Is Blood Pressure Improving in Children With Chronic Kidney Disease?
A Period Analysis

Gina-Marie Barletta, Christopher Pierce, Mark Mitsnefes, Joshua Samuels, Bradley A. Warady, Susan Furth, Joseph Flynn

Abstract—Uncontrolled hypertension in children with chronic kidney disease (CKD) has been identified as one of the main factors contributing to progression of CKD and increased risk for cardiovascular disease. Recent efforts to achieve better blood pressure (BP) control have been recommended. The primary objective of this analysis was to compare BP control over 2 time periods among participants enrolled in the CKiD study (Chronic Kidney Disease in Children). Casual BP and 24-hour ambulatory BP monitor data were compared among 851 participants during 2 time periods: January 1, 2005, through July 1, 2008 (period 1, n=345), and July 1, 2010, through December 31, 2013 (period 2, n=506). Multivariable logistic regression to model the propensity of a visit record being in period 2 as a function of specific predictors was performed. After controlling for confounding variables (age, sex, race, socioeconomics, CKD duration, glomerular filtration rate, proteinuria, body mass index, growth failure, and antihypertensives), no significant differences were detected between time periods with respect to casual BP status (prehypertension: 15% versus 15%; uncontrolled hypertension: 18% versus 17%; P=0.87). Analysis of ambulatory BP monitor data demonstrated higher ambulatory BP indices, most notably masked hypertension in period 2 (36% versus 49%; P<0.001). Average sleep BP index (P<0.05) and sleep BP loads (P<0.05) were higher in period 2. Despite publication of hypertension recommendations and guidelines for BP control in patients with CKD, this study suggests that hypertension remains undertreated and under-recognized in children with CKD. This analysis also underscores the importance of routine ambulatory BP monitor assessment in children with CKD. (***Hypertension*****. 2018;71:444-450. DOI: 10.1161/HYPERTENSIONAHA.117.09649.)**
• **Online Data Supplement**

Key Words: blood pressure ■ child ■ hypertension ■ kidney disease ■ masked hypertension

Children with chronic kidney disease (CKD) are at increased risk for cardiovascular morbidity and mortality. Hypertension is a major comorbidity associated with CKD and is one of the main factors contributing to the progression of CKD, increased risk of cardiovascular disease, and impaired neurocognitive function.[1–5] Despite the importance of blood pressure (BP) control in children with CKD, hypertension is frequently underdiagnosed and undertreated.[6] Uncontrolled hypertension in childhood CKD has been identified as an important health problem in a high-risk population, and efforts to achieve better control have been recommended.[6,7]

Few longitudinal studies have investigated trends in BP control for pediatric patients with CKD. Early data from the initial CKiD study (Chronic Kidney Disease in Children) cohort demonstrated overall poor control of hypertension among children with CKD cared for at North American pediatric nephrology centers.[5,6] Many children with CKD were not achieving the BP goals recommended by consensus guidelines in place at the launch of CKiD, nor were they achieving the more recently recommended lower BP targets.[5–11]

In 2011, a second group of children were recruited into the CKiD cohort. These children were aged 1 to 16 years and had higher estimated glomerular filtration rate (GFR) than those originally enrolled in the study. The addition of new subjects to the CKiD study and its longitudinal design provides an opportunity to examine trends in hypertension control over time and whether publication of the initial CKiD data has had an impact on clinical practice among pediatric nephrologists.

The primary objective of this analysis was to compare BP control over 2 time periods among participants enrolled in the CKiD study. We hypothesized that publication of the initial data demonstrating poor BP control in the CKiD study[5,6] would have led clinicians to make efforts to improve BP control[7] that would be reflected in better control of BP in the second time period.

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From the Pediatric Kidney Disease and Hypertension Centers, Phoenix, AZ (G.-M.B.); Johns Hopkins University, Baltimore, MD (C.P.); Cincinnati Children's Hospital, OH (M.M.); McGovern Medical School UT Health, Houston, TX (J.S.); Children's Mercy Hospital, Kansas City, MO (B.A.W.); Children's Hospital of Philadelphia, PA (S.F.); and Seattle Children's Hospital, Seattle, WA (J.F.).

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Correspondence to Gina-Marie Barletta, Pediatric Kidney Disease and Hypertension Centers, 2545 E Thomas Rd, Phoenix, AZ 85016. E-mail gbarletta@akdhc.com

Methods

Data that support the findings of this study are available from the corresponding author on reasonable request. CKiD additionally provides comprehensive publically available data through the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository (https://www.niddkrepository.org/home/).

