Evaluation of blood pressure trajectories versus outcome in critically ill children with initial hypertension on admission to Paediatric Intensive Care.

Clinical Investigation

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Abstract

Objective: Hypertension on PICU is associated with adverse outcomes. Management is complex because hypertension often represents a physiological adaptive response – for example to raised intracranial pressure. International treatment consensus for (non-adaptive) hypertension is to gradually reduce blood pressure (-25% in first 8 hours). The risks and benefits of this guidance will depend on case mix. Our objective was to analyse first 24-hour blood pressure trajectories of these critically ill hypertensive children and correlate these profiles with adverse outcomes.

Design: Single centre retrospective observational study

Setting: A large, quaternary care PICU.

Patients: 534 children admitted to PICU in 2016 - 2018 with initial blood pressure above the 95th centile and with available high-resolution data.

Interventions: None

Measurements and Main Results: Individual blood pressure trajectories were analysed regarding both *time spent* and *magnitude* below a *threshold* - set 25% below the admission blood pressure. A total of 3,259,111 SBP (99.4% invasive) measurements were available in the first 24-hours. Pre-existing hypertension was documented in 4.9% of patients. The Spearman correlation coefficient for our primary outcome *organ support free days at day 28* and percentages of measurements (or time spent) below the threshold was -0.13 (95% CI -0.20 to -0.04), and average z-score (or magnitude) below the threshold -0.17 (95% CI -0.25 to -0.08). This correlation was not seen after accounting for the PIM score, chronic hypertension or raised intra-cranial pressure. Creatinine was more likely to rise with time and the magnitude of blood pressure spent below the threshold, and this was preserved following multi-variable analysis.

Conclusions: We found univariable associations between the time and distance below a threshold BP value and duration of organ support, mortality and rise in creatinine. Possibly suggesting BP should not be rapidly normalised, although perhaps we should not intervene to maintain the blood pressure above normal levels.

Introduction

Both *hypotension (1-3)* and *hypertension (1, 2, 4)* at admission to the paediatric intensive care unit (PICU) have been associated with adverse outcomes. Although the harm associated with hypotension can be explained by poor organ perfusion, with hypertension the cause may be multi-factorial. Some disease states, such as raised intracranial pressure (ICP), can present with adaptive hypertension and may lead to a poor outcome. However, this is unlikely to fully account for the association completely: hypertension remains an independent risk factor for mortality on the Paediatric Index of Mortality (PIM) score (5).

The early reversal of *hypotension* in paediatric patients is associated with improvement in outcomes (6-8). Regarding *hypertension,* there are no data available supporting rapid reversal of high blood pressure (BP) leading to improved outcomes. On the contrary, rapid normalisation may cause harm in many contexts given concerns about abnormal cerebral autoregulation in chronic hypertension (9-11). Patients with measured or suspected raised ICP are even maintained at a supra-physiological BP to maintain adequate cerebral perfusion pressure (12).

Gradual reduction of hypertension is reflected by the consensus guidance for the treatment of malignant hypertension advising a controlled reduction of the systolic BP in hypertensive emergencies by 25% over the first 8 hours after presentation and then gradually normalizing the BP over 36-48 hours (13, 14) .

A corollary, therefore, may be that a rapid normalisation of BP in children with hypertension at admission to PICU may be associated with poor outcomes. To test this hypothesis, we studied the 24-hour BP profile of children with hypertension at admission to our pediatric intensive care. We tested the association between the time and magnitude spent below a threshold BP for each patient and PICU outcomes. The null hypothesis was that amongst children with hypertension at PICU admission, there was no difference in the distribution of organ support free survival with post admission BP profiles.

Material and Methods

We conducted a single centre retrospective observational study of children with hypertension on admission to a large quaternary general paediatric and neonatal intensive care unit (PICU) between January 1, 2016 and December 31, 2018. The project was registered with and approved by the Institutional Audit Department as a service evaluation project. Individual patient consent was not sought as only routinely collected data were analysed by members of the clinical team.

