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Hypertension and Health Outcomes in the Pediatric Intensive Care Unit

Brett J. Ehrmann, MS¹, David T Selewski, MD¹, Jonathan P. Troost, BS¹, Susan M. Hieber, BA¹, and Debbie S. Gipson, MS, MD¹

¹University of Michigan Health System, Department of Pediatrics, Division of Pediatric Nephrology, CS Mott Children's Hospital - Floor 8, 1540 E Hospital Dr SPC 4259, Ann Arbor, Michigan, 48109

Abstract

Objectives—Reports of the burden of hypertension in hospitalized children are emerging, but the prevalence and significance of this condition within the pediatric intensive care unit (PICU) are not well understood. The aims of this study were to validate a definition of hypertension in the PICU and assess the associations between hypertension and acute kidney injury (AKI), PICU length of stay (LOS), and mortality.

Design and Setting—Single center retrospective study using a database of PICU discharges between July 2011 and February 2013.

Patients—All children discharged from the PICU with LOS > 6 hours, aged 1 month through 17 years. Exclusions were traumatic brain injury, incident renal transplant, or hypotension.

Measurements and Main Results—Potential definitions of hypertension utilizing combinations of standardized cutoff percentiles, durations, initiation or dose escalation of antihypertensives, and/or billing diagnosis codes for hypertension were compared using receiver operator characteristic curves against a manual medical record review. Multivariable logistic and linear regression analyses were conducted using the selected definition of hypertension to assess its independent association with AKI and PICU LOS, respectively. A definition requiring 3 systolic and/or diastolic readings above standardized 99th percentiles plus 5 mmHg over 1 day was selected (area under the curve 0.91, sensitivity 94%, specificity 87%). Among the 1,215 patients in this analysis, the prevalence of hypertension was 25%. Hypertension was independently associated with AKI (OR 2.89, 95% CI 1.64–5.09, $P < 0.01$) and increased PICU LOS (1.50 days, 95% CI 0.94–2.05, $P < 0.01$) in multivariable analyses. Deaths were rare—0 in the normotension group and 3 (1%) in the hypertension group—but were statistically different ($P = 0.02$).

Conclusions—Hypertension is common in the PICU and is associated with worse clinical outcomes. Future studies are needed to confirm these results.

Correspondence/Reprints. Address to Brett Ehrmann, Department of Pediatrics, Division of Pediatric Nephrology, CS Mott Children's Hospital - Floor 8, 1540 E Hospital Dr SPC 4259, Ann Arbor, Michigan, 48109 Phone: 734-936-4185. Fax: 734-763-699. behrmann@med.umich.edu. No reprints will be ordered.

All work pertinent to this manuscript was performed at the CS Mott Children's Hospital.

Conflicts of Interest

For all authors, no conflicts of interest were declared.

Keywords

Hypertension; Pediatrics; Pediatric Intensive Care Unit; Acute Kidney Injury; Length of Stay; Mortality

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Introduction

Much is known about the burden of pediatric hypertension in the outpatient setting. Recent large studies using repeat measurements and wide age ranges have suggested a prevalence of 3–4% [1, 2], with an increasing trend [3] over recent decades that may be partly explained by the obesity epidemic [3, 4]. Hypertension in childhood has been associated with left ventricular hypertrophy, increased carotid intima-media thickness, and retinal vessel damage, presenting as early as late childhood and adolescence [5–7].

Data characterizing pediatric hypertension in the inpatient setting are emerging. A recent study using a nationally representative database of pediatric hospitalizations found that approximately 1% of discharge diagnoses were for hypertension [8]. These diagnoses were associated with increased length of stay (LOS), a diagnosis of end stage renal disease (ESRD), and increased hospital charges [8]. Another study examining single admission blood pressure readings in children observed that approximately 24% were found to be hypertensive, with hypertension associated with overweight, obesity, and admission to a surgical service [9].

Within the pediatric intensive care unit (PICU), little is known about hypertension or its significance. One study comparing different methods of blood pressure measurement in the PICU demonstrated that approximately 19% of blood pressure readings were in the hypertensive range [10]. This study did not estimate hypertension prevalence. The prevalence of hypertension in the PICU remains poorly understood partly because there is not a validated, consensus definition. An association between hypertension and acute kidney injury (AKI) has not been characterized in the PICU. The relationship between hypertension and LOS is also poorly understood.

The primary objective of this study was to characterize the burden of hypertension in the PICU by developing a validated definition for this setting. The secondary objective was to identify and quantify associations between hypertension and AKI, PICU LOS, and mortality in this patient population.

Materials and Methods

Study Design and Patient Population

This was a retrospective cohort study using a database generated from the electronic health records of all patients discharged from the Pediatric Cardiothoracic Intensive Care Unit (PCTU) or PICU at the C.S. Mott Children's Hospital between July, 2011 and February, 2013. The PCTU portion of the database was not used due to the high use of antihypertensive medications solely for cardiac indications. Inclusion criteria were the first PICU admission > 6 hours. Assessment of AKI and mortality was restricted to 30 days.

Exclusion criteria were patients < 1 month or > 17 years, diagnosis of traumatic brain injury (by ICD-9-CM code) [11], incident renal transplant, and clinically significant hypotension (requiring vasopressor therapy). Hypotension at baseline is a known risk factor for adverse health outcomes in the PICU. Therefore hypotensive patients were excluded so the effect of hypertension could be assessed relative to a normotensive group. Study flow through the inclusion and exclusion criteria is shown in Figure 1. A derivation cohort of 110 (8%) patients meeting all inclusion and exclusion criteria was used to compare 24 potential hypertension definitions. This cohort was not used in the analysis of outcomes.

