pressure (CPAP) with cross-over allowed.[24] Overall, patients in both groups were rarely intubated, with similar rates of rescue using the alternative non-invasive modality, suggesting that clinician preference may be more important than the modality chosen even

though initial randomization to HFNC was slightly less efficacious. Finally, a review by Moreira and Sapru in ICM discuss the potential for targeted use of epithelial, endothelial, coagulation, and inflammatory biomarkers to treat children with acute lung disease, further emphasizing the complexity in data-driven approaches to mechanical ventilation and other novel lung therapies.[25]

Pain and Sedation

A multidisciplinary taskforce published clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children in ICM in 2016. Similar to mechanical ventilation, the authors noted a limited literature with most recommendations based on few data.[26] Addressing one aspect, Vet and colleagues compared protocolized sedation with versus without a daily sedation interruption and found no difference in ventilator-free days or length stay but a higher mortality in the interruption arm. Unfortunately, the study was terminated early for slow recruitment, hindering data quality.[27]

Post-ICU Survivor Outcomes

In 2017, the long-awaited results of the therapeutic hypothermia after *in-hospital* cardiac arrest were published.[28] Similar to the previously reported *out-of-hospital* THAPCA trial, there was no benefit for moderate hypothermia compared to controlled normothermia on survival with a good neurobehavioral outcome. Of note, the investigators used the Vineland Adaptive Behavior Scale to measure their primary outcome with substantial caregiver reporting. However, van Zellem et al. showed that parents and teachers systematically reported different levels of function following survival from cardiac arrest.[29] Thus, even when outstanding attempts are

made to collect longer-term morbidity outcomes, the most appropriate measures remain unclear. Finally, Verstraete and colleagues demonstrated that there may also be risk factors right under our noses that we fail to consider when they showed that environmental phthalate exposure leaching from indwelling medical devices was common in PICU patients, with higher levels associated with long-term attention deficits.[30]

Conclusions

Sherlock Holmes' skill was to solve challenging cases by finding clarity despite seemingly limited data. Paediatric intensivists are arguably faced with similar challenges, but without necessarily the same genius. Holmes understood *"there is nothing like first-hand evidence."* The work we highlight here (Table) may assist us non-sleuths to make better decisions.

Table: Select Recent Pediatric Critical Care Trials

Trial	Population	N / Sites	Intervention	Control	Outcome
HALF-PINT [6]	PICU, non-cardiac disease	713 / 32	Tight glycemic control	Mild glycemic control	No difference in ICU-free days
THAPCA [28]	In-hospital cardiac arrest	329 / 37	Moderate hypothermia (33 °C)	Controlled normothermia (36.8 °C)	No difference in 1-year survival with good function
PRBC transfusion [31]	PICU	180 /1	Restrictive transfusion (Hgb <7 g/dL)	Liberal transfusion (Hgb <10 g/dL)	Improved hemodynamics with restrictive transfusion
PRBC transfusion [32]	CICU	162 / 1	Restrictive transfusion (Hgb <7 g/dL)	Liberal transfusion (Hgb <9.5 g/dL)	No difference in perfusion or clinical outcomes
TRAMONTANE [24]	Moderate-severe bronchiolitis	142 / 5	HFNC 2 L/kg/min	CPAP 7 cm H2O	Higher failure rate with initial HFNC
Fluid bolus [33]	ED, PICU	96 / 1	15-20 minute bolus	5-10 minute bolus	Lower mechanical ventilation in 15-20 minute bolus group
Hydrocortisone [20]	PICU	57 / 7	Hydrocortisone	Placebo	Feasible to enroll in RCT
PEPaNIC [34]	PICU	1440 / 3	Early parenteral nutrition (<1 day)	Late parenteral nutrition (>7 days)	Improved outcomes in late parenteral nutrition group
Nitric oxide [21]	CPB	101 / 1	Standard gas + nitric oxide	Standard gas	Reduced cardiogenic shock in nitric oxide group
Sedation [27]	PICU	129 / 3	Protocolized sedation + daily sedation interruption	Protocolized sedation	Increased mortality with daily sedation interruption

HALF-PINT, Heart and Lung Failure-Pediatric Insulin Titration; THAPCA, Therapeutic Hypothermia After Pediatric Cardiac Arrest; PRBC, packed red blood cell; TRAMONTANE, High flow nasal cannula versus nasal continuous positive airway pressure for the initial respiratory management of acute viral bronchiolitis; PEPaNIC, Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit; PICU, pediatric intensive care unit; CICU, cardiac intensive care unit, ED, emergency department; CPB, cardiopulmonary bypass; HFNC, high-flow nasal cannula; CPAP, continuous positive early pressure; RCT, randomized controlled trial

