A Retrospective Cohort Study Comparing Outcomes of Pediatric Intensive Care Patients after Changing from Higher to Permissive Blood Pressure Targets

Ahmed Shakir Mohammed[1] Hilary Klonin[2]

[1] Department of Paediatrics, Diana Princess of Wales Hospital, Grimsby, United Kingdom
[2] Department of Paediatrics, Hull and East Yorkshire, Hull, United Kingdom

Address for correspondence Hilary Klonin, B Med Sci, BM, BS, FRCPCH, Department of Paediatrics, Hull and East Yorkshire, Hull, United Kingdom (e-mail: hilary.klonin1@nhs.net).

Abstract

Keywords
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► sepsis
► outcome
► pediatric intensive care

New neurological morbidity post pediatric intensive care (PIC) poses substantial problems, with a need to understand the relationship of outcome to blood pressure (BP) targets. The aim of the study is to see whether a change from a higher BP targeted strategy to a permissive one improved outcomes for development of new neurological morbidity, length of stay (LOS), and PIC-acquired infection. A retrospective cohort analysis was undertaken, comparing outcomes before and after the change. The higher BP cohort targets were set using standardized age-based centiles. In the permissive cohort, lower BPs were allowed, dependent on physiological variables. Targeted treatment continued throughout the critical illness. New neurological morbidity was defined as any deterioration from baseline, attributable to the admission, measured by post discharge clinical and records review over a minimum period of 4 years. Results were analyzed with IBM SPSS Statistics v26. Of 123 admissions in the permissive and 214 admissions in the higher BP target cohorts, 88 (72%) and 188 (88%) survived without new neurological morbidity (permissive vs. higher cohort OR 0.348 [95% CI 0.197–0.613] p <0.001). Median LOS was 2 (interquartile [IQ] range 2–5) and 3 (IQ range 2–6) days for the permissive and higher cohorts, respectively ($p = 0.127$). Three (2.4%) and 7 (3.3%) admissions in the permissive and higher BP cohorts respectively suffered PIC-acquired infection ($p = 0.666$). A higher BP targeted strategy was associated with protection from new neurological morbidity as compared with a permissive strategy, supporting the need for prospective studies into BP targets.

Introduction

New functional impairment occurs in up to 50% of pediatric intensive care (PIC) survivors.[1,2] Amelioration of the frequency and severity of post-intensive care syndrome could help to reduce the significant burden on children, families, resources and services worldwide caused by the physical, psychological and neurocognitive disability associated with the syndrome.[3]

One strategy to improve morbidity could be identification and achievement of optimal blood pressure (BP) targets.

There is uncertainty as to the most appropriate level of BP in critically ill children to achieve the best neurological outcome. In an erratum note to a study of admission BPs for PIC patients Matettore et al[4] state that the lowest mortality correlates with "median centile" BP by age. Application of the APLS/PALS guidelines to children presenting with shock to Emergency Departments, including resuscitation to normal BP, has been associated with a reduction in mortality and new neurological morbidity.[5] In addition, in-hospital mortality has been shown to be directly related to admission BP below the 75th centile for age and gender in children with isolated severe traumatic brain injury (TBI).[6] Furthermore, a cerebral perfusion pressure (CPP) approach improved outcomes for mortality and neurological disability in meningitis and encephalitis[7] and prolongation of organ dysfunction in sepsis has been shown to adversely affect outcome.[8]

These studies imply that both achievement and maintenance of optimal perfusion facilitate good recovery from critical illness, and in 2002, the American College of Critical Care Medicine (ACCM) Task Force Committee Members consensus guidelines for pediatric and neonatal patients in septic shock[9] stated that perfusion pressure (PP), defined as mean arterial pressure (MAP) minus central venous pressure (CVP), needs to remain above a defined level to allow adequate organ perfusion. On the other hand, the finding of increased mortality in African children with severe sepsis undergoing bolus fluid treatment for poor perfusion,[10] despite possible confounding factors,[11] introduced a note of caution regarding strategies to target higher BPs. Indeed, fluid overload in itself is associated with increased mortality in shock,[12,13] although this effect may be partially ameliorated by improved renal perfusion and increased urinary output as a result of higher BP.[14] Ensuring adequate renal blood flow is central to the argument for maintaining PP in sepsis,[9] but the techniques used to achieve this may carry risks of their own, including adverse effects of inotropic agents,[15] increased length of stay (LOS) because of the need to wean interventional therapies, and prolongation of the period during which invasive devices must stay in situ, thereby increasing the chance of infection.[16]