Variables of Interest

A matrix of the possible components in each hypertension definition is shown in Table 1. The 95th percentile or 99th percentile plus 5 mmHg threshold was based on standardized percentiles from the National High Blood Pressure Education Program (NHBPEP) Working Group's second report [12] for children aged 1 month through 11 months, or the NHBPEP fourth report [13] for children aged 1 year through 17 years. Readings that were recorded when patients were in significant pain, defined as requiring an initiation or dose escalation of opiate therapy or a Face, Legs, Activity, Cry, Consolability (FLACC) [14] score > 5, were excluded to avoid misclassification of spuriously elevated readings. Patients aged 1 – 17 years were assumed to be at the 50th percentile for height, as height data were not available. Arterial blood pressure readings were used unless unavailable, in which case automated noninvasive oscillometric cuff readings (GE Healthcare, Little Chalfont, UK) were used. Additional potential components for each definition were the initiation or dose escalation of antihypertensive medications and/or an ICD-9-CM diagnosis of hypertension [8]. The list of antihypertensive agents was manually reviewed. Antihypertensives that were commonly used for indications other than acute inpatient hypertension were not used in the hypertension classification to avoid misclassification of hypertension in children receiving these agents. These included angiotensin converting enzyme inhibitors, loop and thiazide diuretics (except hydrochlorothiazide), and select alpha-2 agonists. To determine the accuracy of each potential definition, a random sample of 110 patients (8%, included 10 infants) underwent manual assignment of hypertensive status, serving as the gold standard. Two members of the study team independently determined if the patients had clinically meaningful hypertension by medical record review, answering two guiding questions: a) "does this patient have elevated blood pressures which merit intervention?" and b) "if the patient was treated for hypertension, was the decision to treat reasonable?" In the rare event of a discrepancy for which a consensus could not be reached (<5%), the rater who was blinded to the definition matrix took precedent over the rater who was not blinded.

Additional variables collected included demographic characteristics and illness characteristics (Table 2). Patients with multiple entries for race or insurance status (<1%) were assigned to the non-white and public categories respectively, if present. The Pediatric Risk of Mortality Score (PRISM III) was used for severity of illness [15]. A PRISM-III score of greater than 8 was employed as a cutpoint for illness severity [16, 17]. The billing diagnosis codes recorded for each patient were used to characterize an admission diagnosis of hypertension, the principal diagnosis for the hospitalization, and the presence and type of chronic conditions based on the organization of the ICD-9-CM [11]. Groups that had a

frequency of < 4% and did not significantly differ between hypertension and normotension groups were moved to an “other” category. Diagnoses other than the principal diagnosis were characterized as chronic or not chronic using the Chronic Condition Indicator (CCI), from the Healthcare Cost and Utilization Project [18, 19]. The list of medications administered to each patient during their PICU stay was used to determine whether they received diuretics and/or anti-infectives. Height data were available in 3% of patients and therefore were not included.

The primary outcome for modeling was AKI, as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Guideline [20]. The KDIGO AKI stages were adapted from the Acute Kidney Injury Network (AKIN) [21] to define stage 1 as a 0.3 mg/dL increase in serum creatinine (sCr) over 48 hours or an increase in sCr by 1.5 – 1.9 times within the previous seven days; stage 2 as an increase in sCr by 2 – 2.9 times within the previous seven days; and stage 3 as an increase in sCr by ≥ 3 times within the previous seven days, an absolute sCr ≥ 4 mg/dL, or need for renal replacement therapy [20]. Patients with end stage renal disease (n=12) were not eligible for AKI stage designation and were excluded from this outcome analysis. The definition was modified such that a sCr value of greater than 0.5 mg/dL was required to qualify for AKI. This has been used in prior reports [22], and helps prevent a bias toward classifying AKI as present in young infants, based on fluctuations within a wide normal range that is often below 0.5 mg/dL [23]. Secondary outcomes were PICU LOS and PICU mortality.

Statistical Analysis

To determine the most accurate hypertension definition relative to the gold standard, sensitivity, specificity, and area under the curve (c-statistic) was calculated for each definition using logistic regression modeling. In the event of equal c-statistics, the hierarchy for selection was sensitivity, specificity, then the least number of components.

In bivariate analyses, continuous variables are summarized by median and interquartile range and categorical variables by count and percent. Comparisons between hypertension and normotension groups were made using *Wilcoxon* Rank-Sum tests for continuous variables and χ^2 tests for categorical variables, employing Mantel-Haenszel and Fisher's exact variations as appropriate. Logistic regression was used to calculate adjusted odds ratios of AKI for hypertension. Linear regression was used to assess the adjusted association between hypertension and PICU LOS. Sensitivity analyses were also conducted using the most specific hypertension definition among those with the highest c-statistic and hypertension stratified by treatment status as alternative predictors in multivariable models of AKI and LOS. All multivariable models employed backward selection, with *P* value thresholds for inclusion and retention in the model set at 0.1 and 0.05, respectively. An interaction term for hypertension*age was considered for each model to assess the presence of a differential effect of hypertension across the age spectrum. Additional interaction terms were considered to enhance model fit. This study had 80% power to detect a ≥ 8% difference in AKI and a mean PICU LOS difference of ≥ 1.9 fold between hypertension and normotension groups, using χ^2 testing and student's *t*-testing after log transformation, respectively. Comparisons were considered significant when the two-sided *P* value was

<0.05. All of the analyses were performed with SAS Version 9.3 (SAS Institute Inc, Cary, NC).