Hypertension was defined as systolic BP (SBP) greater than the 95th centile for age and sex - with an assumed 50th centile for height due to absence of height data- using data from the Fourth Report on the Diagnosis, Evaluation and Treatment of High BP in Children and Adolescents (14). Patients less than 4 weeks corrected gestational age were excluded. For children under 1 year of age the 95th centile value for 1 year was used.

SBP data in the first 24 hours post admission to PICU were extracted from the Etiometry T3 system (Etiometry Inc, MA, USA), recorded directly from the patient bedside monitor at 5-second intervals. Data were not available during patient retrieval. We utilized data for 24 hours starting from the time of arrival on PICU, even if the admission SBP recorded in the PIM score may have preceded this. Both invasive and non-invasive SBP measurements were considered. In the case of both values being available at a time-point, the invasive SBP was used. The site of measurement was not recorded. Extreme values of SBP <30 mmHg or >250 mmHg were excluded as spurious. SBP values were converted to z-scores using the centile values for age and sex using the LMS method (15). This allowed comparison of SBP across ages.

Age, weight, and PIM data were collected for children who had an admission SBP z-score ≥2. Children with pre-existing hypertension and clinical suspicion of raised intra cranial pressure were identified by searching their PICU free-text notes from the Electronic Health Record (EHR) (Intellivue Critical Care and Anaesthesia, Philips Electronics, Netherlands) using the search terms 'hypertension', 'intra cranial pressure, 'ICP', and 'neuroprotection', followed by manual verification. Data on organ support were extracted from the EHR, including mode of ventilation, both invasive or non-invasive but excluding high flow nasal cannula oxygen; any vasoactive infusions including inotropes (epinephrine, dopamine, milrinone), vasoconstrictors (norepinephrine, vasopressin) or anti-hypertensives (labetalol, esmolol, hydralazine, sodium nitroprusside, glyceryl trinitrate); and use of

continuous renal replacement therapy. Length of stay, survival status and creatinine data during ICU stay were extracted from the EHR.

Clinical management

During the study period there was no clinical guideline for the management of hypertension on PICU. Raised ICP was managed to optimise cerebral perfusion pressure (CPP), targeting a CPP>40mmHg in children < 6 years and >50mmHg > 6 years. For children with pre-existing hypertension the EHR notes were manually checked for stated SBP lower limit targets in the first 24 hours of admission. Children managed on continuous vasoactive drug infusions would usually be monitored with continuous invasive SBP measurements. Radial arterial catheters were used preferentially however femoral or axillary arterial catheters were used as alternatives.

Outcome measures

Organ support free days at day 28 was the primary outcome measure. Duration of ICU organ support was calculated as the time from admission to the time of the last mode of support being removed. Death was considered as 0 organ support free days at day 28. PICU mortality and percentage rise in creatinine – as a sign of acute kidney injury (AKI) - during admission were secondary outcome measures. The rise in creatinine (%) was calculated as the highest creatinine value during PICU stay minus the first recorded value, as a percentage of the first recorded value. If the creatinine level decreased during PICU stay, or if only a single value was measured, the percentage rise was considered 0. Given the pressure-blood flow relationship for the kidneys is relatively steep amongst organ systems, this was thought likely to be a sensitive indicator of organ damage from BP changes and hypertension (16).

Statistical Analysis

As the hypothesis aimed to test if relative hypotension early during PICU admission was associated with adverse outcomes in those with hypertension at admission, the percentage of measurements in the first 24-hours of PICU admission below a target threshold was used as the metric to test this association *(%$BP_{belowthreshold}$)*. Unless pre-specified in those with pre-existing hypertension, the threshold SBP was selected as 25% below the admission SBP, based on management guidelines for those with malignant hypertension (9, 13). Secondly, to consider the magnitude below the threshold, the difference in the SBP z-scores below the threshold were added together and divided by the number of SBP measurements below the threshold (*mean $zBP_{belowthreshold}$*) (Figure 1). Missing SBP values were not imputed – only measurements available were used. As data were recorded every 5-seconds, for

each patient there could be a maximum of 24 x 60 x 12 = 17,280 data values in the first 24 hours. Therefore, the mean distance from the threshold was used, rather than the area under the curve.

