Serial Free Bisphenol A and Bisphenol A Glucuronide Concentrations in Neonates

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Objective To determine the balance of metabolism of free bisphenol A (BPA) to the inactive conjugate, BPA glucuronide (BPAG), in neonates.

Study design Free BPA and BPAG concentrations were measured in 78 urine samples collected between December 2012 and August 2013 from a cohort of 44 healthy full term (≥37 weeks' gestation) neonates at 2 intervals (3-6 days and 7-27 days of age). A questionnaire was administered at the time of sample collection. Neonates recruited into the study were born in an urban, tertiary care hospital.

Results Only BPAG was detected in the urine samples; concentrations ranged from <0.1 μg/L to 11.21 μg/L (median: 0.27 μg/L). Free BPA concentrations were below the limit of quantification of 0.1 μg/L. Age, but not sex or type of diet, was significantly associated with urinary BPAG concentration (P = .002).

Conclusions Our results illustrate widespread BPA exposure in healthy full-term neonates and efficient conjugation of BPA to its readily excretable and biologically inactive form (BPAG) as early as 3 days of age. Factors other than type of diet may be important contributors to BPA exposure in neonates. *(J Pediatr 2015; ■: ■-■).*

Bisphenol A (BPA) is a high-production volume chemical present in food and drink can liners, dental sealants, medical equipment, and cash register receipts.[1] Detection of BPA in urine of 90% of the general population in countries around the world demonstrates widespread exposure,[2-5] primarily through dietary consumption. BPA leaches into food from packaging, especially the linings of cans.[6] Through its estrogenic properties, BPA may induce a variety of adverse outcomes, including developmental effects (on the brain, lung, and reproductive organs), diabetes, obesity, cancer, and cardiovascular disease.[7-15]

Upon ingestion, BPA is metabolized into BPA glucuronide (BPAG), a biologically inert form that is rapidly cleared in the urine (half-life <6 hours).[16] Glucuronidation of some compounds is limited in the newborn (eg, bilirubin), and this impairment has been hypothesized to slow clearance of BPA and increase serum and urine concentrations of free BPA in neonates.[17-20] Sensitive and specific methods are available to separately quantify free BPA and BPA conjugates in human biological samples, but contamination of samples with BPA from background sources in the laboratory and in the field has hampered the use of urinary biomarkers to study BPA metabolism in humans.[21]

In a previous study, we measured urinary free BPA and BPAG concentrations in a small cohort of young infants using methods that reduce sample contamination.[22] The data demonstrated universal BPA exposure in those infants, with free BPA concentrations below the limit of quantification (0.1 μg/L). Given the rapid increase in hepatic metabolism in the neonatal period,[17,18] we sought to assess changes in BPA glucuronidation through the first month of life. We hypothesized that less efficient BPA metabolism in the first week of the neonatal period would result in higher urine free BPA concentrations in neonates during the first week of life compared with the later part of the neonatal period.

Methods

Postpartum mothers and their healthy, full-term neonates (≥37 0/7 weeks gestation) were recruited during their hospitalization in the Full Term Nursery at the Johns Hopkins Hospital between December, 2012 and August, 2013. Newborns receiving pediatric primary care at the Johns Hopkins Harriet Lane Primary Care Clinic were eligible to participate. Babies were excluded if they were either large or small size for gestational age, were diagnosed with intrauter-

BPA	Bisphenol A
BPAG	BPA glucuronide
GM	Geometric mean
LOQ	Limit of quantitation
NICU	Neonatal intensive care unit

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Supported by the Johns Hopkins Center for a Livable Future Lerner Fellowship, the Wendy Klag Memorial Fund, and the National Institutes of Health (P01 ES006052, P30 ES003819, P30 CA006973, N01-CO-12400, and T32 ES007141). The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the United States Government. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.03.036

ine growth restriction, had an Apgar score of less than 5 at 5 minutes of age, had delayed voiding or stooling (greater than 24 hours after birth), were admitted to the neonatal intensive care unit (NICU) for management of hyperbilirubinemia, or had certain specific risk factors for hyperbilirubinemia (eg, cephalohematoma, polycythemia). Infants born to mothers with documented tobacco use during pregnancy, a positive urine toxicology screen for cocaine, marijuana, heroin, or methadone at delivery, and/or anti-epileptic drug use in pregnancy were also excluded. Infants with hyperbilirubinemia not requiring a NICU admission or with blood type incompatibility with the mother (ABO or Rh) were included. Recruitment and follow-up protocols were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board, and participant mothers provided informed consent.