Ethics

This study was reviewed and approved with a waiver for informed consent by the University of Michigan Institutional Review Board.

Results

Cohort Characteristics

Demographic and clinical characteristics of the full included cohort are compared with the excluded cohort in Table 2. The excluded cohort was older and had more frequent mechanical ventilation, PRISM-III score > 8, use of anti-infectives, diuretics, and death (all $P<0.01$). Excluded patients also had more chronic conditions and AKI (both $P<0.01$).

Hypertension Definition Determination

The prevalence of hypertension in the derivation cohort ($n=110$) was 16%. Median differences between arterial and cuff readings in the validation cohort ($n=1,215$) were 2 mmHg and 0.5 mmHg for systolic and diastolic blood pressure, respectively. A comparison of the area under the curve, sensitivity, and specificity for the 24 potential hypertension definitions is shown in Table 3. Definitions 3 (3 readings over the 99th percentile plus 5 mmHg over one day), 11 (3 readings over the 99th percentile plus 5 mmHg over one day or the initiation/dose escalation of antihypertensive therapy), 12 (5 readings over the 99th percentile plus 5 mmHg over one day or the initiation/dose escalation of antihypertensive therapy), and 20 (5 readings over the 99th percentile plus 5 mmHg over one day or the initiation/dose escalation of anti-hypertensive therapy or an ICD-9-CM code of hypertension) had an equal area under the curve (0.91). Of these definitions, the highest sensitivity was 94%, observed in both definitions 3 and 11. These definitions were also identical in specificity. Both definitions correctly and incorrectly classified the same patients. Definition 11 additionally included an antihypertensive therapy component. Thus, with identical sensitivity and specificity but greater simplicity, definition 3 was selected as the preferred hypertension definition.

Characteristics of Patients with Hypertension

Demographic and clinical characteristics of patients with hypertension compared with patients with normotension are shown in Table 4. The prevalence of hypertension was 25%. Nine of these children (3%) had a preexisting diagnosis of hypertension (not shown). In bivariate analyses, children with hypertension were younger ($P<0.01$), and had a higher proportion of mechanical ventilation, PRISM-III score > 8, use of anti-infectives, and diuretics (all $P<0.01$). They were also more likely to have a cardiac or hematologic/oncologic principal diagnosis and had more chronic conditions, particularly endocrinologic/metabolic, hematologic/oncologic, cardiac, and congenital anomalies (all $P<0.01$). Patients with hypertension had a longer median length of stay (4 days versus 1 day, $P<0.01$) and had more AKI at each stage ($P<0.01$). Among the 45 patients with hypertension who also had AKI, AKI preceded hypertension in 35 patients (78%). Three patients had a fatal outcome,

and all three had hypertension ($P=0.02$). There was no difference in the race distribution between groups ($P=0.75$).

Hypertension and Acute Kidney Injury

Adjusted multivariable regression analysis of the association between hypertension and AKI among patients with complete covariate data ($n=1,151$) is shown in Table 5. Patients with hypertension had significantly higher odds of having AKI compared to patients with normotension (OR 2.89, 95% CI 1.64–5.09, $P<0.01$). Additional covariates independently associated with AKI included age (OR 1.16, $P<0.01$), PRISM-III > 8 (OR 3.52, $P<0.01$), mechanical ventilation (OR 2.40 $P<0.01$), and use of diuretics (OR 3.37, $P<0.01$). Using the most specific hypertension definition with an area under the curve of 0.91 (Definition 12, 5 readings over the 99th percentile plus 5 mmHg over one day or the initiation/dose escalation of antihypertensive therapy) as an alternate primary predictor, the adjusted odds ratio of AKI was 4.09 (95% CI 2.31–7.24, $P<0.01$, not shown). Patients with treated hypertension ($n=50$, 4%) had an adjusted odds ratio for AKI of 4.19 (95% CI 1.84–9.53, $P<0.01$), whereas those with untreated hypertension ($n=237$, 21%) had an adjusted odds ratio for AKI of 2.49 (95% CI 1.34–4.64, $P<0.01$).

Hypertension and Length of Stay

Table 6 shows the adjusted multivariable regression analysis for PICU LOS among patients with complete covariate data ($n=1,148$). Hypertension was independently associated with a LOS increase of 1.50 days compared to normotension (95% CI 0.94–2.05, $P<0.01$). Covariates also independently associated with increases in LOS were PRISM-III score > 8 (1.58 days, $P<0.01$), mechanical ventilation (1.99 days, $P<0.01$), use of anti-infectives (1.07 days, $P<0.01$), use of diuretics (6.29 days, $P<0.01$), AKI stage 2 (2.14 days, $P<0.01$), and AKI stage 3 (2.81 days, $P<0.01$). Using the most specific hypertension definition with an area under the curve of 0.91 (Definition 12, 5 readings over the 99th percentile plus 5 mmHg over one day or the initiation/dose escalation of antihypertensive therapy) as an alternative primary predictor, the adjusted LOS increase was 1.17 days (95% CI 0.50–1.84, $P<0.01$, not shown). Patients with treated hypertension had an adjusted LOS increase of 3.00 days (95% CI 1.82–4.20, $P<0.01$), whereas those with untreated hypertension had an adjusted LOS increase of 1.28 days (95% CI 0.70–1.85, $P<0.01$).