This analysis was based on longitudinal data from children enrolled in the CKiD study—a prospective observational cohort study of children aged 1 to 16 years with mild-to-moderate CKD from 55 pediatric nephrology centers in North America. Study design and objectives have been previously reported.[12] Participant demographic and clinical data were collected at annual visits. Institutional review boards at all CKiD study–participating sites approved the research protocol, and informed consent/assent was obtained from study participants and their parents/guardians according to local institutional review board requirements.

Casual BP (cBP) and 24-hour ambulatory BP monitoring (ABPM) data were compared among CKiD participants during 2 calendar time periods, each 3.5 years in length: January 1, 2005, through July 1, 2008 (period 1), and July 1, 2010, through December 31, 2013 (period 2). Subject visits missing cBP measurements were excluded from this pool of data as were visits with estimated GFR >100 mL/min per 1.73 m^2. Each child was allowed to contribute data from one observation (visit) within the 2 time periods. For children with multiple CKiD visits during either or both of the time periods, one visit was selected at random, giving priority to visits with available ABPM data.

BP control was evaluated using cBP and ABPM measurements. At each study visit, cBP was determined as the average of 3 BP measurements obtained by auscultation using an aneroid sphygmomanometer. The specific details of the standardized procedure for BP measurement in the CKiD study have been previously published[6] and described in detail in the online-only Data Supplement accompanying this publication. Casual systolic BP (cSBP) and casual diastolic BP (cDBP) measurements were standardized (*Z* scores and percentiles) for age, sex, and height according to the National High Blood Pressure Education Program Fourth Report on the diagnosis, evaluation, and treatment of high BP in children and adolescents.[8]

cBP status was categorized as uncontrolled hypertensive (cSBP or cDBP ≥95th percentile), uncontrolled prehypertensive (cSBP or cDBP ≥90th percentile and <95th percentile), or normotensive (cSBP and cDBP <90th percentile).[8]

ABPM was performed at biannual visits beginning with the first follow-up visit and was generally limited to children aged ≥5 to 6 years who were felt able to tolerate the procedure, although some younger children did undergo ABPM. The specific standardized procedure for ABPM assessment in the CKiD study has been previously published[13] and described in detail in the online-only Data Supplement accompanying this publication. The mean systolic BP (SBP) and diastolic (DBP) were determined for 24-hour, wake, and sleep periods. ABPM wake and sleep SBP and DBP index were calculated as the mean measured values divided by the 95th percentile 1997 Soergel limits.[14] BP load was defined as the percentage of BP readings that exceeded the ABPM 95th percentile thresholds for sex and height.[14,15] Ambulatory hypertension was defined as: mean wake and/or sleep SBP or DBP ≥95th percentile for ABPM and/or SBP or DBP load ≥25%. Criteria for defining BP categories used in the CKiD study were adapted from the American Heart Association recommendations and have been previously described.[13,15,16]

Overall hypertensive classification status was based on the combination of cBP and ABPM and was defined regardless of whether the participant received antihypertensive medication(s):

- Normotension: normal cBP (BP <95th percentile) and normal ABPM (mean BP <95th percentile and BP load <25%).
- Confirmed hypertension: presence of both cBP and ABPM hypertension.
- White coat hypertension: cBP hypertension with normal ABPM.
- Masked hypertension: ABPM hypertension with normal cBP.[15,16]

GFR was estimated as a function of the child's serum creatinine (sCr) and height using the CKiD-developed bedside formula:

$$GFR_{bed} = 41.3 \times height / sCr$$

(height measured in meters and sCr measured in milligrams per deciliter).[17]

Each child was classified as having either nonglomerular or glomerular CKD. Urinary protein and creatinine measurements were obtained from first-morning urine samples collected for the study visit. Total urine protein and creatinine concentrations were measured using the Bayer Advia 2400 analyzer. Proteinuria was defined by the urine protein to creatinine ratio (uP:Cr) as normal/minimal (uP:Cr <0.5 mg/mg), significant (0.5–2.0 mg/mg), or nephrotic range (≥2.0 mg/mg). All laboratory measurements were performed centrally at the biochemical central laboratory (University of Rochester).

Additional nonlaboratory data included in this analysis are as follows: age, sex, race, Hispanic ethnicity, household income, maternal education, body mass index, growth failure (defined as height <5th percentile for age and sex), current medication use, and duration of CKD measured in years. Height and body mass index percentiles were calculated for age and sex using standard national growth charts.[18] Current medication use, specifically antihypertensive and corticosteroid therapy, were self-reported for the 30 days before each study visit.

Statistical Analysis

BP measurements, hypertension indices, and other clinical and demographic characteristics were summarized from each time period using median (interquartile range) for continuous variables and percent (frequency) for categorical variables. Differences in clinical and demographic characteristics between the 2 time periods were assessed using Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables.