Collection of urine samples and administration of a questionnaire took place at the Harriet Lane Clinic by trained research staff during scheduled pediatric well visits at 3-6 days of age (visit 1) and at 7-27 days of age (visit 2). At each of the 2 appointments, urine samples were collected from each infant using BPA-free pediatric urine collection bags (U-Bag; Hollister, Inc, Libertyville, Illinois). All urine collection bags were purchased at the outset of the study and were from the same lot. The bags and other equipment used to handle and store samples were tested for the presence of BPA using a BPA-free synthetic urine mixture to generate quality control samples.[23] All free BPA and BPAG concentrations in the quality control samples fell below the limit of quantification (LOQ) (0.1 μg/L). Urine samples were transported to the laboratory on ice within 3 hours of sample collection and were stored at −80°C until laboratory analysis.

Urine samples were analyzed using high performance liquid chromatography with tandem mass spectrometry following derivatization with dansyl chloride according to a previously modified published method.[24] Modifications included direct measurement of BPAG, which eliminated the need for enzymatic hydrolysis or solvent extraction of the samples. D6-BPAG was added as an internal standard. In addition, the high performance liquid chromatography column was changed from a 1 mm inside diameter C8 to a 2 mm inside diameter C18, which also required a flow increase from 80-250 μL/min. The LOQ was 0.1 μg/L for both free BPA and BPAG. Urine specific gravity was measured by handheld refractometer (Model: PAL 10-S; Atago, Bellview, Washington).

Statistical Analyses

Statistical analysis was performed using STATA 10 (StataCorp, College Station, Texas) and Excel 2010 (Microsoft, Redmond, Washington). The contribution of potential sources of BPA to exposure in the study population was evaluated by multiple linear regression, performed using a generalized estimating equation with urinary BPAG as the dependent variable.[25] Covariates in the model were age (dichotomous) and sex of the neonate, and a dietary variable for formula and/or breast milk intake. A uniform correlation structure was specified to account for correlation between measurements from the same individual (Spearman $\rho = 0.46$). Prior to regression analysis, BPAG concentrations were normalized based on specific gravity (reference value: 1.003) and log-transformed.[26] A Wald test was performed to determine the significance of the effect of dietary type. Sample concentrations below the LOQ were replaced by the LOQ divided by the square root of 2.

Results

Out of 66 eligible mothers and infants, 51 were enrolled into the study. At least 1 sample was collected from each of the 44 neonates who participated. Samples at visit 1 and visit 2 were collected from 34 participants. For 5 participants, a sample was collected at visit 1, but not at visit 2, and for 5 others, a sample was collected at visit 2, but not at visit 1. At the time of the first sample collection, 51% of the neonates in the study were fed exclusively formula, 28% were exclusively breast fed, and 21% were fed a combination of breast milk and formula (**Table I**). These diets remained relatively stable between the 2 visits, with only 3 infants who were exclusively breast fed at visit 1 switching to either formula or a combination of breast milk and formula by visit 2.

Seven participants who enrolled in the study were lost to follow-up, because mostly of late or early clinic arrival (when research staff was not present) or infant hospitalization. One participant elected to withdraw from the study for unspecified reasons.

Urinary Free BPA and BPAG Concentrations

Free BPA concentrations were below the LOQ in all of the 78 urine samples collected (**Table II** and **Figure 1**). BPAG was quantifiable in 71% of the samples (77% at visit 1, 64% at visit 2) (**Figure 2**). Median BPAG concentrations at age 3-6 days were higher compared with those at age 7-27 days. Four outliers, the highest observed BPAG concentrations, 3.67, 4.41, 8.49, and 11.21 μg/L were all measured in samples collected at ages 3-6 days. BPAG concentrations in urine collected from these 4 individuals at the second visit (at ages 7-27 days) were <LOQ, 0.13, 0.80, and 0.61 μg/L, respectively.