Discussion

This study represents the first detailed effort to characterize hypertension and its significance in critically ill children. Using a definition that was highly accurate compared to thorough medical record review, hypertension is common, with an estimated prevalence of 25%. Hypertension is independently associated with nearly 3-fold increased odds of AKI and a 1.5 day increase in LOS in multivariable analyses. Although rare ($<1\%$), mortality was associated with hypertension.

Prior reports have suggested that hypertension is relatively common in pediatric inpatients. Sleeper et al [9] found that the prevalence of hypertension, as measured by frequency of admission blood pressures above standardized 95th percentiles [13], was 24%. Similarly,

Holt et al [10] used the same blood pressure thresholds to find that the frequency of elevated arterial line blood pressures in the PICU was 19%. The current study reports a prevalence of hypertension similar to these prior reports, and complements them by using the entire range of blood pressures recorded across the ICU stay (up to 30 days) and applying a validated hypertension definition to a larger cohort.

Other published studies have started to establish the significance of hypertension in pediatric inpatients. Tran et al [8] found that carrying an ICD-9-CM diagnosis of hypertension was associated with a two-fold increase in mean LOS (8 days versus 4 days), three-fold increase in mean hospital charges (\$53,000 versus \$18,000), and a significant increase in a concomitant diagnosis of end stage renal disease (6.2% versus 0.4%). Sleeper et al [9] found that an elevated blood pressure on admission was associated with overweight and obesity, which other reports have shown is associated with increased LOS and hospital charges [24, 25]. In this study, hypertension was independently associated with prolonged LOS, but the role of overweight and obesity in this relationship was not assessed. The association observed between hypertension and AKI has not previously been demonstrated, but AKI is a known risk factor for the development of hypertension and chronic kidney disease in children [26, 27]. The role of hypertension in the PICU as a risk factor for those who may go on to develop to chronic kidney disease warrants further investigation.

Although hypertension was associated with mortality in this study, the mortality rate in the included cohort was lower than the reported 5% mortality rate in other PICU studies [28–30]. The lower observed mortality rate in this study is likely due to criteria which excluded patients on vasopressor therapy and/or less than one month of age. These patients would be more likely to die than the included patients.

There were four potential definitions for hypertension with equal areas under the curve, and this study used the simplest of the two definitions with the highest sensitivity and specificity. This conferred 94% sensitivity and 87% specificity for hypertension. Although this definition falls short of perfect (100% sensitivity and 100% specificity), inclusion of truly normotensive patients in the hypertension group would have resulted in a conservative estimate of the association between hypertension and AKI, compared with the most specific of the four definitions. Analyses using definition 12 (5 readings over the 99th percentile plus 5 mmHg over one day or the initiation/dose escalation of antihypertensive therapy) revealed a significantly larger adjusted association between hypertension and AKI (OR=4.09). A similar association was observed between hypertension and length of stay (β =1.17 days). All of the definitions with the highest areas under the curve were based on 1 day of significantly elevated (greater than the 99th percentile plus 5 mmHg) readings, suggesting that one day of elevated blood pressure readings may have clinical significance in critically ill children. In addition, only one of these definitions included an ICD-9-CM component. This may reflect undercoding of hypertension among pediatric inpatients, and future studies may focus on further characterizing a disparity between hypertension as defined by blood pressure elevations versus billing diagnosis codes in this setting. Although three of the four best definitions included an antihypertensive treatment component, it did not improve sensitivity when the ideal blood pressure criteria were used. This, along with the stronger effect estimates observed among those with treated hypertension, suggests that the use of

antihypertensives may not have identified additional hypertensive patients, but rather may have been a surrogate for hypertension severity.

This study had several limitations. Although this study established an association between hypertension and AKI, the relationship between AKI and hypertension can be bidirectional [31]. Although AKI often preceded hypertension in this study, the absence of renal biomarker or blood pressure readings before ICU admission makes assessment of the precise temporal relationship between AKI and hypertension challenging and an area for further investigation. The blood pressure percentile thresholds used in the hypertension definitions were developed in an outpatient setting and a healthy population. Prior studies in pediatric inpatients, including one in critically ill children, have employed these percentiles [9, 10]. Blood pressure values preferentially came from arterial rather than oscillometric readings. Prior reports in critically ill children have shown that arterial readings are more accurate than oscillometric readings when compared to a sphygmomanometer [10, 32]. Reliance on arterial line blood pressures without the ability to verify an adequate wave form may have resulted in some inaccurate readings, but these were unlikely to be differentially distributed between groups. Data indicating the location of noninvasive blood pressure measurement were not available. The use of the NHBPEP fourth report and missing height data necessitated the imputation of 50th percentile heights. This likely represents a conservative estimate, since many critically ill children are also affected by chronic conditions that can limit growth [33, 34]. Missing height data also precluded the ability to assess for a relationship between preexisting obesity and hypertension in the PICU. This study at times relied on ICD-9-CM coding for classification, which may be prone to inaccuracy [35]. Despite this, three percent of hypertensive patients had an admission diagnosis code for hypertension, suggesting that a small portion of hypertension captured in this report reflects prevalent hypertension. Hypertension was ultimately not defined using an ICD-9-CM component, thereby reducing the potential impact of imprecise ICD-9-CM coding.