Reference: http://picutrials.net

References

1. Peters MJ, Argent A, Festa M, Leteurtre S, Piva J, Thompson A, Willson D, Tissieres P, Tucci M, Lacroix J, (2017) The intensive care medicine clinical research agenda in paediatrics. Intensive Care Med 2017 Mar 17. doi: 10.1007/s00134-017-4729-9. [Epub ahead of print]
2. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Cromphaut S, Schetz M, Van den Berghe G, (2009) Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 373: 547-556
3. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R, (2001) Intensive insulin therapy in critically ill patients. N Engl J Med 345: 1359-1367
4. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R, (2006) Intensive insulin therapy in the medical ICU. N Engl J Med 354: 449-461
5. Investigators N-SS, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hebert PC, Heyland DK, Robinson BG, (2012) Hypoglycemia and risk of death in critically ill patients. N Engl J Med 367: 1108-1118
6. Agus MS, Wypij D, Hirshberg EL, Srinivasan V, Faustino EV, Luckett PM, Alexander JL, Asaro LA, Curley MA, Steil GM, Nadkarni VM, Investigators H-PS, the PN, (2017) Tight Glycemic Control in Critically Ill Children. N Engl J Med 376: 729-741

7. Agus MS, Steil GM, Wypij D, Costello JM, Laussen PC, Langer M, Alexander JL, Scoppettuolo LA, Pigula FA, Charpie JR, Ohye RG, Gaies MG, Investigators SS, (2012) Tight glycemic control versus standard care after pediatric cardiac surgery. N Engl J Med 367: 1208-1219

8. Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, Parslow R, Tasker RC, Elbourne D, Investigators CH, (2014) A randomized trial of hyperglycemic control in pediatric intensive care. N Engl J Med 370: 107-118

9. Yamada T, Shojima N, Hara K, Noma H, Yamauchi T, Kadowaki T, (2017) Glycemic control, mortality, secondary infection, and hypoglycemia in critically ill pediatric patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Med 2017 Apr 19. doi: 10.1007/s00134-017-4801-5. [Epub ahead of print]

10. Ronco C, Ricci Z, (2015) Pediatric continuous renal replacement: 20 years later. Intensive Care Med 41: 985-993

11. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A, (2017) Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. N Engl J Med 376: 11-20

12. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, Okhuysen-Cawley RS, Relvas MS, Rozenfeld RA, Skippen PW, Stojadinovic BJ, Williams EA, Yeh TS, Balamuth F, Brierley J, de Caen AR, Cheifetz IM, Choong K, Conway E, Jr., Cornell T, Doctor A, Dugas MA, Feldman JD, Fitzgerald JC, Flori HR, Fortenberry JD, Graciano AL, Greenwald BM, Hall MW, Han YY, Hernan LJ, Irazuzta JE, Iselin E, van der Jagt EW, Jeffries HE, Kache S, Katyal C, Kissoon N, Kon AA, Kutko MC, MacLaren G,

Maul T, Mehta R, Odetola F, Parbuoni K, Paul R, Peters MJ, Ranjit S, Reuter-Rice KE, Schnitzler EJ, Scott HF, Torres A, Jr., Weingarten-Abrams J, Weiss SL, Zimmerman JJ, Zuckerberg AL, (2017) The American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock: Executive Summary. Pediatr Crit Care Med 18: 884-890

13. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, Okhuysen-Cawley RS, Relvas MS, Rozenfeld RA, Skippen PW, Stojadinovic BJ, Williams EA, Yeh TS, Balamuth F, Brierley J, de Caen AR, Cheifetz IM, Choong K, Conway E, Jr., Cornell T, Doctor A, Dugas MA, Feldman JD, Fitzgerald JC, Flori HR, Fortenberry JD, Graciano AL, Greenwald BM, Hall MW, Han YY, Hernan LJ, Irazuzta JE, Iselin E, van der Jagt EW, Jeffries HE, Kache S, Katyal C, Kissoon NT, Kon AA, Kutko MC, MacLaren G, Maul T, Mehta R, Odetola F, Parbuoni K, Paul R, Peters MJ, Ranjit S, Reuter-Rice KE, Schnitzler EJ, Scott HF, Torres A, Jr., Weingarten-Abrams J, Weiss SL, Zimmerman JJ, Zuckerberg AL, (2017) American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med 45: 1061-1093

14. Schlapbach LJ, MacLaren G, Festa M, Alexander J, Erickson S, Beca J, Slater A, Schibler A, Pilcher D, Millar J, Straney L, Australian, New Zealand Intensive Care Society Centre for O, Resource E, Australian, New Zealand Intensive Care Society Paediatric Study G, (2017) Prediction of pediatric sepsis mortality within 1 h of intensive care admission. Intensive Care Med 43: 1085-1096

15. Cvetkovic M, Lutman D, Ramnarayan P, Pathan N, Inwald DP, Peters MJ, (2015) Timing of death in children referred for intensive care with severe sepsis: implications for interventional studies. Pediatr Crit Care Med 16: 410-417

16. Weiss SL, Balamuth F, Hensley J, Fitzgerald JC, Bush J, Nadkarni VM, Thomas NJ, Hall M, Muszynski J, (2017) The Epidemiology of Hospital Death Following Pediatric Severe Sepsis: When, Why, and How Children With Sepsis Die. Pediatr Crit Care Med