To formally compare BP measurements and hypertension indices while controlling for potential non-BP clinical and demographic differences (confounding) between the 2 periods, we used multivariable logistic regression to model the propensity of a visit record being in period 2 as a function of specific predictors, including age, sex, black race, Hispanic ethnicity, baseline household income, baseline maternal education, GFR, log-transformed uP:Cr, CKD diagnosis, years of CKD, corticosteroid use, body mass index *Z* score, and growth failure.[19,20] Unless otherwise noted, all predictor (independent) variables were measured concomitantly at the visit being modeled. In turn, stabilized inverse probability weights were generated that reflected the probability that a given observation was in the time period that it was observed given its set of predictors. Because they came from a distinct subset of analytic records, separate weights were generated for the ABPM measurements. Weighting the records with stabilized inverse probability weights, we statistically compared BP measurements and hypertension indices between the time periods using *t* tests for continuous variables and χ^2 tests for categorical variables. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

Data from 851 children enrolled in the CKiD study with cBP measurements and estimated glomerular filtration rate <100 mL/min per 1.73 m^2 were available for analysis: 345 children were included from period 1 and 506 children from period 2. Results obtained from 498 complete ABPM were included in this analysis (201 for period 1 and 297 for period 2). The prevalence of inadequate (unsuccessful) ABPM studies in CKiD was 4.4%.

Demographic and clinical characteristics are outlined in Table 1. In period 2, children were older (P=0.018), had higher baseline maternal education (P=0.012), more patients with glomerular CKD (P=0.004), higher GFR (P<0.001), lower uP:Cr (P<0.001), and had less overall growth failure (P=0.003).

Table 1. Demographic and Clinical Characteristics

Characteristic*	Time Period		*P* Value for Difference†
	Period 1	Period 2	
Patient Visits (n)	n=345	n=506	
Age, y	12 (9–15)	13 (9–16)	0.018‡
Male sex	63 (217)	62 (312)	0.72
Black race	20 (70)	24 (119)	0.28
Hispanic ethnicity	14 (48)	15 (73)	0.92
Baseline household income, US$			0.20
≤36 K	41 (136)	40 (198)	
36–75 K	32 (106)	27 (134)	
>75 K	28 (93)	33 (163)	
Baseline maternal education			0.012‡
High school	46 (154)	36 (176)	
Some college	25 (85)	29 (144)	
College or more	29 (97)	35 (175)	
Years of CKD			
Nonglomerular	11 (8–15)	11 (8–15)	0.14
Glomerular	5 (3–10)	6 (2–9)	0.92
Glomerular CKD	23 (81)	33 (165)	0.004‡
GFR, mL/min per 1.73 m^2	38 (27–52)	58 (41–72)	<0.001‡
uP/C	0.67 (0.23–1.67)	0.25 (0.08–0.87)	<0.001‡
Normal (<0.5)	42 (141)	63 (307)	<0.001‡
Significant (0.5–2.0)	36 (120)	25 (122)	
Nephrotic (≥2.0)	21 (71)	12 (57)	
BMI (percentile)	61 (35–88)	69 (36–92)	0.18
Overweight (BMI percentile ≥85)	28 (98)	34 (164)	0.096
Growth failure (height percentile <5)	22 (75)	14 (70)	0.003‡
Low birth weight	17 (56)	20 (93)	0.41

Missing data: Hispanic, n=12; income, n=21; maternal education, n=20; uP/C, n=33; BMI percentile, n=25; and low birth weight, n=47. BMI indicates body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; and uP/C, urine protein:creatinine ratio.

*Values are represented as median (IQR) for continuous variables and % (n) for categorical variables.

†Based on Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables.

‡Statistical significance (*P*<0.05).

Table 2 outlines the unadjusted (unweighted) comparison of BP measurements and hypertension indices for the 2 time periods. In general, during period 2, cBP percentiles were lower (period 1 versus 2: cSBP percentile: 64 versus 54; *P*<0.001 and cDBP percentiles: 68 versus 59; *P*=0.017), there were more normotensive patients in period 2 (63% versus 70%; *P*=0.044), and there was a lower prevalence of uncontrolled hypertension in period 2 (22% versus 16%; *P*=0.044). No significant