Conclusions

In this study, a hypertension definition of at least 3 systolic and/or diastolic readings above standardized 99th percentiles over 1 day was highly accurate compared to manual medical record review for clinically significant hypertension in the PICU. Hypertension was common and associated with adverse clinical outcomes in this setting. This study complements outpatient and emerging inpatient literature highlighting the burden and significance of pediatric hypertension. Further analyses comparing hypertension, hypotension, and normotension may be of value to evaluate the potential of a “J-shaped” curve in the relationship between blood pressure and negative outcomes in critically ill children. A detailed evaluation of the costs associated with hypertension in critically ill children would also complement this study. If confirmed, future studies should prospectively investigate the long-term consequences of hypertension and assess the benefit of treatment of hypertension in the PICU.

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References

1. Lo JC, Sinaiko A, Chandra M, et al. Prehypertension and hypertension in community-based pediatric practice. *Pediatrics*. 2013; 131(2):e415–e424. [PubMed: 23359583]
2. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA*. 2007; 298(8):874–879. [PubMed: 17712071]
3. Din-Dzietham R, Liu Y, Bielo MV, et al. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. *Circulation*. 2007; 116(13):1488–1496. [PubMed: 17846287]
4. Chioloro A, Cachat F, Burnier M, et al. Prevalence of hypertension in schoolchildren based on repeated measurements and association with overweight. *J Hypertens*. 2007; 25(11):2209–2217. [PubMed: 17921814]
5. McNiece KL, Gupta-Malhotra M, Samuels J, et al. Left ventricular hypertrophy in hypertensive adolescents: analysis of risk by 2004 National High Blood Pressure Education Program Working Group staging criteria. *Hypertension*. 2007; 50(2):392–395. [PubMed: 17592068]
6. Sorof JM, Alexandrov AV, Garami Z, et al. Carotid ultrasonography for detection of vascular abnormalities in hypertensive children. *Pediatr Nephrol*. 2003; 18(10):1020–1024. [PubMed: 12883975]
7. Mitchell P, Cheung N, de Haseth K, et al. Blood pressure and retinal arteriolar narrowing in children. *Hypertension*. 2007; 49(5):1156–1162. [PubMed: 17372033]
8. Tran CL, Ehrmann BJ, Messer KL, et al. Recent trends in healthcare utilization among children and adolescents with hypertension in the United States. *Hypertension*. 2012; 60(2):296–302. [PubMed: 22710648]
9. Sleeper EJ, Ariza AJ, Binns HJ. Do hospitalized pediatric patients have weight and blood pressure concerns identified? *J Pediatr*. 2009; 154(2):213–217. [PubMed: 18835489]
10. Holt TR, Withington DE, Mitchell E. Which pressure to believe? A comparison of direct arterial with indirect blood pressure measurement techniques in the pediatric intensive care unit. *Pediatr Crit Care Med*. 2011; 12(6):e391–e394. [PubMed: 21666539]
11. Buck, CJ. ICD-9-CM volumes 1, 2 & 3 for hospitals. Professional Edition. St. Louis: Elsevier; 2013.
12. Report of the Second Task Force on Blood Pressure Control in Children--1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics*. 1987; 79(1):1–25. [PubMed: 3797155]
13. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004; 114(2 Suppl 4th Report):555–576. [PubMed: 15286277]
14. Merkel SI, Voepel-Lewis T, Shayevitz JR, et al. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997; 23(3):293–297. [PubMed: 9220806]
15. Pollack MM, Patel KM, Ruttimann UE. PRISM III: An updated Pediatric Risk of Mortality score. *Critical Care Medicine*. 1996; 24(5):743–752. [PubMed: 8706448]
16. Tan GH, Tan TH, Goh DY, et al. Risk factors for predicting mortality in a paediatric intensive care unit. *Ann Acad Med Singapore*. 1998; 27(6):813–818. [PubMed: 10101556]
17. Volakli EA, Sdougka M, Drossou-Agakidou V, et al. Short-term and long-term mortality following pediatric intensive care. *Pediatr Int*. 2012; 54(2):248–255. [PubMed: 22168527]
18. HCUP Chronic Condition Indicator. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; 2011 Nov. Available at: www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp. [Accessed May 2, 2013]
19. Perrin EC, Newacheck P, Pless IB, et al. Issues involved in the definition and classification of chronic health conditions. *Pediatrics*. 1993; 91(4):787–793. [PubMed: 8464668]
20. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int*. 2012; 2(Suppl.):1–138.
21. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007; 11(2):R31. [PubMed: 17331245]