Distributions of continuous variables were summarised using median and inter-quartile ranges and categorical variables as numbers and frequencies. Spearman's correlation co-efficient was used to test univariable associations between $\%BP_{belowthreshold}$, and mean $zBP_{belowthreshold}$, and continuous outcome measures (organ support free days at day 28, duration of organ support in survivors and percentage rise in creatinine from admission). A Mann-Whitney test was used to test the unadjusted difference in $\%BP_{belowthreshold}$, and mean $zBP_{belowthreshold}$, between survivors and non-survivors.

Adjusted associations were explored using Bayesian multiple regression models, using gamma models for the organ support free days at day 28 and the % rise in creatinine from baseline, and a logit model for PICU mortality. Separate models were used for each of the SBP profile measures (i.e., $\%BP_{belowthreshold}$, and mean $zBP_{belowthreshold}$). All models adjusted for PIM score to account for the risk of mortality as well as two comorbidity indicators for chronic hypertension and raised ICP.

The use of the Bayesian framework is particularly helpful since, as it is expected that the risk of relative hypotension in children with these conditions would increase, we are able to encode this information using different prior distributions for the associated regression coefficients. In particular, the models for the primary and secondary outcomes analyses use non-informative priors, but we performed sensitivity analyses for the primary outcome to evaluate the impact of mildly informative priors for comorbidities on the outcome. For these latter models, one for each of the SBP profile measures, we assumed that comorbidities have a negative prior effect on the organ support free days at day 28.

Separate models were used for the three outcome measures - organ support free days at day 28, PICU mortality and the percentage rise in creatinine for admission. The models included either the percentage of time spent below a SBP threshold (either defined a priori, or taken as 25% below the admission SBP) in the first 24 hours, $\%BP_{belowthreshold}$, or the mean distance of the age and sex standardised blood systolic pressure threshold, mean $zBP_{belowthreshold}$. The Paediatric Index of Mortality-3 (PIM) score, presence of chronic hypertension, or suspected or measured raised intra-cranial pressure were co-variates in the models. Assuming that lowering the SBP is

associated with a greater risk of an adverse outcome in those with chronic hypertension or raised intra-cranial pressure, the priors were adjusted to double the risk of those without either co-morbidity.

All analyses were carried out using *R software* version 4.x (R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 3069 admissions to PICU over the 36-month period. Of these, 667 admissions aged between 4 weeks corrected gestational age and 16 years had an admission SBP above the 95th centile (21.7% of admissions). High resolution data were available for 534/667 (80.0%) admissions in the first 24-hours, which were analysed further. The baseline characteristics for these admissions are shown in **Table 1**.

A total of 3,259,111 SBP measurements were available in the first 24-hours. There were a median of 2531 measurements per admission (IQR 36-13001). Of these 3,242,581 (99.4%) were invasive arterial measurements from 295 children, and 16,530 were non-invasive from 409 children (non-invasive measurements were only considered if an invasive measurement was not available). Twenty-six (4.9%) had a pre-existing diagnosis of hypertension, 9 of whom had pre-specified SBP targets documented in the first 24 hours. Thirty-one (5.8%) children had suspected or monitored ICP, with a mean BP target. The percentage of measurements in the first 24-hours of PICU admission below the target threshold $\%BP_{belowthreshold}$ ranged between 0 and 100, with a median of 16.1 (IQR 2.3-52.8). The mean $zBP_{belowthreshold}$ ranged between 0 and 4.99. with a median of 0.75 (IQR 0.05-1.22). The distribution is shown in Figure 1. An exemplary BP pattern is shown in **Supplemental Figure 1**.