Table 2. Unadjusted Comparison of BP Measurements and HTN Indices

Characteristic*	Time Period		*P* Value for Difference†
	Period 1	Period 2	
Patient Visits (n)	n=345	n=506	
Casual SBP percentile	64 (34–88)	54 (27–79)	0.001‡
Casual DBP percentile	68 (40–88)	59 (35–84)	0.017‡
Casual BP status			0.044‡
Normotensive	63 (216)	70 (353)	
Uncontrolled pre-HTN	15 (53)	15 (74)	
Uncontrolled HTN	22 (76)	16 (79)	
SR high BP diagnosis	56 (185)	57 (285)	0.83
Current antihypertensive use	71 (244)	65 (328)	0.075
Current ACE/ARB	59 (205)	56 (282)	0.29
ACE	56 (182)	54 (249)	0.51
ARB	13 (41)	12 (57)	0.91
β-Blocker	5 (16)	3 (15)	0.27
α-Blocker	1 (4)	2 (8)	0.77
α/β-Blocker	3 (10)	2 (10)	0.49
Calcium channel blocker	17(54)	15 (70)	0.55
Centrally acting α-2 agonist	3 (10)	3 (13)	0.83
Direct vasodilator	<1 (3)	<1 (3)	0.69
Diuretic	10 (32)	7 (32)	0.15
Current corticosteroid	6 (21)	7 (36)	0.58
ABPM measurements (n)	n=201	n=297	
ABPM HTN	56 (112)	62 (184)	0.19
Index			
Wake SBP			
Mean>limit	16 (33)	15 (44)	0.70
Sleep SBP			
Mean>limit	19 (38)	20 (58)	0.91
Wake DBP			
Mean>limit	13 (27)	11 (32)	0.40
Sleep DBP			
Mean>limit	20 (41)	22 (64)	0.82
Load			
Wake SBP			
>25	35 (70)	33 (97)	0.63
Sleep SBP			
>25	31 (63)	39 (115)	0.11
Wake DBP			
>25	31 (62)	32 (96)	0.77
Sleep DBP			
>25	42 (85)	43 (129)	0.85

(*Continued*)

Table 2. Continued

Characteristic*	Time Period		*P* Value for Difference†
	Period 1	Period 2	
ABPM Measurements (n)	n=201	n=297	
Casual/ABPM hypertension status			0.014‡
Normotensive	42 (84)	37 (111)	
White coat HTN	2 (5)	<1 (2)	
Masked HTN	37 (74)	49 (146)	
Confirmed HTN	19 (38)	13 (38)	

Missing data: SR high BP, n=21; medications, n=64. ABPM indicates ambulatory BP monitoring; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BP, blood pressure; DBP, diastolic BP; HTN, hypertension; IQR, interquartile range; SBP, systolic BP; and SR, self-reported.

*Values are represented as median (IQR) for continuous variables and % (n) for categorical variables.

†Based on Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables.

‡Statistical significance ($P<0.05$).

differences were detected between the periods with regard to antihypertensive ($P=0.075$), diuretic ($P=0.15$), or corticosteroid use ($P=0.58$). No significant differences were detected between the time periods regarding the diagnosis of ambulatory hypertension ($P=0.19$). However, the combined cBP/ABPM hypertension classification status distribution was significantly different with period 2 having lower prevalence of normotension and confirmed hypertension but a higher prevalence of masked hypertension compared with period 1 ($P=0.014$).

Table 3 outlines the weighted distribution (using stabilized inverse probability weights) of non-BP clinical and demographic characteristics in the time periods. A total of 689 patients had complete predictor data and were assigned a weight: 281 patients in period 1 and 408 patients in period 2. Clinical and demographic differences between the time periods (Table 1) were no longer present in the weighted analysis confirming that the weighting process successfully balanced the time periods with respect to potential confounders.

Table 4 shows the weighted (adjusted) distribution of casual and ABPM BP indices in the time periods. After controlling for potential confounding, no differences were observed in the cBP measurements and classification between the time periods. Records that could be weighted for a comparison of ABPM measurements consisted of 169 patients in period 1 and 246 patients in period 2. Among the ABPM measurements and indices, period 2 demonstrated more ambulatory hypertension (51% versus 63%; $P=0.036$). Period 2 had higher mean sleep SBP and DBP index values ($P<0.05$); sleep SBP and DBP loads were also significantly higher in period 2 ($P<0.05$). Period 2 had lower prevalence of normotension, white coat hypertension, and confirmed hypertension ($P=0.001$). As in the unweighted comparison, overall prevalence of masked hypertension was significantly higher in period 2 (36% versus 49%; $P<0.001$). Comparison of antihypertensive use between the time periods showed no significant differences in overall self-reported use of antihypertensive therapies (68% versus 63%; $P=0.18$).