22. Selewski DT, Jordan BK, Askenazi DJ, et al. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. *J Pediatr*. 2013; 162(4):725–729. e721. [PubMed: 23149172]
23. Boer DP, de Rijke YB, Hop WC, et al. Reference values for serum creatinine in children younger than 1 year of age. *Pediatr Nephrol*. 2010; 25(10):2107–2113. [PubMed: 20505955]
24. Trasande L, Liu Y, Fryer G, et al. Effects of childhood obesity on hospital care and costs, 1999–2005. *Health Aff (Millwood)*. 2009; 28(4):w751–w760. [PubMed: 19589800]
25. Wier LM, Encinosa W. Obesity in Children: Hospitalizations from 2000 to 2009: Statistical Brief #138. 2006
26. Mammen C, Al Abbas A, Skippen P, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2012; 59(4):523–530. [PubMed: 22206744]
27. Askenazi DJ, Feig DI, Graham NM, et al. 3–5 year longitudinal follow-up of pediatric patients after acute renal failure. *Kidney international*. 2006; 69(1):184–189. [PubMed: 16374442]
28. Namachivayam P, Shann F, Shekerdemian L, et al. Three decades of pediatric intensive care: Who was admitted, what happened in intensive care, and what happened afterward. *Pediatr Crit Care Med*. 2010; 11(5):549–555. [PubMed: 20124947]
29. Pollack MM, Cuerdon TT, Patel KM, et al. Impact of quality-of-care factors on pediatric intensive care unit mortality. *JAMA*. 1994; 272(12):941–946. [PubMed: 8084061]
30. Ruttimann UE, Patel KM, Pollack MM. Length of stay and efficiency in pediatric intensive care units. *J Pediatr*. 1998; 133(1):79–85. [PubMed: 9672515]
31. Sharfuddin, AA.; Weisbord, SD.; Palevsky, PM., et al. Acute Kidney Injury. In: Taal, MW.; Chertow, GM.; Marsden, PA.; Skorecki, K.; Yu Alan, SL.; Brenner, BM., editors. *Brenner and Rector's The Kidney*. Ninth Edition. Philadelphia: Elsevier; 2011. p. 1044-1099.
32. Derrico DJ. Comparison of blood pressure measurement methods in critically ill children. *Dimens Crit Care Nurs*. 1993; 12(1):31–39. [PubMed: 8500385]
33. Turkel S, Pao M. Late consequences of chronic pediatric illness. *Psychiatr Clin North Am*. 2007; 30(4):819–835. [PubMed: 17938047]
34. Dosa NP, Boeing NM, Ms N, et al. Excess risk of severe acute illness in children with chronic health conditions. *Pediatrics*. 2001; 107(3):499–504. [PubMed: 11230589]
35. O'Malley KJ, Cook KF, Price MD, et al. Measuring diagnoses: ICD code accuracy. *Health Serv Res*. 2005; 40(5 Pt 2):1620–1639. [PubMed: 16178999]

Figure 1.

Study inclusion and exclusion criteria flowchart

PICU, Pediatric Intensive Care Unit; TBI, Traumatic Brain Injury.

^a Where PICU admission was greater than 6 hours. Number reflects the first qualifying stay within the date frame.^b Defined as carrying a discharge diagnosis code of TBI based on the International Classification of Diseases, 9th revision, Clinical Modification.¹¹^c Defined as use of vasopressor therapy during PICU stay.

Table 1**Matrix of Potential Components of Hypertension Definition**

Component	Possible Values
Elevated SBP and/or DBP Threshold ^a	95th percentile 99th percentile + 5 mmHg
Number of Elevated Readings	3 5
Duration of elevated readings	1 day 2 days
Antihypertensive therapy (initiation or dose escalation)	Included in definition Not included in definition
ICD-9-CM Diagnosis of Hypertension at Hospital Discharge	Included in definition Not included in definition

SBP, systolic blood pressure; DBP, diastolic blood pressure; ICD-9-CM, International Classification of Diseases, Clinical Modification 9th Revision.

^aStandardized threshold percentiles are from the National High Blood Pressure Education Program Working Group's (NHBPEP) 2nd Report¹² for infants (1–11 months old) and the NHBPEP 4th report¹³ for children 1 – 17 years old.

Table 2

Comparison of demographic and clinical characteristics between total and excluded samples of children discharged from the PICU between 7/2011 and 2/2013

Variable ^a	Included Cohort n=1,215	Excluded Cohort n=413	P Value ^b
Age, years	5 (1–12)	8 (1–16)	<0.01
Male	642 (53)	235 (57)	0.15
Infants	197 (16)	43 (10)	<0.01
Race ^c			
White/Caucasian	917 (79)	294 (77)	0.64
Black/African-American	170 (15)	62 (16)	
Other ^d	70 (6)	26 (7)	
Insurance Status ^e			
Private/Other	859 (71)	294 (71)	0.94
Public	351 (29)	119 (29)	
Mechanically Ventilated	312 (26)	196 (47)	<0.01
PRISM-III Score ^f	0 (0–4)	4 (0–9)	<0.01
>8	98 (8)	117 (29)	<0.01
Post-operative status	416 (34)	117 (28)	0.03
Use of Anti-infectives	749 (62)	327 (79)	<0.01
Number of chronic conditions ^g	2 (0–4)	3 (1–6)	<0.01
0	359 (30)	82 (20)	<0.01
1–2	413 (34)	98 (24)	
3–4	229 (19)	76 (18)	
5+	214 (18)	157 (38)	
Use of Diuretic	142 (12)	124 (30)	<0.01
ICU LOS, days	2 (1–3)	3 (1–9)	<0.01
Acute Kidney Injury ^h	89 (7)	102 (27)	<0.01
Stage 1	37 (3)	18 (5)	
Stage 2	25 (2)	24 (6)	
Stage 3	27 (2)	60 (16)	
Mortality	3 (0)	32 (8)	<0.01

PRISM-III, Pediatric Risk of Mortality Score, 3rd Revision.

^aData are presented as median (IQR) for continuous variables and n (%) for categorical variables. Percentages may not sum to 100 due to rounding.

^bComparisons made using *Wilcoxon* Rank-Sum tests for continuous variables and χ^2 tests for categorical variables.