Determinants of BPA Exposure

Urinary BPAG concentrations decreased with age, with the difference between the 2 age groups being statistically significant ($P = .002$). Concentrations were higher in males (geometric mean [GM]: 0.36 μg/L) than females (GM: 0.24 μg/L), but the difference was not significant ($P = .133$). Neonates fed exclusively breast milk had higher concentrations of BPAG in the urine (GM: 0.39 μg/L) than those fed either formula alone (GM: 0.32 μg/L) or a combination of breast milk and formula, (GM: 0.17 μg/L). After normalizing BPAG concentrations to specific gravity, neonates fed exclusively formula had the highest concentrations, followed by those fed exclusively breast milk, and those fed a combination of formula and breast milk. However, both with and without specific

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Table I. Population characteristics

Mother-neonate pairs*	44
Sex of neonate	
Male	25 (57%)
Female	19 (43%)
Maternal race	
African American	43 (98%)
Hispanic	1 (2%)
Age (d)	
Sample 1	4.3 (±1.0)
Sample 2	12.1 (±3.8)
Feeding type (visit 1; visit 2)	
Breast milk only	11 (28%); 8 (21%)
Formula only	20 (51%); 21 (54%)
Both	8 (21%); 10 (25%)

*A total of 78 samples were collected from 44 neonates: 39 at the first time point (visit 1) and 39 at the second time point (visit 2).

gravity normalization, the differences in BPAG concentrations between the 3 feeding regimens were not statistically significant based on a Wald test with 2 degrees of freedom.

Discussion

In this study, we examined whether healthy full-term neonates efficiently form glucuronide conjugates of BPA. The question of the balance of free BPA to BPAG is critical to efforts to evaluate health risks from BPA exposure because free BPA mimics estrogen and may have deleterious effects on developing neonates. Because of BPA's short half-life, urinary BPAG concentrations reflect recent exposure but also demonstrate effective conversion to a biologically inert form. We measured BPAG concentrations in 71% of urine samples collected at age 3-6 days and age 7-27 days. In every sample, free BPA concentrations fell below the LOQ of 0.1 μg/L. These findings demonstrate both widespread exposure to BPA and efficient glucuronidation during the neonatal period.

Although in vitro studies and animal model experiments have provided some insight into neonatal BPA metabolism, studies of BPA glucuronidation using human biomarkers have been sparse and hindered by analytical technology.[27,28] We previously reported urinary concentrations of BPAG in samples from 11 neonates and 1 young infant between 7 and 44 days of age; free BPA was below the LOQ in all 12 individuals as in the present study.[22] BPAG concentrations were above the LOQ in 100% of the samples in the previous study but only 71% in this study, which could reflect a downward trend in BPA exposure in the population, possibly attributable to reduced use of BPA in consumer products, including baby bottles and formula packaging.[29-31]

Table II. Concentrations of free BPA and BPAG in the urine of 44 neonates (μg/L)

Analyte	Age group	N*	Mean	SD	25%	50%	75%	Maximum
BPAG	3-6 d	39	1.2	2.3	0.10	0.49	1.09	11.21
	7-27 d	39	0.37	0.48	<0.1	0.16	0.33	2.02
	All ages	78	0.79	1.7	<0.1	0.27	0.91	11.21
Free BPA	3-6 d	39	<0.1	-	<0.1	<0.1	<0.1	<0.1
	7-27 d	39	<0.1	-	<0.1	<0.1	<0.1	<0.1
	All ages	78	<0.1	-	<0.1	<0.1	<0.1	<0.1

*The populations at ages 3-6 (N = 39) and at ages 7-27 (N = 39) differ slightly; each includes 5 participants who are not in the other age group.

Several studies have reported measurements of free and total BPA (ie, the sum of free BPA and BPAG) in the urine of infants. Volkel et al demonstrated efficient glucuronidation in infants as early as 1 month of age.[32] In another study of infants 2-15 months of age, free BPA was detected in 28% of urine samples, but study investigators speculated that free BPA in the urine may have resulted from sample contamination during sample collection and handling.[33] In a study of premature infants in a NICU, free BPA was detected in 92% of samples, suggesting that poor glucuronidation capacity may impact free BPA internal dose and clearance in infants who are born preterm.[34] Higher BPA levels among the preterm population because of BPA exposure (from NICU medical equipment) and possible developmental differences in glucuronidation activity between preterm and full-term neonates and infants may account for the difference between those data and our results.

Although our findings indicate widespread BPA exposure in our study population, the major sources of this exposure are unclear. BPAG concentrations were lower in neonates who were exclusively breast fed or drank a combination of breast milk and formula compared with those who drank formula only, but the difference was not significant. This finding is consistent with a report that diet did not contribute to urinary total BPA in infants in a NICU.[35] Although BPA has been detected in both breast milk and liquid formula, powder formula is not a likely source of BPA exposure.[36,37] The presence of BPAG in 20 (80%) of samples from infants who drank exclusively powder formula was surprising and unexplained. Although used and mixed with powder formula by 88% of parents of these infants, commercially sold bottled water is not a known source of BPA exposure.[38] Baby bottles were an unlikely source as most baby bottle manufacturers switched from polycarbonate to non-BPA-based materials in 2009.[39] Study participants were asked about the age of the bottles and none reported using bottles purchased before 2009. Overall, our findings suggest that nondietary sources may contribute to BPA exposure in neonates.