By 2020 the ACCM panel, highlighting the relative lack of evidence regarding targeting PP, refrained from providing a recommendation regarding optimal MAP.[17] Opinion was split between, on the one hand, maintaining BP between 5th and 50th centile or, on the other, above 50th centile. It is therefore crucial to determine whether higher BP goals diminish neurological morbidity by improving perfusion to critical organs, including the brain, or exacerbate morbidity by prolonging potentially hazardous therapies.

Our hospital practice for children requiring resuscitation historically followed the PALS recommendation to maintain 50th centile BP for age, regarding a drop in BP as a signal of decompensation indicating treatment.[18] This strategy was later relaxed because of concerns that targeting higher level BPs could lead to the adverse effects described above. This change in policy provided an opportunity to analyze data from two cohorts of our PIC population: the first group, where 50th centile or higher BP was targeted; and the subsequent cohort, where lower BP levels were accepted. Our primary objective was to see whether a permissive BP strategy protected patients from the development of new neurological morbidity, with secondary objectives of assessing changes in LOS and the development of PIC acquired infection.

Materials and Methods

Study Design
This is a retrospective, observational study comparing two cohorts of PIC patients, admitted before and after the change in BP target strategy.

Patient Population
The study took place in Hull Royal Infirmary, Hull, UK. The sample comprised all children up to 16 years of age presenting to a single center for Level 2 or level 3 PIC[19] (►Table 1). The higher BP cohort included all admissions from 1st January 2003 until 31st December 2007, when either a median centile BP[18] or defined end organ PP was targeted (►Supplementary Appendix A, available in the online version only).[20] The practice changed in 2008 to acceptance of lower BPs. The lower BP (permissive) cohort included all admissions from 1st January 2008 until 31st December 2012. Patients requiring Level 1 PIC[19] (►Table 1) were nursed on a pediatric high dependency unit (PHDU) and excluded from the study. PHDU patients included those with arterial or central venous access catheters or on low levels of inotropes. Newborn infants were admitted to the neonatal intensive care unit and were excluded. Only those patients who survived to outpatient follow up and for whom there was a full set of clinical admission data were included in the sample taken forward for analysis (►Fig. 1).

Treatment Pathways
In the higher BP cohort, patients acutely unwell within the sepsis continuum, defined according to ACCP/SCCM Consensus Conference Committee,[21] had raised intracranial pressure (ICP), (defined as signs of cerebral herniation syndrome, Cushing's triad, measured ICP >20 cm H_2O or neuroimaging showing cerebral edema or hydrocephalus) TBI with a Glasgow Coma Score of 8 or less, emergency surgery for removal of intracranial hematoma, convulsive status epilepticus with cardiovascular derangement, cardiac failure or shock, BP goals were directed toward 50th centile for age or specified end organ PP using standardized protocols including cerebral PP targets for TBI (►Supplementary Appendix A, available in the online version only). The guideline for the treatment of sepsis was based on the ACCM international consensus guidelines[9] with a fluid restrictive modification of consideration of inotropes at or around 40mls/kg fluid bolus rather than 60 mL/kg. In the permissive cohort such targets were not set. In TBI a specified range of BPs were accepted (►Supplementary Appendix A, available in the online version only) and for others BP was maintained above the lower limit for age[18,20] (►Supplementary Tables S1–S4, available in