^cFor this analysis, n for included cohort=1,157 and n for excluded cohort=382, due to missing race data.

^dIncludes American Indian, Alaskan Native, Asian, Bi/Multiracial, Middle Eastern, Native Hawaiian, and Pacific Islander, all with frequencies <4%.

^eFor this analysis, n for included cohort=1,210 due to charity care or missing insurance data (represent <1% of group).

^fFor this analysis, n for included cohort=1,161 and n for excluded cohort=397, due to missing PRISM data.

^gDefined by the Healthcare Cost and Utilization Project's Chronic Condition Indicator.¹⁸

^hDefined by modified KDIGO criteria.²⁰ For this analysis, n for included cohort=1,203 and n for excluded cohort=378, due to excluded ESRD patients.

Table 3

Comparison of hypertension definitions using hierarchy of area under the curve, sensitivity, specificity, and simplicity identified definition 3 as the best definition

Definition Number	Elevated SBP and/or DBP Threshold ^a	Number of Elevated Readings	Duration of Elevated Readings	Anti-HTN Therapy	ICD-9 HTN Diagnosis	AUC	Sens ^b (%)	Spec (%)
1	>95th percentile	3	1 day	—	—	0.80	100	61
2	>95th percentile	5	1 day	—	—	0.84	94	74
3*	>99th percentile + 5 mmHg	3	1 day	—	—	0.91	94	87
4	>99th percentile + 5 mmHg	5	1 day	—	—	0.88	83	93
5	>95th percentile	3	2 days	—	—	0.80	78	83
6	>95th percentile	5	2 days	—	—	0.84	78	90
7	>99th percentile	3	2 days	—	—	0.87	78	96
8	>99th percentile + 5 mmHg	5	2 days	—	—	0.80	61	98
9	>95th percentile	3	1 day	+	—	0.80	100	61
10	>95th percentile	5	1 day	+	—	0.87	100	74
11	>99th percentile + 5 mmHg	3	1 day	+	—	0.91	94	87
12	>99th percentile + 5 mmHg	5	1 day	+	—	0.91	89	93
13	>95th percentile	3	2 days	+	—	0.83	83	83
14	>95th percentile	5	2 days	+	—	0.87	83	90
15	>99th percentile + 5 mmHg	3	2 days	+	—	0.90	83	96
16	>99th percentile + 5 mmHg	5	2 days	+	—	0.85	72	98
17	>95th percentile	3	1 day	+	+	0.80	100	60
18	>95th percentile	5	1 day	+	+	0.86	100	73
19	>99th percentile + 5 mmHg	3	1 day	+	+	0.90	94	86
20	>99th percentile + 5 mmHg	5	1 day	+	+	0.91	89	92
21	>95th percentile	3	2 days	+	+	0.82	83	82
22	>95th percentile	5	2 days	+	+	0.86	83	89
23	>99th percentile + 5 mmHg	3	2 days	+	+	0.89	83	95
24	>99th percentile + 5 mmHg	5	2 days	+	+	0.87	78	97

SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, Hypertension; ICD-9, International Classification of Diseases, 9th Revision; Sens, Sensitivity; Spec, Specificity; AUC, Area Under the Curve (equivalent to the C-statistic); +, included; —, not included.

^aStandardized threshold percentiles are from are from the National High Blood Pressure Education Program Working Group's (NHBPEP) 2nd Report¹² for infants (1–11 months old) and the NHBPEP^{4th} report¹³ for children 1 – 17 years old.

^bValues for accuracy (sensitivity, specificity, AUC) utilize a gold standard of blinded medical record review for clinically significant hypertension.

Table 4

Comparison of Demographic and Clinical Characteristics among Hypertensive and Normotensive Groups

Variable ^a	Hypertension ^b n=303	Normotension n=912	P Value ^c
Age, years	2 (1–8)	6 (2–13)	<0.01
Male	167 (55)	475 (52)	0.36
Insurance status ^d			
Private/Other	195 (65)	664 (73)	0.01
Public	104 (35)	247 (27)	
Infants	63 (21)	134 (15)	0.01
Mechanically Ventilated	139 (46)	173 (19)	<0.01
PRISM-III Score>8 ^e	39 (13)	59 (7)	<0.01
Principal Diagnosis Category ^f			
Hematologic/Oncologic	41 (14)	77 (9)	<0.01
Endo/Metabolism	12 (4)	62 (7)	
Neurologic	27 (9)	105 (12)	
Cardiac	21 (7)	16 (2)	
Respiratory	80 (28)	255 (29)	
Congenital Anomalies	36 (13)	85 (10)	
Injury/Poisoning	37 (13)	151 (17)	
Other ^g	33 (12)	117 (13)	
Number of Chronic Conditions ^h	2 (1–4)	1 (0–3)	<0.01
0	62 (20)	297 (33)	<0.01
1–2	96 (23)	317 (35)	
3–4	73 (24)	156 (17)	
5+	72 (34)	142 (16)	
Chronic Condition Category			
Endo/Metabolism	65 (21)	128 (14)	<0.01
Hematologic/Oncologic	55 (18)	90 (10)	<0.01
Cardiac	103 (34)	101 (11)	<0.01
Congenital Anomalies	74 (24)	160 (18)	<0.01
Post-operative status	95 (31)	321 (35)	0.22
Use of Anti-Infectives	224 (74)	525 (58)	<0.01
Use of Diuretic	87 (29)	55 (6)	<0.01
ICU LOS, days	4 (2–8)	1 (1–2)	<0.01
Acute Kidney Injury ⁱ	45 (15)	44 (5)	<0.01
Stage 1	13 (4)	24 (3)	
Stage 2	14 (5)	11 (1)	
Stage 3	18 (6)	9 (1)	
Mortality	3 (1)	0 (0)	0.02

PRISM-III, Pediatric Risk of Mortality Score, 3rd Revision. Endo, Endocrinologic.

