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Melamine-Contaminated Powdered Formula and Urolithiasis in Young Children

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ABSTRACT

BACKGROUND

A recent epidemic of melamine contamination of baby formula in China has been associated with the development of urinary tract stones, though the clinical manifestations and predisposing factors are incompletely delineated.

METHODS

We administered a questionnaire to the parents of children 36 months of age or younger who were being screened for a history of exposure to melamine and symptoms of, and possible predisposing factors for, urinary tract stones. In addition, we performed urinalysis, renal-function and liver-function tests, urinary tests for biochemical markers and the calcium:creatinine ratio, and ultrasonography. Powdered-milk infant formulas were classified as having a high melamine content (>500 ppm), a moderate melamine content (<150 ppm), or no melamine (0 ppm); no formulas contained between 150 and 500 ppm of melamine.

RESULTS

Contaminated formula was ingested by 421 of 589 children. Fifty had urinary stones, including 8 who had not received melamine-contaminated formula; 112 were suspected to have stones; and 427 had no stones. Among children with stones, 5.9% had hematuria and 2.9% had leukocyturia, percentages that did not differ significantly from those among children who were suspected to have stones or those who did not have stones. Serum creatinine, urea nitrogen, and alanine aminotransferase levels were normal in the 22 children with stones who were tested. Four of the 41 children (9.8%) who had stones and in whom urinary markers of glomerular function were measured had evidence of abnormalities; none had tubular dysfunction. Children exposed to high-melamine formula were 7.0 times as likely to have stones as those exposed to no-melamine formula. Preterm infants were 4.5 times as likely to have stones as term infants.

CONCLUSIONS

Prematurity and exposure to melamine-contaminated formula were associated with urinary stones. Affected children lacked typical signs and symptoms of urolithiasis.

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AN EPIDEMIC OF URINARY TRACT STONES in young children, most under 36 months of age, recently occurred in China. On September 12, 2008, the Chinese government announced that the epidemic was most likely related to melamine contamination of powdered-milk formula for infants, and a policy of free screening for urinary stones in children was instituted. The addition of melamine to food boosts the apparent protein content, since melamine contains 66% nitrogen by mass; this covert practice appears to have been the cause of the melamine contamination of infant formula. Although an epidemic of renal failure, including some deaths, had occurred in 2007 in animals exposed to pet food contaminated with melamine,¹ the relationship between melamine ingestion and urinary stones in humans was initially unclear in the recent epidemic among children. The present report details an investigation of melamine-linked urinary stones in children exposed to contaminated formula.

METHODS

Immediately after the announcement of melamine contamination of formula and the government-sponsored screening, we initiated a multidisciplinary cross-sectional study. The prespecified primary outcome was the presence of urinary stones. Secondary outcomes were clinical manifestations and laboratory abnormalities, as well as other possible factors, associated with melamine exposure. We developed a questionnaire that was administered by several trained investigators. For the other assessments, all involved investigators, pediatricians, ultrasonographers, and laboratory staff were trained to use uniform criteria and procedures. Identifying information concerning patients and samples was concealed from the laboratory and ultrasonography personnel. The rapid implementation of this study rendered it likely that some data would be incomplete.

PATIENTS

We studied all children 36 months of age or younger who were brought to Peking University First Hospital for screening for urinary stones between September 17 and October 3, 2008. The study was approved by the hospital's ethics committee. All the parents or guardians provided written informed consent.

QUESTIONNAIRE

We administered a questionnaire designed to obtain information about demographic characteristics, including sex and age; the history of exposure to contaminated formula, including the brand, melamine content, duration of exposure, use of formula alone or a combination of breast milk and formula; birth type (preterm or term); and symptoms such as fever or vomiting and diarrhea within the 3-day period before the visit. Other signs and symptoms, such as oliguria, unexplained crying (especially on urination), and edema, and any history of passing stones were recorded.

CATEGORIZATION OF CONTAMINATED FORMULA

The General Administration of Quality Supervision, Inspection, and Quarantine of the People's Republic of China reported that 22 brands of infant formula were contaminated (with reported concentrations of melamine ranging from 0.1 to 2500 ppm). On the basis of the amount of melamine contamination, we grouped the formulas into three categories: high-melamine formula (melamine content, >500 ppm), moderate-melamine formula (<150 ppm), and no-melamine formula. None of the brands tested contained melamine at a concentration between 150 and 500 ppm. Children had to have been fed formula for at least 30 days to be considered to have been exposed. The content of individual formulas is listed in the Supplementary Appendix (available with the full text of this article at NEJM.org).