Table 1 Definitions of levels of pediatric critical care[a]

| Level 1 Critical care/PHDU	• Requirement for closer observation and monitoring than available on the general ward, including invasive monitoring. • Single organ support. • Step up or step down from PIC. • Following major surgery. • Advanced analgesic techniques. • Receiving non-invasive ventilation. • Receiving invasive ventilation via endotracheal tube as part of resuscitation, prior to transfer to Level 2 care. • Receiving invasive ventilation via tracheostomy as part of long-term respiratory support.
Level 2 critical care	• Receiving invasive ventilation with endotracheal tube. • Two or more organ systems needing support requiring monitoring and regular interventions. • One acute organ failure receiving support, plus one chronic organ failure. • Two or more organ systems requiring technological support including advanced respiratory support as one of these systems.
Level 3 critical care	• Two or more organs requiring technological support including advanced respiratory support as one of these systems.

Abbreviation: PHDU, pediatric high dependency unit.
[a]Derived from the National Coordinating Group on Pediatric Critical Care report to Department of Health, 1997.[19]

the online version only) as long as physiological variables, described below, were deemed acceptable by the attending clinician. In sepsis, apart from the change with respect to BP, guidelines were otherwise similar to the higher BP cohort.

Fig. 1 Flow chart diagram of admissions, eligibility and analysis. BP, blood pressure; LOS, length of stay; n, number; PIC, pediatric intensive care.

For both cohorts treatment was initiated at the point of clinical deterioration. Trends in heart rate and capillary refill time, urine output, acid base status, arterial or capillary lactate and biochemical profile were monitored and treatment adjusted by the attending clinician. Although fluid guidelines were provided, decisions regarding fluid strategy were taken by the individual clinician, including timing of introduction of enteral nutrition, fluid restriction for certain conditions and requirement for additional fluid bolus. Invasive catheters were placed as soon as possible to monitor BP and take blood samples (Cook Medical, Bloomington) either in peripheral or femoral arteries. Until invasive arterial lines were placed, non-invasive monitoring was set to automatically record BP at 3 - 5 minute intervals. Central intravenous catheters (Cook Medical, Bloomington) were placed in the femoral or internal jugular vein to measure CVP or administer vasoactive medication. All lines remained in situ until the patient was stable and breathing spontaneously off invasive respiratory support. ICP monitoring devices were placed when patients who had sustained TBI were deemed to be at risk of raised ICP. For patients with TBI, targeted treatment lasted until the attending neurosurgeon advised it was no longer required. For other patients, hemodynamic support was gradually weaned once stability was achieved, for instance attempting to wean an inotrope and assessing the resulting changes in BP, heart rate, urine output and acid base status. Guidelines did not specify an exact length of time for therapies to continue.

The service guidelines on fluid therapy, inotrope doses, sedation and ventilation practice and treatment of head injury apart from BP parameters, did not change substantially over the course of the study. The use of human albumin solution for fluid bolus was replaced over time with the use of sodium chloride solution. Antibiotic schedules were updated according to microbiology advice. For general drug doses, the British National Formulary was used.
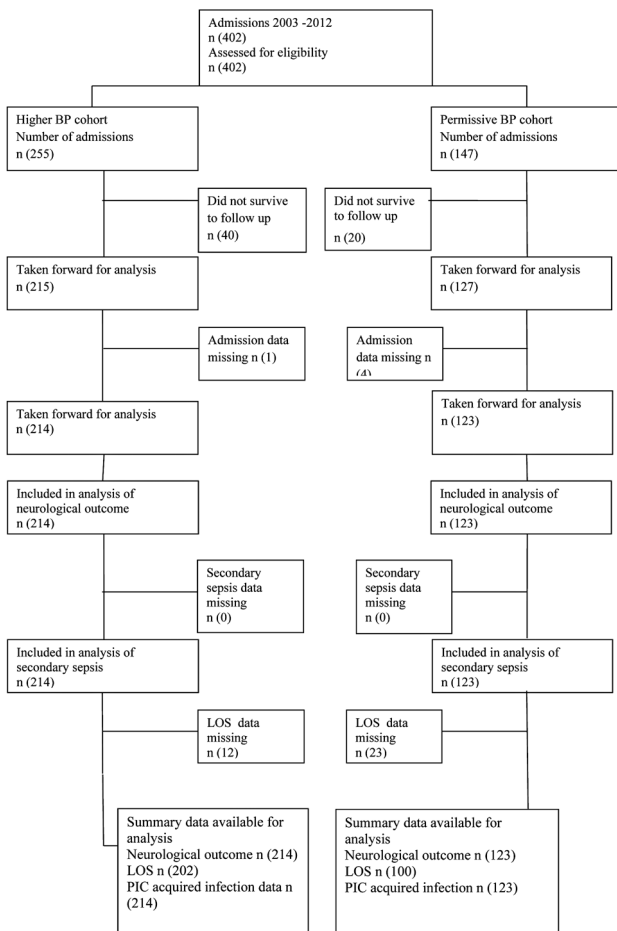
Data Collection