^aData are presented as median (IQR) for continuous variables and n (%) for categorical variables. Percentages may not sum to 100 due to rounding.

^bDefined as ≥ 3 SBP and/or DBP readings above the National High Blood Pressure Working Group's^{12,13} standardized 99th percentile plus 5 mmHg over 1 day.

^cComparisons made using *Wilcoxon* Rank-Sum tests for continuous variables and χ^2 tests for categorical variables.

^dFor this analysis, n for hypertension=299 and n for normotension=912, due to charity care or missing insurance data (represent < 1% of group).

^eFor this analysis, n for hypertension=294 and n for normotension=867, due to missing PRISM data.

^fFor this analysis, n for hypertension=287 and n for normotension=868, due to missing diagnosis data. Categories defined by the International Classification of Diseases, Clinical Modification, 9th Revision.¹¹

^gIncludes genitourinary, neurodevelopmental, perinatal, childbirth-related, ill-defined, musculoskeletal, infectious/immunologic, gastrointestinal and skin/subcutaneous diagnoses.

^hDefined by the Healthcare Cost and Utilization Project's Chronic Condition Indicator.¹⁸

ⁱDefined by modified KDIGO criteria.²⁰ For this analysis, n for hypertension=294 and n for normotension=909, due to excluded ESRD patients.

Table 5

Adjusted Multivariate Logistic Regression Analysis of the Association between Hypertension and Acute Kidney Injury^a among 1,151 patients with complete covariate data

Predictor	Unadjusted OR (95% CI)	Unadjusted P Value ^b	Adjusted OR (95% CI)	Adjusted P Value ^c
Hypertension	3.55 (2.29, 5.51)	<0.01	2.89 (1.64, 5.09)	<0.01
Age, Years	1.11 (1.07, 1.16)	<0.01	1.16 (1.10, 1.21)	<0.01
PRISM-III Score>8	6.16 (3.66, 10.36)	<0.01	3.52 (1.94, 6.40)	<0.01
Mechanically Ventilated	3.85 (2.48, 5.97)	<0.01	2.40 (1.39, 4.17)	<0.01
Use of Diuretic	6.23 (3.89, 9.97)	<0.01	3.37 (1.78, 6.38)	<0.01

PRISM-III, Pediatric Risk of Mortality Score, 3rd Revision.

^a Defined as binary outcome of No Acute Kidney Injury vs. Acute Kidney Injury of any stage, with stages defined by modified KDIGO Criteria.²⁰

^b Comparisons made by Wald χ^2 tests.

^c Comparisons made by Wald χ^2 tests, controlling for endocrinologic/metabolic and congenital anomaly chronic conditions. Anti-infectives, hematologic/oncologic principal diagnoses, number of chronic conditions, hematologic/oncologic chronic condition and cardiac chronic condition did not remain in the final model, using backward selection. Cardiac principal diagnosis and hypertension*age did not meet p-value criterion for model inclusion.

Table 6

Adjusted Multivariate Linear Regression Analysis of the Association between Hypertension and PICU Length of Stay^a among 1,148 patients with complete covariate data

Predictor	Unadjusted β (95% CI)	Unadjusted <i>P</i> value ^b	Adjusted β (95% CI)	Adjusted <i>P</i> Value ^c
Hypertension	4.03 (3.44, 4.62)	<0.01	1.50 (0.94, 2.05)	<0.01
PRISM-III Score>8	3.97 (2.98, 4.96)	<0.01	1.58 (0.74, 2.42)	<0.01
Mechanically Ventilated	4.61 (4.04, 5.19)	<0.01	1.99 (1.43, 2.55)	<0.01
Use of Anti-Infectives	2.56 (2.01, 3.10)	<0.01	1.07 (0.59, 1.54)	<0.01
Use of Diuretic	7.59 (6.85, 8.33)	<0.01	6.29 (5.41, 7.17)	<0.01
Acute Kidney Injury ^d				
Stage 1	1.60 (0.78, 3.13)	0.04	-0.48 (-1.78, 0.82)	0.47
Stage 2	5.24 (3.40, 7.09)	<0.01	2.14 (0.57, 3.70)	<0.01
Stage 3	7.10 (5.32, 8.88)	<0.01	2.81 (1.25, 4.36)	<0.01

PRISM-III, Pediatric Risk of Mortality Score, 3rd Revision.

^a time unit is in days

^b Comparisons made using Student's t-testing.

^c Comparisons made by Student's t-testing, controlling for hematologic/oncologic, cardiac and congenital anomaly chronic conditions as well as hematologic/oncologic chronic condition*diuretic use. Age, public insurance, cardiac principal diagnosis, number of chronic conditions and endocrinologic/metabolic chronic condition did not remain in the final model, using backward selection. Hematologic/Oncologic principal diagnosis and hypertension*age did not meet p-value criterion for model inclusion.

^d Defined by modified KDIGO Criteria.²⁰