Age was the only statistically significant determinant of BPA exposure, which may indicate a source of BPA exposure unique to the first week of the neonatal period, such as residual in utero exposure. However, correlation between measurements from the same individual also suggests a common postnatal source of exposure at both time points. The impact of age on BPAG concentration in our study may be attributable to lower fluid intake (ie, more concentrated urine) among neonates in the younger age group. Of the 4 individuals with the highest BPAG concentrations at age 3-6 days of age, 3 were exclusively breast fed, indicating that maternal lactogenesis, which occurs over a period of days during the first week, likely impacted breast fed neonates' fluid intake.[40,41] In our data analysis, we controlled for variability in fluid intake by normalizing BPAG concentrations based on specific

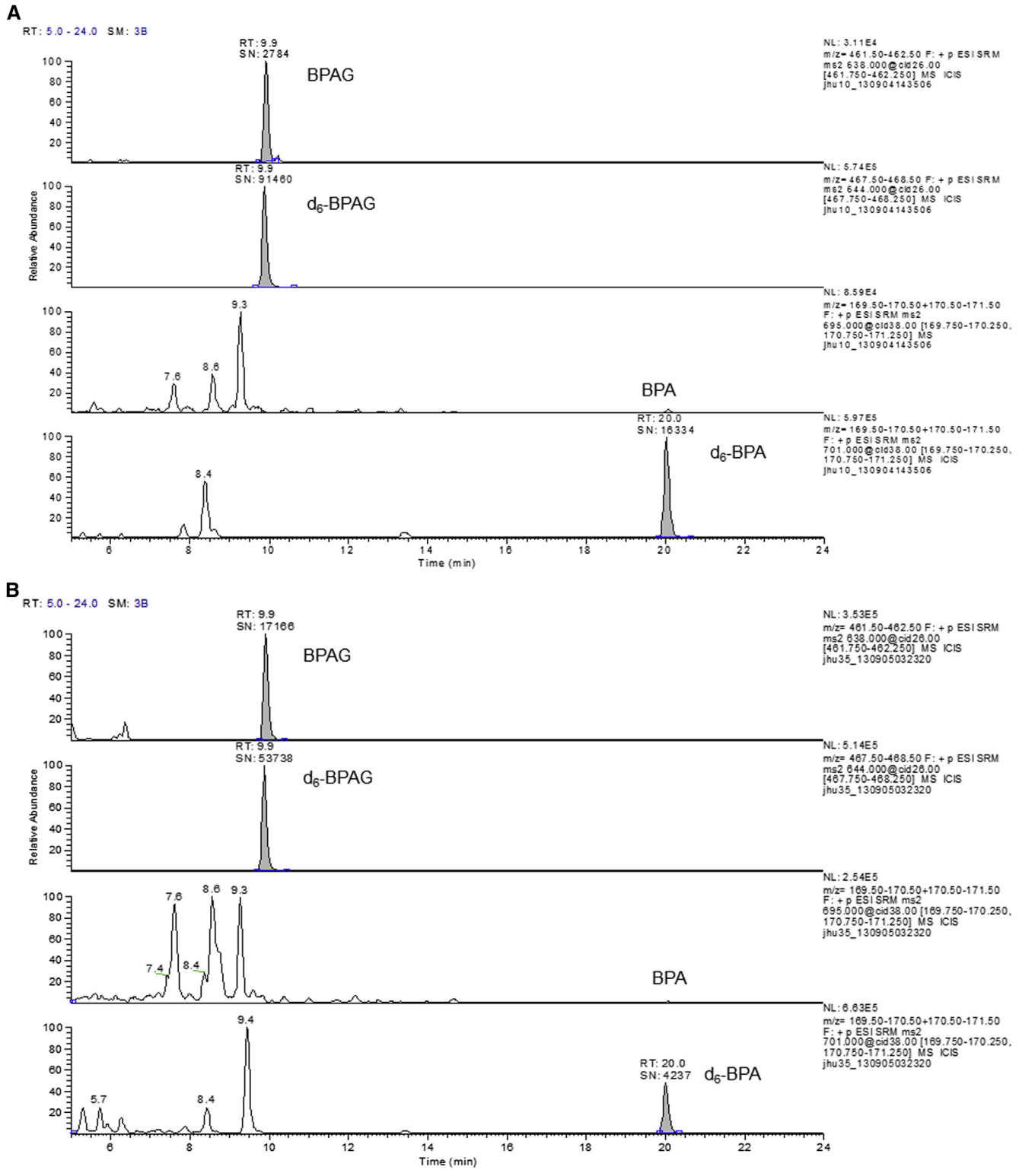

Figure 1. Representative chromatogram for urine sample with a BPAG concentration of **A,** 0.8 μg/L and **B,** 8.5 μg/L.