Table 3. Weighted Distributions of Risk Factors/Potential Confounders

Period	Period 1	Period 2	
	n=281	n=408	
	Sum Weights=270.4	Sum Weights=414.0	
Patient Visits (n)	% or Mean (95% CI)	% or Mean (95% CI)	*P* Value for Difference
Age, y	12.4 (11.9 to 12.8)	12.3 (11.8 to 12.7)	0.69
Male sex	60	61	0.85
Black race	19	20	0.82
Hispanic ethnicity	15	15	0.83
Baseline income, US$			0.90
≤36K	42	41	
36–75K	29	29	
>75K	29	30	
Baseline maternal education			0.87
High school	40	38	
Some college	28	29	
College or more	32	33	
Glomerular CKD	25	26	0.76
Years of CKD			
Nonglomerular	11.4 (10.8 to 11.9)	11.2 (10.7 to 11.8)	0.76
Glomerular, HUS	5.7 (0.9 to 10.4)	8.8 (6.5 to 11.1)	0.20
Glomerular, non-HUS	6.7 (5.4 to 8.0)	5.6 (4.7 to 6.5)	0.16
GFR, mL/min per 1.73 m^2	49 (46 to 51)	49 (47 to 52)	0.59
Log_2(uP/C)	−1.17 (−1.40 to −0.94)	−1.26 (−1.48 to −1.03)	0.59
BMI *Z* score	0.43 (0.28 to 0.57)	0.40 (0.29 to 0.51)	0.75
Growth failure, height percentile <5	16	15	0.67
Low birth weight	19	19	0.85
SR high BP diagnosis	55	56	0.85
Current corticosteroid	7	7	0.94
Antihypertensive use	68	63	0.18

BMI indicates body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; HUS, hemolytic uremic syndrome; SR, self-reported; and uP/C, urine protein:creatinine ratio.

Discussion

Our analysis of BP data from 2 time periods in the CKiD cohort study demonstrated notable differences in BP parameters over time and highlights the importance of ABPM in the evaluation of BP control in children with CKD. In the unadjusted comparison analysis of BP measurements and hypertension indices for the time periods, we found that period 1 had overall higher cBP percentiles, including more children with confirmed and uncontrolled hypertension compared with period 2. This likely

Table 4. Weighted Distributions of Various BP Indices

	Time Period		
	Period 1	Period 2	
	n=281	n=408	
Patient Visits (n)	Sum Weights=270.4	Sum Weights=414.0	*P* Value for Difference
Casual SBP *Z* score	0.29 (0.17–0.42)	0.24 (0.13–0.35)	0.54
Casual DBP *Z* score	0.40 (0.29–0.52)	0.44 (0.34–0.54)	0.65
Casual BP status, %			0.87
Normotensive	67	68	
Uncontrolled pre-HTN	15	15	
Uncontrolled HTN	18	17	
ABPM measurements (N)	n=169	n=246	
	Sum weights=165.36	Sum weights=249.44	
ABPM HTN, %	51	63	0.036*
Index			
Wake SBP	0.90 (0.89–0.92)	0.92 (0.91–0.93)	0.076
Mean>limit, %	13.2	16.3	0.043
Sleep SBP	0.91 (0.89–0.92)	0.93 (0.92–0.94)	0.038*
Mean>limit, %	13.8	20.1	0.13
Wake DBP	0.87 (0.86–0.89)	0.89 (0.88–0.91)	0.088
Mean>limit, %	11.3	12.3	0.78
Sleep DBP	0.90 (0.88–0.92)	0.93 (0.91–0.94)	0.026*
Mean > limit, %	15.0	22.4	0.094
Load			
Wake SBP	20.5 (16.6–24.3)	22.6 (19.0–26.1)	0.44
>25, %	32.0	32.1	0.98
Sleep SBP	19.3 (14.8–23.8)	26.1 (21.9–30.2)	0.031*
>25, %	26.0	41.0	0.005*
Wake DBP	20.3 (16.6–24.0)	22.3 (18.9–25.7)	0.44
>25, %	29.1	31.8	0.63
Sleep DBP	23.7 (19.5–27.9)	29.9 (26.1–33.8)	0.033*
>25, %	38.8	46.6	0.18
Casual/ABPM hypertension status, %			0.001*
Normotensive	45	37	
White coat HTN	4	0	
Masked HTN	36	49	
Confirmed HTN	15	14	

ABPM indicates ambulatory BP monitoring; BP, blood pressure; DBP, diastolic BP; HTN, hypertension; and SBP, systolic BP.

*Statistical significance ($P<0.05$).

reflected that period 1 comprised children with more advanced stages of CKD compared with the population of children included in period 2. Children in period 2 had a higher median GFR, less proteinuria, and less overall growth failure. These associated factors likely impacted the higher prevalence of confirmed hypertension (presence of both casual and ambulatory hypertension) among children during the first time period. However, the ABPM data did demonstrate an overall lower prevalence of normotension and white coat hypertension but a higher prevalence of masked hypertension in period 2.