Case identification was performed with the help of the hospital records service. All PIC patients were entered into the UK Pediatric Intensive Care Audit Network (PICanet) database.[22] Pediatric Index of Mortality 2 (PIM2)[23] scores were provided by PICanet. Aggregated mortality data summarizing the two cohorts was supplied by PICanet. Data was collected on age, sex, whether this was an emergency, elective or post-operative admission. Other background data was collected and analyzed based association with outcome: invasive mechanical ventilation,[24] TBI,[24] raised ICP,[6] presence of previous complex chronic conditions (CCC),[1,25] sepsis,[26] presence of seizures[24,27] or status epilepticus[27] and previous history of epilepsy. PIM2[23] scores were used to obtain the expected mortality rate to assess comparability of the two cohorts.

Information on development of new neurological morbidity was collected during a 40 minute follow up clinic appointment 6 weeks to 4 months after discharge, depending on patient and clinic slot availability. The assessment included history and examination by a consultant clinician, with enquiry about previous and current motor, visual and hearing development, current morbidity and new neurological problems. Deterioration from previous state was documented. This data was collated onto a standardized template adapted from the Pediatric Cerebral Performance Category[28] (►**Supplementary Table S5**, available in the online version only). The clinical records were independently interrogated on two further occasions, with a concluding records review, at least four years from the date of the final patient admitted into the study. The records analysis included details of clinical and laboratory data, all other outpatient appointments, contacts from the family about the patient, correspondence from other services such as community health services, developmental and educational needs assessments and requirement for additional support from services. If the patient had more than one admission, any deterioration was noted following the related admission, but if the condition then remained stable, the deterioration was not recounted as a new deterioration for later episodes.

The information collected was used to inform an overall score of neurological disability. Survival without new neurological morbidity was defined as no new neurological morbidity identified from any of these sources as compared with admission.[29] To achieve the result of no new neurological morbidity the outcome needed to be consistent on both clinic review and longer term follow up data. PIC LOS was counted as calendar days with the admission date being day one. PIC acquired infection was defined as presence of new infection after the first 48 hours of PIC admission.[30]

Statistical Analysis

Analysis was undertaken using IBM SPSS Statistics v26. Categorical data to describe the case mix are reported as counts and percentages. Continuous data are reported as mean and standard deviation. Standardized mortality rate (SMR) was calculated as a ratio of observed to expected deaths.

Logistic regression was undertaken to investigate the relationship between the following variables and survival without new neurological morbidity: age, sex, cohort, post-operative admission, PIM2 score, CCC, sepsis, raised ICP, seizures, status epilepticus, trauma, TBI and being invasively ventilated. Those variables reaching significance were then entered into a multivariate logistic regression model. For multivariate models, a backward likelihood ratio method was used. A p-value <0.05 was considered to be statistically significant. Given the debate regarding optimal BP strategy for patients with sepsis, we used logistic regression to look for an association between sepsis and cohort. LOS data are given as median and IQ ranges for the entire group and analyzed by independent samples median test. The odds of acquiring an infection while in the PIC unit were compared between the two groups.