LABORATORY INVESTIGATIONS

Routine serum-chemical measurements included blood urea nitrogen, creatinine, and alanine aminotransferase levels. Urinalysis was performed, and we measured levels of urinary microalbumin (reference range, 0 to 19 mg per liter), transferrin (reference range, 0 to 2 mg per liter), α_1 -microglobulin (reference range, 0 to 12 mg per liter), and *N*-acetyl- β -D-glucosaminidase (reference range, 0 to 21 U per liter). Urinary calcium and creatinine levels were also measured. Detailed methods are found in the Supplementary Appendix.

ULTRASONOGRAPHY OF THE URINARY TRACT

Ultrasonography of the kidneys and lower urinary tract was performed with the use of an ultrasonography system (ProSound SSD-5000SV, Aloka) and an attached scanner monitor (5 to 6 MHz). Assess-

ments included renal size; the shape of the pyelocalyceal region, ureter, and bladder; echogenicity; and parenchymal thickness. Findings with regard to urinary stones were categorized as follows: definite stones, suspected stones (increased, sporadic, punctiform echogenicity in the kidneys or pyelocalyceal system), or no stones. Patients who had urinary stones without other urinary tract abnormalities and who had been exposed to melamine-contaminated formula for 30 days or more were considered to have melamine-associated urolithiasis.

STATISTICAL ANALYSIS

The software program EpiData (version 3.0, www.epidata.dk/) was used for data management. Statistical analyses were performed with SPSS software (version 14.0, SPSS). Frequencies and percentages were used to describe the distributions of diagnoses on ultrasonography among the children according to sex, age, melamine content in the formula received, clinical manifestations, and laboratory results. Chi-square tests and Fisher's exact test were used to compare categorical data. Multivariate analyses were conducted with the use of a multinomial logistic model, in which age group, sex, birth type, the use of formula alone or in combination with breast milk, and the melamine content in the formula received were included. Odds ratios and 95% confidence intervals for risk were calculated on the basis of model-variable coefficients and standard errors, respectively. Patients without stones served as the reference group.

Two models were used for analysis. In model 1, the missing data from measured variables were excluded, leaving 400 observations. In model 2, missing binary data were coded as not present,

an approach that biases the relationship between covariate and outcome toward the null hypothesis. Missing categorical data, such as birth type and use of formula alone or in combination with breast milk, were coded as "unknown"; a total of 589 observations were used in the model. The approach used in model 2 allows for the contribution of other existing variables for each observation and may provide insight into the distribution of missing data.²

All reported P values are two-sided (with values less than 0.05 considered to indicate statistical significance) and were not adjusted for multiple testing except for the evaluation of differences in rates of glomerular dysfunction between any two groups of patients (those who had stones, those who were suspected to have stones, and those who did not have stones). For this analysis, the P value used to indicate statistical significance for the hypothesis tested was adjusted for multiple comparisons by means of the Bonferroni correction, for a threshold value of 0.017 (0.05 ÷ 3).

RESULTS

STUDY POPULATION

In all, 589 children were screened: 341 boys (57.9%) and 248 girls (42.1%). All 589 children were consecutively enrolled in the study after written informed consent had been provided by their parents or guardians. Characteristics of the children and the melamine content in the formula they received are listed in Table 1.

EXTENT OF EXPOSURE AND PRESENCE OF STONES

Contaminated formula was ingested by 421 of the 589 children (Table 1); 50 of the 589 children

Table 1. Melamine Exposure and Other Characteristics of the 589 Children Studied, According to the Presence or Absence of Urinary Tract Stones.

Group	Age			Sex		Birth Type*		Melamine Content in Formula		
	0 to ≤1 Yr (N=160)	>1 to ≤2 Yr (N=224)	>2 to ≤3 Yr (N=205)	Male (N=341)	Female (N=248)	Preterm (N=36)	Term (N=431)	High (N=121)	Moderate (N=300)	None (N=168)
	<i>number (percent)</i>									
Children with stones	11 (6.9)	24 (10.7)	15 (7.3)	30 (8.8)	20 (8.1)	7 (19.4)	29 (6.7)	23 (19.0)	19 (6.3)	8 (4.8)
Children with suspected stones	30 (18.8)	36 (16.1)	46 (22.4)	64 (18.8)	48 (19.4)	7 (19.4)	87 (20.2)	30 (24.8)	58 (19.3)	24 (14.3)
Children without stones	119 (74.4)	164 (73.2)	144 (70.2)	247 (72.4)	180 (72.6)	22 (61.1)	315 (73.1)	68 (56.2)	223 (74.3)	136 (81.0)

* Birth type was known for only 467 of the 589 children studied. High melamine content was defined as more than 500 ppm, and moderate content less than 150 ppm.