gravity. However, specific gravity, like creatinine, is an imperfect measure of urine dilution in neonates.[32]

To avoid selection of a study population with an underlying predisposition toward efficient glucuronidation, we included neonates with hyperbilirubinemia not requiring admittance to the NICU in the study (though different isoforms of uridine diphosphate-glucuronosyltransferase are responsible for bilirubin and BPA metabolism).[42,43] Of the

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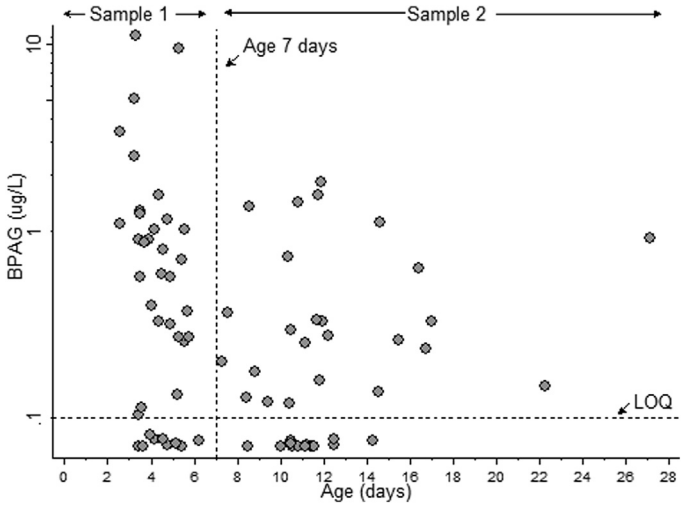

Figure 2. Urinary BPAG concentrations in neonates by age.

neonates participating in this study, 2 required phototherapy for hyperbilirubinemia. BPAG was quantifiable in urine samples from both neonates. As in the rest of the study population, no free BPA was detected in the urine these neonates.

A particular strength of this study was the prevention of sample contamination during sample collection and laboratory analysis. In this study, because all free BPA concentrations fell below the LOQ and BPAG is not expected in the environment, we can confidently report that field contamination did not influence our results or conclusions. The use of repeated measurements in the same neonate further strengthens our data. Because measurements from the same individual were correlated, the use of the generalized estimating equation allowed us to make inferences about the contribution of age, sex, and diet, to BPAG concentration despite a relatively small sample size.[25,44]

Limits to the generalizability of this study include the restriction of our cohort to healthy newborns from one center. The prevalence of certain genetic variants for UGT2B15 (and other uridine diphosphate-glucuronosyltransferase isoforms that play a role in BPA metabolism) varies by race, and all but 1 mother in our cohort self-identified as African American.[43,45] Subsets of neonates, such as those born prematurely or with other biological predisposition toward poor glucuronidation (eg, liver disease), could be less efficient at metabolizing BPA than the neonates in this study. In addition, these results may not apply to neonates who are more highly exposed to BPA, such as those spending time in a NICU. ■

We acknowledge Alison S. Geyh, PhD (Johns Hopkins Bloomberg School of Public Health, deceased), Barry Solomon, MD, MPH (Division of General Pediatrics and Adolescent Medicine), and Pamela Donohue, ScD (Eudowood Neonatal Pulmonary Division, Johns Hopkins University School of Medicine) for their contributions to the design of this study. In addition we thank the Pediatric Nurse Practitioners in the Full Term Nursery at the Johns Hopkins Hospital (Christa Bay, MSN, CPNP; Kristen Byrnes, MSN, CRNP; Krista Kline, CRNP; Carol Long, CRNP IBCLC; Krystina Mints, CPNP; Kimberly Alice Rice, MSN, CPNP; Suzanne Rubin, DNP, MPH, CRNP-P; Patricia H. Smouse, MSN, CPNP; Jo-Ann Swartz, MSN, CRNP) for screening patients for eligibility. We also thank the leadership and nursing staff of the Harriet Lane Clinic for their assistance.

Submitted for publication Oct 15, 2014; last revision received Jan 23, 2015; accepted Mar 17, 2015.

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