Results

There were 402 admissions between 2003 and 2012. From the admission events, 342 resulted in survival (►**Fig. 1**). In the higher BP cohort 215/255 admissions resulted in survival and 127/147 in the permissive cohort. The expected mortality was 14% in the higher BP cohort and SMR 0.73 (95% CI 0.49–1.04). The expected mortality was 9% and SMR 1.167 (95% CI 0.67–1.86) in the permissive cohort. Admission clinical data was missing in five cases which were excluded from further analysis of survivors (►**Fig. 1**). There were three elective admissions in the higher BP cohort and none in the permissive group. In the higher BP cohort, seven patients were admitted twice and two patients were admitted three times and in the permissive cohort, four patients were admitted twice, two patients were admitted three times and one patient was admitted seven times. Only two patients were admitted to both cohorts. All were treated as independent events.

►**Table 2** shows the clinical characteristics of each group.

Survival without new neurological morbidity occurred in 88 (72%) and 188 (88%) of the permissive and higher BP cohorts, respectively. The size of this association was explored: the unadjusted odds ratio (OR) for survival without new neurological morbidity in the permissive versus the higher BP cohort was 0.348 (95% CI 0.197–0.613, Wald 13.3, p <0.001).

Being in the permissive cohort, being invasively ventilated, having raised ICP, or suffering from trauma or TBI were associated with significantly lower odds of survival without new neurological morbidity in univariate unadjusted analyses (►**Table 3**). Multivariate logistic regression analysis was undertaken to ascertain the effects of cohort, invasive mechanical ventilation, raised ICP, trauma, and TBI on the (adjusted) likelihood of survival without new neurological morbidity: all variables were biologically plausible.[6,24,26,27] The final model fit was good: Nagelkerke R-squared 0.261 and Hosmer and Lemeshow Chi-square 2.00 ($p = 0.737$). Results of variables included in the final model are shown in ►**Table 4** and demonstrate that the odds of survival without new neurological morbidity were significantly

Table 2 Characteristics of each cohort

	Cohort	Permissive BP strategy	Higher BP strategy
Baseline characteristics	Number of patients with complete data and included in analysis	123 (after 4 excluded due to missing data)	214 (after 1 excluded due to missing data)
	Age (y): mean (std)	4.15 (5.40)	4.46 (4.64)
	Sex: number of males: *n* (%)	76 (62)	133 (62)
	PIM2 score: mean (std)	0.046 (0.076)	0.051 (0.075)
Characteristics during PICU stay	Postoperative admission: *n* (%)	26 (21)	34 (16)
	CCC: *n* (%)	63 (51)	103 (48)
	Primary sepsis: *n* (%)	45 (37)	80 (37)
	Raised ICP: *n* (%)	19 (15)	55 (26)
	Seizures: *n* (%)	38 (31)	62 (29)
	Status epilepticus: *n* (%)	37 (30)	55 (26)
	Trauma: *n* (%)	18 (15)	55 (26)
	TBI: *n* (%)	13 (11)	43 (20)
	Invasive mechanical ventilation: *n* (%)	103 (84)	172 (80)

Abbreviations: BP, blood pressure; CCC, complex chronic condition; ICP, intracranial pressure; *n*, number; PIM, pediatric index of mortality[23]; SD, standard deviation; TBI, traumatic brain injury; y, year.

Table 3 Univariate (unadjusted) binary logistic regression to ascertain effect of each variable on the likelihood of survival without new neurological morbidity

Variable	OR	95% CI for OR	Wald	*p*-Value
Age (y)	0.986	0.933–1.043	0.23	0.628
Cohort	0.348	0.197–0.613	13.3	<0.001[a]
Sex	0.857	0.487–1.509	0.29	0.594
CCC	1.504	0.857–2.639	2.02	0.155
PIM2	0.317	0.012–8.592	0.45	0.495
Postoperative admission	0.758	0.381–1.509	0.623	0.430
Raised ICP	0.179	0.098–0.325	31.9	<0.001[a]
Seizures	1.700	0.876–3.299	2.45	0.117
Sepsis	1.055	0.593–1.879	0.034	0.855
Status epilepticus	1.888	0.935–3.811	3.147	0.076
Trauma	0.276	0.152–0.502	17.9	<0.001[a]
TBI	0.224	0.119–0.422	21.4	<0.001[a]
Invasive mechanical ventilation	0.343	0.131–0.896	4.77	0.029[a]