Clinical outcomes are shown in **Table 2**. The Spearman correlation coefficient for organ support free days at day 28 and $\%BP_{belowthreshold}$ was -0.14 (95% CI -0.22 to -0.06) i.e. a greater percentage of measurements below the target was associated with fewer organ support free days at day 28. Similarly, the correlation coefficient for organ support free days at day 28 and mean $zBP_{belowthreshold}$ was -0.13 (95% CI -0.22 to -0.04) (**Figure 2**) suggesting the greater the mean distance below the threshold, the fewer the number of organ support free days at day 28. **Figure 3** shows the effect of the $\%BP_{belowthreshold}$ below varying BP thresholds and the correlation co-efficient for organ support free days at day 28. **Figure 4** shows the correlation between the number of organ support free days at day 28 and the percentage of BP measurements above a range of thresholds.

Results from the Bayesian regression model for the primary outcome show that the odds ratio for predicting organ support free days at day 28 was 1.00 (95% credible interval 0.997-1.003) for $\%BP_{belowthreshold}$. In the sensitivity analysis with stronger priors for the risk of lowering SBP in those with chronic hypertension and those with raised ICP, the odds ratio did not change (1.00, 95% CrI 0.997-1.003). When considering the mean

$zBP_{belowthreshold}$, the odds ratio was 0.974 (95% CrI 0.861-1.109) for organ support free days at day 28. Once again, there was minimal change when imposing informative priors to account for an increased risk in those with chronic hypertension and raised ICP (OR 0.973, 95% CrI 0.855-1.108).

PICU mortality and percentage rise in creatinine were used as secondary outcome measures. There was no difference in the $\%BP_{belowthreshold}$ between those who survived or died on PICU when compared using a Mann-Whitney test (p-value 0.20). However, mean $zBP_{belowthreshold}$ was higher in those who died (Mann-Whitney p-value 0.02). Using a Bayesian logit regression model, adjusting for PIM, hypertension and raised intra-cranial pressure, the odds ratio of death was 1.004 (95% CrI 0.992-1.016) for $\%BP_{belowthreshold}$, and increased at 1.338 (95% CrI 0.826-2.054) for mean $zBP_{belowthreshold}$.

The percentage rise in creatinine from admission was positively correlated with $\%BP_{belowthreshold}$ (Spearman's correlation coefficient 0.15, 95% CI 0.05-0.23) and mean $zBP_{belowthreshold}$ (Spearman's correlation coefficient 0.21, 95% CI 0.12-0.29) (**Supplementary Figure 2**). Results from Bayesian regression analysis, adjusting for PIM score, hypertension and raised intra-cranial pressure, revealed that the odds ratio was 1.011 (95% CrI 1.004-1.018) for $\%BP_{belowthreshold}$, and 1.530 (95% CrI 1.118-2.143) for mean $zBP_{belowthreshold}$. Therefore, for each unit rise in the mean $zBP_{belowthreshold}$ there was an increase in the % rise in creatine from admission by 0.53.

All model coefficients are shown in **Table 3.**

Discussion

Our study aimed to explore BP patterns in critically ill pediatric patients with hypertension on admission and the association of these BP patterns and intensive care outcome measures (mortality, organ support free days, creatinine rise). Increasing time and magnitude spent below a threshold value, chosen as 25% below the admission systolic BP, was associated with an increase in the need for organ support on univariable analysis, although this effect was not seen after accounting for the PIM score, the presence of chronic hypertension or those with raised intra-cranial pressure. Creatinine was more likely to rise with time and magnitude of BP spent below the threshold, and this was preserved following multi-variable analysis.

Hypertension is a significant burden for PICU patients. As comparable to our findings, the prevalence during PICU admission is reported in up to 25% of all critically ill children (4), and associations with negative PICU outcomes have been described. The incomplete understanding of the association between initial hypertension and negative PICU outcomes motivated the hypothesis tested in this study.