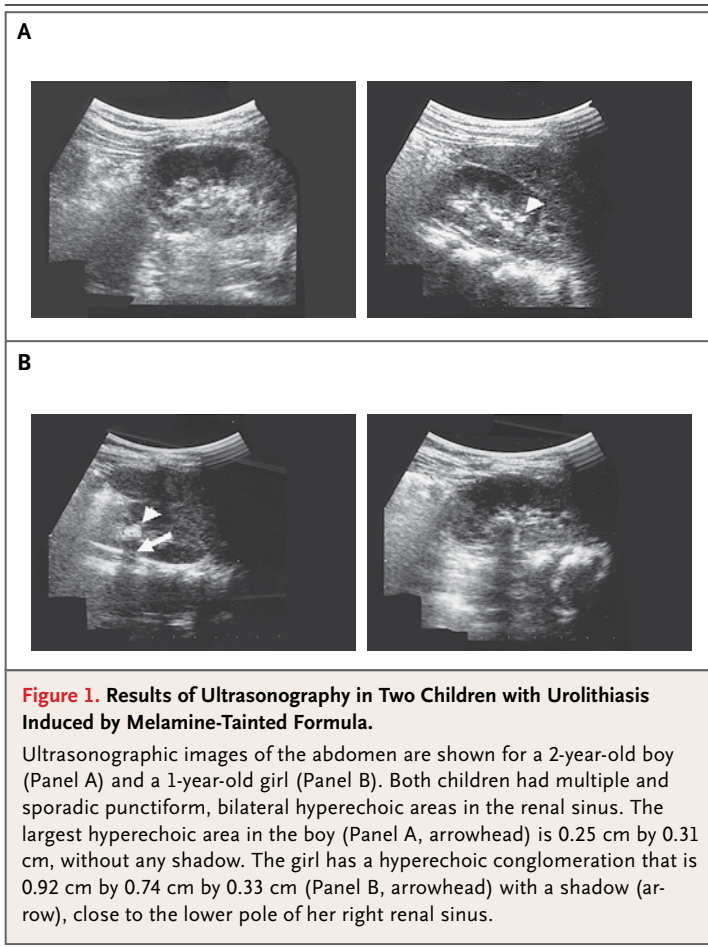


Figure 1. Results of Ultrasonography in Two Children with Urolithiasis Induced by Melamine-Tainted Formula.

Ultrasonographic images of the abdomen are shown for a 2-year-old boy (Panel A) and a 1-year-old girl (Panel B). Both children had multiple and sporadic punctiform, bilateral hyperechoic areas in the renal sinus. The largest hyperechoic area in the boy (Panel A, arrowhead) is 0.25 cm by 0.31 cm, without any shadow. The girl has a hyperechoic conglomeration that is 0.92 cm by 0.74 cm by 0.33 cm (Panel B, arrowhead) with a shadow (arrow), close to the lower pole of her right renal sinus.

had stones (overall prevalence, 8.5%); 112 were suspected to have urinary stones, and 427 had no stones. Grossly, the stones were mainly grainy and goblet-shaped (irregular and nubby) and did not cause shadowing on ultrasonography. Most were localized to the renal pelvis (Fig. 1). Four children who had stones also had evidence of urinary tract obstruction on ultrasonography, though none of these children had symptoms of obstruction. Most of the children with stones did not have oliguria, crying on urination, edema, or passing of stones. The presence of symptoms did not distinguish children who had stones from those who were suspected to have stones or those who did not have stones (Table 2).

LABORATORY EXAMINATIONS

Urinalysis was performed in 372 children (34 of the 50 who had stones, 76 of the 112 who were suspected to have stones, and 262 of the 427 who

did not have stones) (Table 3). Hematuria was present in 5.9% of the children with stones (2 of 34), and leukocyturia in 2.9% (1 of 34). No child suspected to have stones had hematuria, and only 1 of 76 (1.3%) had leukocyturia. Proteinuria was rare, and its frequency did not differ significantly among the groups.

We considered the elevation of urinary microalbumin levels, transferrin levels, or both to be evidence of glomerular dysfunction. Among the children for whom these data were available, glomerular dysfunction was found in 4 of the 41 children (9.8%) who had stones, 12 of the 88 children (13.6%) suspected to have stones, and 15 of the 269 (5.6%) who did not have stones ($P=0.04$ for the three-way comparison). The incidence of glomerular dysfunction among children suspected to have stones, as compared with children who did not have stones, was significantly increased ($P=0.01$). The incidence of renal tubular dysfunction, as indicated by elevation of the urinary β_2 -microglobulin level, did not differ significantly among the three groups ($P=0.42$) (Table 3).

Serum creatinine, urea nitrogen, and alanine aminotransferase levels were measured in 56 children — 22 who had stones, 21 suspected to have stones, and 13 who did not have stones. All 56 children had normal serum creatinine and urea nitrogen levels. In one child suspected to have stones and one child who did not have stones, alanine aminotransferase levels were increased (201 and 243 IU per liter, respectively [normal range, 0 to 40]). Neither of these two children had received high-melamine formula, and neither had symptoms of infection such as fever and diarrhea.