Abbreviations: CCC, complex chronic condition; CI, confidence interval; ICP, intracranial pressure; OR, Odds ratio; PIM2, pediatric index of mortality[23]; N, no; TBI, traumatic brain injury; Y, yes.
[a]*p*-Value significant at *p* <0.05 level.

lower in the permissive cohort and in subjects with raised ICP, with a requirement for invasive mechanical ventilation of borderline significance.

In the higher BP cohort, 76 out of 80 patients (95%) with primary sepsis survived without new neurological morbidity. In the permissive cohort, 27 out of 45 (60%) with primary sepsis survived without new neurological morbidity. The results of logistic regression for cohort, sepsis, and the interaction between cohort and sepsis are shown

in ►**Table 5**. Model fit was satisfactory (Nagelkerke *R*-square 0.117, Hosmer and Lemeshow Chi-square <0.001, *p* = 0.999). The interaction term was significant such that survival without new neurological morbidity was greater in the higher BP cohort than in the permissive cohort.

LOS data was missing in 35 patients, 23 in the permissive cohort and 12 in the higher BP cohort, leaving 100 and 202 patients, respectively for analysis in each cohort (►**Fig. 1**). ►**Fig. 2** shows a bar chart of LOS according to

Table 4 Multiple binary logistic regression to analyze adjusted odds of survival without new neurological morbidity

Variables included in final model	OR	95% CI for OR	Wald	p
Cohort (permissive vs. higher BP strategy)	0.214	0.108–0.421	19.8	<0.001[a]
Invasive mechanical ventilation (Y vs. N)	0.389	0.142–1.065	3.37	0.066
Raised ICP (Y vs. N)	0.118	0.142–1.065	36.1	<0.001[a]

Abbreviations: BP, blood pressure; CI, confidence interval; N, no; OR, odds ratio; p, p-value; vs., versus; Y, yes.
Note: Total number of patients included in analysis: 337. Total number of events (survivors without new neurological morbidity): 276. Total number of "non-events": 77.
[a]p-Value significant at $p < 0.05$ level.

Table 5 Results of logistic regression analysis of sepsis, cohort, and interaction between sepsis and cohort on likelihood of survival without new neurological morbidity

Variables	OR	95% CI for OR	Wald	P
Sepsis	1.249	0.631–2.472	0.408	0.523
Cohort	0.236	0.119–0.467	17.2	<0.001[a]
Cohort by sepsis interaction	0.112	0.029–0.439	9.87	0.002[a]

Abbreviations: CI, confidence interval; OR, odds ratio; p, p-Value.
[a]p-Value significant at $p < 0.05$ level.
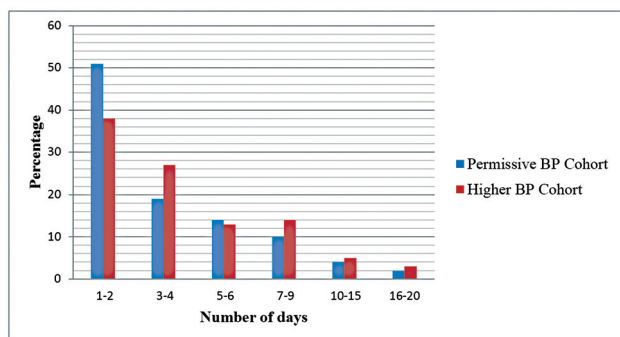
Fig. 2 *Percentage frequency of length of stay.* BP, blood pressure.

time epochs. Median LOS was 2 days (IQ range 2–5) for the permissive BP cohort and 3 days (IQ range 2–6) for the higher BP cohort. Test statistic = 2.717, $N = 302$, d$f = 1$, asymptotic two-tailed p with Yates continuity correction $p = 0.127$ which was not significant. The unstandardized effect size estimate is 0.000 with 95% CI −1.00 to 0.00, using the independent samples Hodges-Lehman median difference test.