After attempting to make the time periods similar with regard to multiple confounding clinical and demographic characteristics (periods were matched for age, sex, race, socioeconomic status, duration of CKD, glomerular/nonglomerular CKD, GFR, degree of urinary protein, body mass index, growth failure, and antihypertensive use), little difference was detected between the time periods with respect to cBP measurements. No significant differences were detected over time with regard to frequency of casual uncontrolled prehypertension and uncontrolled hypertension. For each time period, ≈30% of participants had either uncontrolled casual prehypertension or uncontrolled hypertension. However, ABPM data revealed significant differences between the time periods with regard to ambulatory BP indices. There was a significantly higher prevalence of masked hypertension and lower prevalence of normotension and white coat hypertension in period 2. Thus, despite publication of the initial CKiD hypertension data recommendations and guidelines for stricter BP control in patients with CKD, it seems that hypertension remains underrecognized and undertreated in children with CKD.[5–11,15]

The findings of this study underscore the importance of routine ABPM as a standard of care for children with CKD. Rates of abnormal ABPM findings, particularly masked hypertension, occur in ≈7% of the general pediatric population.[21] However, in this evaluation of children with CKD, we noted a prevalence of masked hypertension in 36% for period 1 and almost 50% for period 2. These results are similar to previously reported prevalence of 38% in pediatric CKD[22] and 19% to 32% in pediatric renal transplant populations.[23–28] The importance of detection of masked hypertension is reflected by the findings that children with CKD and masked hypertension are at increased risk for development of left ventricular hypertrophy.[22] In addition, pediatric renal transplant recipients with abnormal ABPM (particularly, masked hypertension) are at an increased risk for left ventricular hypertrophy and worse allograft function when compared with patients who are normotensive (with normal ABPM) or with controlled hypertension.[22,23,29] Adult studies have also demonstrated a greater prevalence of end-organ injury and poorer outcomes in patients with masked hypertension.[30,31] For example, in adult patients with CKD, masked hypertension was associated with an increased rate of progression to end-stage kidney disease compared with those with normal BP.[32] Given these associations, it seems evident that assessment with ABPM to detect masked hypertension should be a routine component of CKD management.

Because BP has been shown to track from childhood into adulthood, interventions to improve recognition and treatment of hypertension in pediatric CKD are urgently needed.[7] Traditional risk factors for cardiovascular disease present in childhood have been demonstrated to be predictive of disease in adulthood.[33–35] In addition to increased risk for cardiovascular events, uncontrolled hypertension is known to accelerate the progression of CKD.[36] Therefore, greater efforts are needed to identify and effectively treat hypertension in these vulnerable pediatric patients, to slow the progression of CKD and reduce the future burden of adult cardiovascular disease.

Despite guidelines and recommended standards of care in clinical practice, physicians may experience difficulty with compliance and follow-up. Clinical standards of care and clinical practice recommendation guidelines should provide a means to effectively improve quality of care and enhance patient outcomes. However, implementation of such standards in clinical patient care is not always optimal. Several reviews have demonstrated that standard-of-care guidelines can be minimally effective in modifying clinical physician practices.[37,38] Several potential barriers have been identified that can impact the implementation of practice guidelines—including appropriate practitioner training, level of patient education, organizational framework, and social/cultural context.[37–41] Because recommendations within consensus guidelines may present various barriers, it might be more useful to focus on the development of specific strategies to implement guidelines into practice.[38–40] It is our hope that knowledge of these issues would change practice behaviors and ultimately lead to improved BP management in children with CKD.

A major strength of this study was the large pediatric sample size evaluated over prolonged time periods. With utilization of the CKiD database (one of the largest study populations of children with CKD), we provided analysis from standardized data collection and evaluation of a large number of complete ABPM assessments in children with CKD. One potential limitation of the present study was that there were substantial differences between the 2 time periods because of confounding patient variables. However, to minimize the impact of such variables, we used propensity score modeling for risk factors/potential confounding variables. We were able to control for many clinical and demographic differences between the time periods that were evaluated. Furthermore, the primary difference between the 2 time periods by recruitment criteria was one of disease severity: those in the second cohort were considered earlier in their disease progression. Another limitation of this study was that we were unable to determine patient compliance and adherence with respect to prescribed antihypertensive medication therapy—which would affect control of BP. Although noncompliance and nonadherence can be a significant problem in this patient population, it is presumed that overall patient compliance and adherence would likely be similar across time periods—thereby impacting both periods equally. Finally, our novel approach using propensity score methods to describe average differences between 2 time points is not the only analytic strategy to assess the effect of an intervention at a particular point in time. Interrupted time series, or regression discontinuity, may be alternative approaches for this question, and these may be best suited in larger cohorts or with BP measurements temporally closer to the time of change.