There is multifactorial aetiology of hypertension in PICU. Hypertension might be of secondary origin e.g. inadequate sedation/analgesia or a drug side effect. In some patients the elevated BP may be adaptive, and too rapid normalisation to an age-appropriate standard may explain some of the adverse outcomes. These patients might suffer from relative hypotension i.e. perfusion pressure deficit. Whilst novel in this context, this concept of BP below a patient specific threshold being associated with harm has been demonstrated in adults (10, 17) and in children post-cardiac arrest (8). In both, the duration and magnitude below the threshold could be correlated with adverse outcomes. In adults on vasopressors, Panwar et al hypothesised that duration and magnitude below the pre-illness BP, in a cohort where 59% had a history of chronic hypertension, would be associated with acute kidney injury. The underlying mechanism is presumed to be the adaptation to a higher perfusion pressure in those with chronic hypertension (10).

Chronic hypertension is less common in the pediatric population, and this is unlikely to be the main mechanistic explanation for our associations seen with rise in creatinine. However, we included pre-existing chronic hypertension as a co-variate in the multi-variable regression model to account for this. Despite undertaking a sensitivity analysis to reflect an increasing risk of adverse outcomes with chronic hypertension, the priors for those

with chronic hypertension remained non-informative. This is a strength of using Bayesian analysis, incorporating prior held knowledge about sub-groups, even in relatively small cohorts.

Similarly, we accounted for a greater risk of children with brain injury and suspected or monitored raised ICP. This reflects the population of post cardiac arrest children studied by Laverriere et al. However, in their study, time spent below the age-associated 5th centile BP was the threshold used, rather than an individual specific threshold. The median the age-standardised z-score for the threshold value of 25% below the admission systolic BP in our cohort was 0.11 (IQR -0.35, 0.37). A z-score of 0.11 represents the 54th centile, -0.35 the 36th centile. It is possible that maintenance of BP above an age-associated threshold is the determinant of harm but this may be lower than the 50th centile.

We used systolic BP rather than the mean. Hypertension is commonly defined by the systolic BP, therefore this was used. In addition, the age-associated systolic reference values are better defined than the mean BP, although the latter have been derived with assumptions (18). It is possible that mean BP changes are more strongly associated with harm (as a deficit in perfusion pressure) but this will need further exploration.

We make the assumption that BP demonstrates a threshold effect: crossing this threshold may be associated with harm. This is strengthened by studies such as those by Panwar and Laverriere. An alternative theory however may be that BP variation, as a marker of loss of autoregulation, may be associated with adverse outcomes. This may warrant further exploration and may be possible with high-resolution datasets such as ours. We chose an arbitrary threshold of 25% below the admission BP as a critical threshold in whom a premorbid based individual threshold was not available. This was based on guidance from the management of severe hypertension (9, 13, 19, 20) although without supporting data in children. Our findings broadly support this although do not justify the exact threshold or identify cohorts who are more or less likely to benefit. We explored the effect of different threshold post-hoc: overall, the correlation between organ support free days at day 28 and $\%BP_{belowthreshold}$ became stronger as the threshold decreased from 95% of the admission BP to 60% of the admission BP (Figure 4).

If those who maintain a high blood pressure have more organ support free days, then is hypertension per se is harmful? Our analysis does not answer this. The risk of hypertension may be present in a sub-group of patients, e.g. those with malignant hypertension or hypertensive encephalopathy, but not all. We explored the effect of BP

remaining *above* different thresholds between 75% and 95% of the admission blood pressure, and explored whether there were different effects in our pre-specified populations. The association between organ support free days and % BP above the threshold weakened as the threshold was increased (Figure 5). This would suggest that a higher blood pressure is associated with a greater duration of organ support. The pattern seems to occur even in those with chronic hypertension and those with raised intracranial pressure, although the size of these sub-groups makes interpretation more difficult.

Whilst making these observations, we must acknowledge that we do not take into account the effect of treatment: maintaining BP above an arbitrary threshold with vasopressor support for example may not provide a favourable risk-benefit profile compared to those who may maintain this without support. Also, we cannot dissociate the effect of treatment from the outcome measure: clinicians may start vasopressors to prevent the blood pressure from falling below a threshold, which will increase the duration of organ support, or may start continuous anti-hypertensives if the blood pressure remains raised.