PIC-acquired infection affected similar proportions of each cohort: seven (3.3%) and three (2.4%) in the higher and targeted cohorts, respectively (OR 0.739, CI 0.188–2.91, $p = 0.666$).

Discussion

New neurological morbidity for PIC survivors, remains a serious problem.[1–3] Because of concerns that targeting higher BPs may lead to over treatment with associated risks and prolonged LOS, our practice for all patients changed at a specific time point, allowing us to test the hypothesis that using a permissive approach could be associated with de-

creased new neurological morbidity post PIC. In fact, 12% of patients in the higher BP cohort and 28% in the permissive cohort showed new neurological morbidity, showing a highly significant difference. Thus, there was a greater risk of new neurological morbidity in the permissive cohort and apparent protection from this in the higher BP cohort. Cases in the permissive cohort were no more unwell, with similar aggregated risk of mortality and comprehensive analysis of baseline characteristics to the higher group, supporting a hypothesis that the poor outcome of the permissive cohort could be an effect of the change of BP strategy.

In a study of healthy anaesthetized children, the lower limit of cerebral autoregulation was found to rest close to the baseline MAP[31] for each individual patient, demonstrating potential for decreased CPP if BP falls. Where population-based centiles are used and lower centile BPs are the cut off for treatment, more patients will be below their normal baseline BP, during their illness, with a possible risk for cerebral under perfusion. This risk could be compounded if there is intermittent drift to even below this lower limit before correction, due to the time lag between the observation of the BP level and institution of therapy. Therefore, organs could be subject to diminished perfusion for a period of time before restorative action is taken. Reduced perfusion occurring after the period of initial resuscitation can lead to further ischemia and subsequent re-perfusion injury.[32] Avoiding such problems with a higher BP approach may be part of the explanation for the strong relationship between the higher BP cohort and protection from new neurological morbidity.

A striking finding was the relationship between sepsis and cohort. Five percent in the higher BP cohort with sepsis and 40% in the permissive cohort suffered new neurological morbidity, although the only change in the treatment

algorithm was the removal of the PP target. In a global perspective trial, 34% of pediatric sepsis survivors showed a decline in functional status at 28 days.[26] In our study sepsis was a risk factor for new neurological morbidity only in the permissive cohort while the higher BP cohort compared favorably with available international data. The PP approach to septic shock, advocated in 2002,[9] may ensure consistent maintenance of adequate blood flow to organs. In a permissive approach, where lower BPs are allowed, signs of reduced organ perfusion such as decreased hourly urine output or increased lactate take time to become detectable, contributing to delays in correction of under perfusion. As acknowledged by Weiss et al, evidence on this question is so limited as to be impossible for an international panel of experts on sepsis to make firm recommendations.[17] If our findings could be reproduced in prospective studies, it would provide an opportunity to make substantial progress in addressing the problem of new neurological morbidity for this population.

In keeping with other studies, raised ICP[6] and the presence of invasive mechanical ventilation[24] were associated with a worse neurological outcome in our patients. The association between higher BP and improved survival for pediatric head injury has already been explored in the literature.[6] In our permissive cohort, rather than allowing BP to be at the lower limit for age, a range of acceptable BPs was set. This may reflect the situation in services which do not have access to immediate neurosurgical interventions to measure intracranial pressure. It is possible when using a range of BPs for differing age groups that these could sometimes be interpreted by attending clinicians in such a way that the accepted BP becomes close to the lower limit of age for an individual patient, increasing the risk of compromising cerebral perfusion. Although we cannot comment further on whether this happened to any of our sample in the permissive group, as we did not collect data on measured BPs, we feel it should be a consideration when writing BP guidelines or undertaking further research for patients with raised ICP. Possibly the effect of invasive positive pressure ventilation on cardiac output[33] is one of the factors relevant to the poor outcome found to be associated with invasive ventilation.[24] The optimal BP strategy could vary according to the illness but larger studies with more patients and detailed analysis of other associated factors may be required to explore this.