Perspectives

Given the findings from the present study, interventions and strategies to optimize the diagnosis and implementation of BP goals recommended by consensus guidelines to improve the recognition and control of hypertension in pediatric CKD are urgently needed. In addition, risks for cardiovascular complications and the high prevalence of abnormal ABPM results (primarily masked hypertension) demonstrated in our study provides substantial support for routine use of ABPM to appropriately detect, provide surveillance, and guide treatment of hypertension in children with CKD.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Comparison of blood pressure (BP) control over 2 time periods among participants enrolled in the National Institutes of Health–funded CKiD cohort study (Chronic Kidney Disease in Children) .
- Baseline casual BP and 24-hour ambulatory BP monitoring data were compared over 2 time periods: January 1, 2005, through July 1, 2008, and July 1, 2010, through December 31, 2013.
- Data from 851 children were evaluated over 2 time periods.

What Is Relevant?

- This study demonstrated little difference in overall BP control between time periods with respect to casual BPs and hypertension indices.
- No significant differences were detected over time with regard to frequency of prehypertension and uncontrolled hypertension (≈30% of participants).
- Analysis of ambulatory BP monitor data noted higher ambulatory BP indices—particularly masked hypertension over the second time period.

Summary

Hypertension remains undertreated and under-recognized in children with chronic kidney disease. Findings from this study underscore the importance of routine ambulatory BP monitoring in children with chronic kidney disease.

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Is Blood Pressure Improving in Children With Chronic Kidney Disease?: A Period Analysis

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IS BLOOD PRESSURE IMPROVING IN CHILDREN WITH CHRONIC KIDNEY DISEASE? : A PERIOD ANALYSIS – SUPPLEMENTAL MATERIAL

Gina-Marie Barletta MD[1], Christopher Pierce[2], Mark Mitsnefes MD[3], Joshua Samuels MD[4], Bradley A. Warady MD[5], Susan Furth MD[6], Joseph Flynn MD[7]

[1]PKDHC, Phoenix, AZ; [2]John's Hopkins, Baltimore, MD; [3]Cincinnati Children's Hospital, OH; [4]McGovern Medical School UT Health, Houston, TX; [5]Children's Mercy Hospital, Kansas City, MO; [6]Children's Hospital of Philadelphia, PA; [7]Seattle Children's Hospital, Seattle, WA

Corresponding Author:

Gina-Marie Barletta MD
Pediatric Kidney Disease & Hypertension Centers (PKDHC)
2545 E. Thomas Road
Phoenix, Arizona 85016
Phone: (602) 903-1532
Fax: (602) 956-0567
Email: gbarletta@akdhc.com

Method of Manual Blood Pressure Measurement[1]

Measurement procedure

CKiD participants have casual BP measurements obtained in the right arm by auscultation at study entry (baseline), then annually thereafter. All participating sites have been provided the same aneroid sphygmomanometer (Mabis MedicKit 5, Mabis Healthcare, Waukegan, IL) by the CKiD Clinical Coordinating Centers (CCC's). The CCC's also provide standardized training and certification in the auscultatory BP measurement protocol described below to all study personnel responsible for casual BP measurement. Recertification in auscultatory BP measurement technique and calibration of each center's aneroid device takes place annually at the CKiD investigator meetings.

At each study visit, prior to BP determination, arm circumference is measured (in centimeters) with a plastic measuring tape at the midpoint of the upper arm between the amicron and olecranon and a cuff is then selected so that the length of the cuff bladder is equal to 80-100% of the arm circumference[2]. Following cuff selection, the peak inflation pressure is determined by inflating the cuff to 60 mmHg and then gradually continuing to inflate in increments of 10 mmHg until the radial pulse is no longer felt – thereby determining the pulse obliteration pressure. An additional 30 mmHg is added to this value and recorded as the peak inflation pressure. The cuff is then inflated to this value for all BP measurements at that study visit.

After 5 minutes of rest, BP measurement begins. Participants are instructed to refrain from caffeine intake, smoking, and exercise at least one half hour prior to and until completion of BP measurement. They are also instructed to refrain from playing video games, using a cell phone, or other activities that may affect BP until all measurements are obtained. First, pulse is measured by palpation of the radial artery. Then three BP measurements at 30-second intervals are obtained by auscultation of the brachial artery, using the first Korotkoff sound for systolic BP (SBP) and the fifth Korotkoff sound for diastolic BP (DBP). The average of the 3 BP measurements is recorded as the participant's BP for the study visit. Participants' BP's so obtained at the baseline visit are included in the present study.