Limitations

Although our study had a novel approach to an understudied group of pediatric intensive care patients we had several limitations, in addition to those discussed above. Regardless of the high-resolution data available, the single centre and retrospective nature of our study limits its value. The admission values were recorded as part of the PIM score, which may have been collected at the point of contact with the intensive care retrieval service, even though high resolution data assessed were from the time of admission to the PICU. There may be changes between the admission BP and start of high-resolution data collection which are unaccounted for. We did not exclude cases where there was a high degree of data missing. Mode of BP measurement differences resulted in a lack of the same amount of data points for all patients equally. Non-invasive measurements were used when invasive measurement data were unavailable: the two may not be interchangeable given described discrepancies between the modes of measurements (21, 22).

Although we studied the duration of organ support and mortality as global outcome measures, functional status and neurodevelopmental outcomes may be more relevant – we did not have retrospective data available for these. The percentage rise in creatinine may be sensitive but may not carry clinical significance – the threshold for acute kidney injury may not have been reached in each case.

Despite these limitations, we believe our results are valuable and in the absence of prospective data support the current practice of slow normalisation of BP in hypertensive patients. However, based on these results we cannot suggest intervening to keep the blood pressure above 75% of the admission blood pressure in those with hypertension at admission. Although we pursued maximal utilization of our data, there should be future prospective randomized and controlled- intervention studies in hypertensive critically ill children examining outcomes in correlation with different BP targets and time frames.

Conclusions

When examining first 24-hour SBP patterns in patients with hypertension at admission to PICU we found univariable associations between the time and distance below a threshold BP value and duration of organ support, mortality and rise in creatinine. This was not seen with multi-variable analysis for duration or organ support or mortality, but there was an increased risk for rise in creatinine. Overall, our results suggest that there may be a weak basis to suggest that BP should not be rapidly normalised in those admitted with high BP, although not enough to suggest we should intervene to maintain the blood pressure above age-associated normal levels.

Acknowledgments

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Figure Legends

Figure 1: Frequency histogram showing (a) $\%BP_{belowthreshold}$, the percentage of SBP measurements below the SBP threshold value in the first 24 hours of admission (left), and (b) mean $zBP_{belowthreshold}$, the mean of the distance of the SBP z-scores below the threshold (right). For 9/26 admissions with pre-existing hypertension this threshold value was specified in the first 24-hours of admissions, for all others it was taken as a value 25% below the admission SBP.

Figure 2: Scatter plots showing the association between the duration of organ support free days at day 28 (y-axis) and the percentage of SBP measurements below the threshold value in the first 24 hours of admission ($\%BP_{belowthreshold}$, left) and the mean of the distance of the SBP z-scores below the threshold (mean $zBP_{belowthreshold}$, right) (x-axis). The red dots represent non-survivors, who were assigned 0 days of organ support free days.

Figure 3: Effect of varying the threshold in the $\%BP_{belowthreshold}$ on the correlation co-efficient for organ support free days at day 28. The threshold was changed between 60% of the admission SBP to 95% (75% of the admission SBP used in the primary analysis). Whiskers represent the 95% confidence incidence around the Spearman correlation co-efficient. The correlation becomes stronger as the threshold is decreased i.e. for patients who had more measurements further below the admission SBP, the number of organ support free days at 28 were lower. The threshold was not changed in the 9 cases where there was a pre-specified threshold.

Figure 4: Correlation between the number of organ support free days at day 28 and the percentage of BP measurements above a range of thresholds. The top plot shows the correlation co-efficient for the whole cohort and the bottom plot according to the pre-specified sub-groups (patients with chronic hypertension in red, raised intra-cranial pressure in blue and others in black). The thresholds ranged from 75% of the admission SBP to 95%. Whiskers represent the 95% confidence incidence around the Spearman correlation co-efficient. The correlation between the percentage of measurements above the threshold and the number of organ support free days at day 28 becomes weaker as the threshold is increased. Despite the smaller numbers in the sub-groups with chronic hypertension and raised intra-cranial pressure, this pattern persisted with the correlation co-efficient point estimates.