17. Matics TJ, Sanchez-Pinto LN, (2017) Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. JAMA Pediatr 171: e172352

18. Ray S, Rogers L, Noren DP, Dhar R, Nadel S, Peters MJ, Inwald DP, (2017) Risk of over-diagnosis of hypotension in children: a comparative analysis of over 50,000 blood pressure measurements. Intensive Care Med 43: 1540-1541

19. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Umberto Meduri G, Olsen KM, Rodgers S, Russell JA, Van den Berghe G, (2017) Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med

20. Menon K, McNally D, O'Hearn K, Acharya A, Wong HR, Lawson M, Ramsay T, McIntyre L, Gilfoyle E, Tucci M, Wensley D, Gottesman R, Morrison G, Choong K, Canadian Critical Care Trials G, (2017) A Randomized Controlled Trial of Corticosteroids in Pediatric Septic Shock: A Pilot Feasibility Study. Pediatr Crit Care Med 18: 505-512

21. James C, Millar J, Horton S, Brizard C, Molesworth C, Butt W, (2016) Nitric oxide administration during paediatric cardiopulmonary bypass: a randomised controlled trial. Intensive Care Med 42: 1744-1752

22. Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J, Hammer J, Macrae D, Markhorst DG, Medina A, Pons-Odena M, Racca F, Wolf G, Biban P, Brierley J, Rimensberger PC, section Respiratory Failure of the European Society for P, Neonatal Intensive C, (2017) Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med 2017 Sep 22. doi: 10.1007/s00134-017-4920-z. [Epub ahead of print]

23. Ray S, Rogers L, Raman S, Peters MJ, Oxy Pi, (2017) Liberal oxygenation in paediatric intensive care: retrospective analysis of high-resolution SpO2 data. Intensive Care Med 43: 146-147

24. 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

25. Moreira A, Sapru A, Rimensberger PC, (2016) What's new about circulating biomarkers in pediatric acute lung disease. Intensive Care Med 42: 803-805

26. Harris J, Ramelet AS, van Dijk M, Pokorna P, Wielenga J, Tume L, Tibboel D, Ista E, (2016) Clinical recommendations for pain, sedation, withdrawal and delirium assessment

in critically ill infants and children: an ESPNIC position statement for healthcare professionals. Intensive Care Med 42: 972-986

27. Vet NJ, de Wildt SN, Verlaat CW, Knibbe CA, Mooij MG, van Woensel JB, van Rosmalen J, Tibboel D, de Hoog M, (2016) A randomized controlled trial of daily sedation interruption in critically ill children. Intensive Care Med 42: 233-244

28. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Browning B, Pemberton VL, Page K, Gildea MR, Scholefield BR, Shankaran S, Hutchison JS, Berger JT, Ofori-Amanfo G, Newth CJ, Topjian A, Bennett KS, Koch JD, Pham N, Chanani NK, Pineda JA, Harrison R, Dalton HJ, Alten J, Schleien CL, Goodman DM, Zimmerman JJ, Bhalala US, Schwarz AJ, Porter MB, Shah S, Fink EL, McQuillen P, Wu T, Skellett S, Thomas NJ, Nowak JE, Baines PB, Pappachan J, Mathur M, Lloyd E, van der Jagt EW, Dobyns EL, Meyer MT, Sanders RC, Jr., Clark AE, Dean JM, Investigators TT, (2017) Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children. N Engl J Med 376: 318-329

29. van Zellem L, Buysse C, Madderom M, Legerstee JS, Aarsen F, Tibboel D, Utens EM, (2015) Long-term neuropsychological outcomes in children and adolescents after cardiac arrest. Intensive Care Med 41: 1057-1066

30. Verstraete S, Vanhorebeek I, Covaci A, Guiza F, Malarvannan G, Jorens PG, Van den Berghe G, (2016) Circulating phthalates during critical illness in children are associated with long-term attention deficit: a study of a development and a validation cohort. Intensive Care Med 42: 379-392

31. Akyildiz B, Ulgen Tekerek N, Pamukcu O, Dursun A, Karakukcu M, Narin N, Yay M, Elmali F, (2017) Comprehensive Analysis of Liberal and Restrictive Transfusion Strategies in Pediatric Intensive Care Unit. J Trop Pediatr

32. Cholette JM, Swartz MF, Rubenstein J, Henrichs KF, Wang H, Powers KS, Daugherty LE, Alfieris GM, Gensini F, Blumberg N, (2017) Outcomes Using a Conservative Versus Liberal Red Blood Cell Transfusion Strategy in Infants Requiring Cardiac Operation. Ann Thorac Surg 103: 206-214

33. Sankar J, Ismail J, Sankar MJ, C PS, Meena RS, (2017) Fluid Bolus Over 15-20 Versus 5-10 Minutes Each in the First Hour of Resuscitation in Children With Septic Shock: A Randomized Controlled Trial. Pediatr Crit Care Med 18: e435-e445

34. Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, Debaveye Y, Vlasselaers D, Desmet L, Casaer MP, Garcia Guerra G, Hanot J, Joffe A, Tibboel D, Joosten K, Van den Berghe G, (2016) Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 374: 1111-1122