Analysis of BP measurements

Participant's BP's in the CKiD study are classified according to the National High Blood Pressure Education Program (NHBPEP) Fourth Report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents[2]: BP readings <90th percentile are categorized as normotensive, those ≥90th and <95th percentiles as pre-hypertensive, and those ≥95th percentile as hypertensive. Measurements in the pre-hypertensive and hypertensive range are defined as elevated blood pressure.

The presence of hypertension was defined as having hypertensive range BP (systolic or diastolic) or a self-report of a history of high BP plus current treatment with antihypertensive medications. Additionally, *controlled blood pressure* was defined as a current use of antihypertensive medication, with BP below the 90th percentile and a self-reported history of hypertension; *uncontrolled blood pressure* was defined as BP (systolic or diastolic) ≥90th percentile and current use of antihypertensive medication.

Method of Ambulatory Blood Pressure Measurement[3]

ABPM procedure

Spacelabs 90217 monitors (SpaceLabs Healthcare, Issaquah, WA) was used for all ambulatory blood pressure monitoring studies, which occurred one year after study entry, and repeated every 2 years thereafter. Monitors were sent from and analyzed at a central site at the University of Texas Health Science Center at Houston (J Samuels, P.I.). Arm circumference was measured at each local site prior to casual BP measurement with appropriate cuffs selected according to the 4th Report recommendations.[2] All participating clinical sites receive annual training in monitor placement from the ABPM Center.

Monitors were set to measure BP every 20 minutes during the day and night at a bleed step of 8 mmHg and participants were instructed to wear the monitor for a continuous 24-hour period. Most monitorings occurred at/near the time of the CKiD study visit. The participant's family was given a diary to complete, noting times of wake, sleep, and any medication administration while wearing the monitor. After completion, the monitor and diary were returned to the ABPM center for data processing and summarizing. For ABP studies that did not fulfill pre-specified quality parameters (see below), a repeat attempt was made. Summarized ABP data was sent to the CKiD data coordinating center at the Johns Hopkins Bloomberg School of Public Health for centralized data management and analysis.

ABPM analysis

All ambulatory blood pressure studies were analyzed at the ABPM Coordinating site using a standardized protocol. Quality of the ABPM studies was defined by the length of time the monitor was actually worn and the number of successful BP recordings. To be acceptable for analysis, the monitor had to be worn for ≥21 hours, have ≥18 hours with at least one valid BP measured per hour. As additional criteria to ensure adequate representation of both wake and sleep periods, each ABPM had to have at least 1 successful BP recording in ≥75% of wake hours and ≥75% of sleep hours.

The ABP parameters of interest included mean systolic and diastolic BP for parental-reported wake, sleep, and 24-hour periods. From this, systolic and diastolic BP dip status was determined by calculating percent nocturnal drop in mean BP from waking mean values. In addition, wake and sleep BP loads were calculated as the percent of readings at or above the 95th percentile, based on published normative pediatric ABPM data[4]. For 24-hour load calculation, a weighted sum of wake and sleep loads was used. Similarly, ABP index was calculated as the mean ambulatory BP divided by the corresponding 95th percentile. Thus, an index of 1 indicates an ambulatory BP equal to the threshold value for a clinical diagnosis of hypertension, and an index of 1.1 is 10% above that threshold.[5] Since the 95th percentile is gender and height specific, this measure allows for comparison of BP across a wide range of pediatric normal values.

ABPM studies were also classified studies based upon the 2009 AHA consensus guidelines for pediatric ABPM.[6] Using both auscultatory clinical and 24-hour readings, participants' blood pressure status was categorized as follows:

- Normal BP: casual BP <95th percentile and wake and sleep mean ABP <95th percentile and wake and sleep load < 25%.
- Ambulatory HTN: casual BP ≥95th percentile and either (1) wake or sleep mean ABP ≥ 95th percentile, or (2) either wake or sleep load ≥ 25%.

- White coat HTN (WCH): casual BP $\geq 95^{th}$ percentile and wake and sleep mean ABP $< 95^{th}$ percentile and wake and sleep load < 25%.
- Masked HTN: casual BP $<95^{th}$ percentile and either (1) wake or sleep mean ABP $\geq 95^{th}$ percentile, or (2) either wake or sleep load $\geq$ 25%.

Given the increased risk of cardiovascular disease in patients with CKD, ABP was considered abnormal when either the ambulatory mean or load was elevated. Thus, subjects with AHA classified pre-hypertension (high casual BP, normal mean ambulatory BP and high ambulatory BP load) were considered hypertensive (i.e., abnormal ABPM) in this analysis. Additionally, those with unclassified AHA BP parameters (normal casual, normal mean ABP, high load) were also considered masked hypertensive in this analysis.

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