Supplementary Figure 1: Example of a plot of SBP in the first 24 hours after admission. The y-axis shows the age and sex standardised SBP z-score. Two measures were used to define the profile a) $\%BP_{belowthreshold}$, the percentage of SBP measurements below the SBP threshold (red dotted line), taken as 25% below the admission SBP; and b) mean $zBP_{belowthreshold}$, the mean of the distance of the SBP z-scores below the threshold (the mean rather than the area under the curve was used as not all patients had the same number of SBP measurements due to different modes of measurement, missing data and artefacts during arterial sampling etc.)

Supplementary Figure 2: Scatter plots showing the association between percentage rise in creatinine from admission (y-axis, log scale) and the percentage of SBP measurements below the threshold value in the first 24 hours of admission ($\%BP_{belowthreshold}$, top) and the mean of the distance of the SBP z-scores below the threshold (mean $zBP_{belowthreshold}$, bottom) (x-axis). The red dots represent those with known pre-existing hypertension.

Tables

Table 1: Baseline characteristics of cohort with admission SBP above the 95th centile

Baseline characteristics	Cohort (n=534)
Age, median (IQR) in months in years	 24 (10-77) 1 (0-6)
Male, n (%)	305 (57.1)
PIM-3 risk of mortality, median (IQR)	0.012 (0.005-0.036)
Admission SBP in mmHg, median (IQR) Less than 1 year (n=139) 1-2 years (n=128) 2-5 years (n=99) 5-12 years (n=122) 12 years or over (n=46)	123 (115-135) 117 (110-126.5) 117 (110-125.2) 124 (116-134) 129.5 (123-140.8) 139 (130-147)
Pre-existing hypertension, n (%)	26 (4.9)
Suspected raised intra-cranial pressure, n (%)	31 (5.8)
First creatinine measurement in micromol/L, median (IQR)	27 (21-39)

Table 2: Outcomes of cohort with admission SBP above the 95th centile

Outcome	Cohort (n=534)
Organ free support days at day 28, median (IQR)	26 (22-27)
Death on PICU, n (%)	37 (6.9)
Days of organ support in survivors, median (IQR)	2 (1-5)
Percentage rise in creatinine from admission, median (IQR)ǂ	4.8 (0-31.3)

ǂ Data were available for 495 admissions, <2 creatinine measurements available in 39 admissions

Table 3: Table of odds ratios for variables included in the six Bayesian regression models, with 95% credible interval limits.

Model	Odds ratio	2.5% centile	97.5% centile
Organ support free days at day 28			
$\%BP_{belowthreshold}$	1.00	1.00	1.00
PIM	0.02	0.00	0.09
Chronic hypertension	0.96	0.63	1.58
Raised intra-cranial pressure	0.93	0.63	1.47
mean $zBP_{belowthreshold}$	0.97	0.86	1.10
PIM	0.02	0.00	0.09
Chronic hypertension	0.97	0.63	1.53
Raised intra-cranial pressure	0.93	0.61	1.46
PICU mortality			
$\%BP_{belowthreshold}$	1.00	0.99	1.02
PIM	6.22×10^5	4.40×10^3	1.24×10^8
Chronic hypertension	2.80	0.70	8.91
Raised intra-cranial pressure	1.84	0.47	6.07
mean $zBP_{belowthreshold}$	1.34	0.83	2.05
PIM	5.75×10^5	3.88×10^3	1.11×10^8
Chronic hypertension	2.76	0.71	8.94
Raised intra-cranial pressure	1.91	0.53	5.81
Percentage rise in creatinine from admission			
$\%BP_{belowthreshold}$	1.01	1.00	1.02
PIM	2.35×10^3	28.76	6.91×10^5
Chronic hypertension	1.62	0.68	5.46
Raised intra-cranial pressure	1.84	0.82	5.53
mean $zBP_{belowthreshold}$	1.53	1.12	2.14
PIM	457.60	4.21	1.44×10^5
Chronic hypertension	1.47	0.60	4.99
Raised intra-cranial pressure	1.98	0.86	5.94