Our study is unusual in examining BP targets in children beyond initial resuscitation, continued through stabilization and into the weaning period. We have not been able to find studies which document actual age appropriate BP measurements through the PIC stay. In a study of adult sepsis patients, targeted treatments were undertaken for up to 5 days, with no association between higher MAP and improvement in mortality.[34] The average age of this study population, however, was 65 years, and higher level group BP target was an MAP of 80 to 85 mm Hg. Normal MAP in adults, ranging from 93 to 105 mm Hg[35] is higher than the study BP targets. This work cannot therefore be compared directly with our study, which assesses the effect of targeted median centile BP, determined by age group, on morbidity.

Shorter stays were more common in the permissive group but did not reach significance. Missing LOS data, affecting 6% of the higher BP cohort and 19% of the permissive cohort, may have affected the validity of our results and was a factor in undertaking only a preliminary analysis. This reflects the problem in retrospective studies of pin pointing the exact date of transfer from PIC. Our service may be unusual with a substantial amount of critical care patients being nursed in an independent PHDU including an ability to institute early proactive critical care, leading to reduced recovery time.[36] Complex patients were stepped down shortly after liberation from invasive mechanical ventilation. A prospective trial could add precision, including hours of PIC stay and overall hospital LOS, to give a more exact picture.

PIC-acquired infection rates were low[37] without a significant difference between groups. This may reflect the relatively short LOS. It is possible, but unlikely, that we missed infection which originated on the PIC unit but manifest after discharge since the patient records were reviewed for new morbidities arising during the hospital stay. The low rates we observed precluded further statistical analysis.

A strength of our study is that we have a nearly complete dataset for survivors. Detailed assessment by a clinician was supplemented by further comprehensive records review, over a minimum period of 4 years, giving ample time for new neurological morbidity to become apparent, decreasing the chance of missing later, but related, morbidity. This gives our study a longer follow-up time than many published studies of new morbidity.[1] Despite this, we accept that subtle changes post PIC could have been missed, possibly more so in children who already suffered from some neurological deficit, but it is unlikely that results from one cohort were more affected than the other, given the length of follow-up, and therefore should not be a source of bias.

A main limitation of our study is the absence of information about the actual BP attained, therefore, we cannot definitively state that our results were associated with protection from hypotension and associated under perfusion of organs. To ensure outcomes are in association with actual achieved BPs, a prospective study with strictly specified centile-based BP definitions, data collection methods, and times lines would be required.

Our results are from a single center, limiting applicability to the general situation but providing an opportunity to pinpoint a specific change in practice, while applying reasonably uniform guidelines and follow-up throughout the study. General trends in resourcing and national directives over time including increased access to centralized services and advice lines may have been confounders, but should improve outcome.[38,39] It has been suggested that improvement in mortality could in fact increase disability in the survivors as extremely unwell children survive, who are more at risk of new neurological morbidity[2] but since the survivor PIM data are similar between cohorts, this does not appear to be the case in our study.

Despite its limitations, this retrospective study shows an important association between a higher BP target strategy and protection from new neurological morbidity, as compared

with a permissive strategy. Further work is needed to explore this association, for example using multi-center cohort data. The gold standard would be prospective multicenter randomized controlled trials of permissive versus higher BP targets, which could include specific pediatric pathologies such as sepsis, trauma, or respiratory failure. Our data suggests that detailed consideration of the classification and avoidance of hypotension in the lower BP trial arm is required.[40]

Conclusion

Changing practice from targeting 50th centile BP or above to a permissive approach where lower BPs were accepted was associated with increased new neurological morbidity. This supports and informs the call for larger prospective studies to delineate the optimal BP targets for PIC patients.

Ethics Approval

Formal approval was obtained from the hospital clinical governance department, reference number, NA.2015.012. The supervising university for submission for thesis contribution for Master of Science waived requirement for further ethical approval. PICanet has permission to collect data under section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001).[22]

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Conflict of Interest

None declared.

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