The urinary calcium:creatinine ratio was measured in 404 children and compared with the published reference values for young children: 7 months of age or younger, 1.96; 8 to 18 months of age, 1.4; and 19 months to 6 years of age, 0.78.³ According to these values, 62 of the children in our study had hypercalciuria: 5 of 42 (11.9%) who had stones, 13 of 88 (14.8%) suspected to have stones, and 44 of 274 (16.1%) who did not have stones ($P=0.34$).

FACTORS ASSOCIATED WITH URINARY STONES

We considered age, sex, birth type, melamine content in the formula received, and use of the formula alone or in combination with breast milk as potential factors influencing urinary stone formation. Complete data were available for 400 of the

Table 2. Signs and Symptoms in the Children Studied, According to the Presence or Absence of Urinary Tract Stones.

Group	Oliguria	Unexplained Crying* <i>number/total number (percent)</i>	Edema	Passing of Stones
Children with stones	3/47 (6.4)	0/48	0/48	0/48
Children with suspected stones	6/109 (5.5)	8/110 (7.3)	1/110 (0.9)	1/110 (0.9)
Children without stones	10/419 (2.4)	17/418 (4.1)	4/416 (1.0)	1/418 (0.2)
All children	19/575 (3.3)	25/576 (4.3)	5/574 (0.9)	2/576 (0.3)
P value†	0.20	0.08	1.00	0.47

* Unexplained crying most commonly occurred on urination.

† P values were calculated for the comparison among the three subgroups of children with the use of Fisher's exact test.

589 children and were analyzed with two statistical models. Model 1 included these 400 patients, and all 589 patients were included in model 2, in which the missing categorical data were coded as "unknown" (Table 4).

Age, sex, and use of formula alone or in combination with breast milk were not significantly associated with the presence or absence of stones; however, preterm birth and a high melamine content in the formula received were significantly associated with the presence of stones.

In model 1, children exposed to high-melamine formula were 7.0 times as likely to have stones as children exposed to no-melamine formula (95% confidence interval [CI], 2.1 to 23.0; $P=0.001$) (unadjusted odds ratio, 5.8; 95% CI, 2.4 to 13.2; $P<0.001$), whereas children exposed to moderate-melamine formula did not have an increased likelihood of stone formation. Preterm infants were 4.5 times as likely to have stones as term infants (95% CI, 1.6 to 12.4; $P=0.003$) (unadjusted odds ratio, 3.5, 95% CI, 1.4 to 8.8; $P=0.009$). In addition, children exposed to high-melamine formula were 2.6 times as likely as those exposed to no-melamine formula to have suspected stones (95% CI, 1.2 to 5.4; $P=0.01$; unadjusted odds ratio, 2.5; 95% CI, 1.4 to 4.6; $P=0.003$).

In model 2, children exposed to high-melamine formula were 5.4 times as likely as those exposed to no-melamine formula to have stones (95% CI, 2.2 to 12.9; $P<0.001$), whereas children exposed to moderate-melamine formula did not have a significantly increased likelihood of stone formation. Preterm infants were 3.7 times as likely as term infants to have stones (95% CI, 1.4 to 9.7; $P=0.009$). In addition, children exposed to high-melamine formula were 2.3 times as likely to have

suspected stones as those exposed to no-melamine formula (95% CI, 1.2 to 4.4; $P=0.008$).

DISCUSSION

In this study, using two different statistical models, we found that exposure to high-melamine formula increased the risk of urolithiasis among young children. The results indicate that most children with melamine-associated urolithiasis had nonspecific symptoms and urinary findings. These findings contrast with the present guidelines posted on the Web site of the Ministry of Health of China (www.moh.gov.cn), which suggest that symptoms are useful in diagnosing the presence of stones. Our results indicate that screening for urinary stones should be based on the history of exposure to melamine rather than on the symptomatology.

In our study, the incidences of hematuria, leukocyturia, and proteinuria did not differ significantly among children who had stones, those who were suspected to have stones, and those who did not have stones. Moreover, the incidences of hematuria and leukocyturia in children with urolithiasis were lower than those in the study by Coward et al.,³ who reported that 55% of the children with urinary stones had hematuria and 30% had urinary tract infections. Since only 5.9% of children with stones in our study had hematuria and only 2.9% had leukocyturia, it would appear that urinalysis is not adequate for screening for melamine-associated urinary stones. Furthermore, none of the four children with urinary tract obstruction documented on ultrasonography in our study had symptoms of obstruction or hematuria, leukocyturia, or proteinuria. Thus, in our view,

Table 3. Laboratory Results in the Children Studied, According to the Presence or Absence of Urinary Tract Stones.

Group	Hematuria	Leukocyturia	Proteinuria	Glomerular Dysfunction	Renal Tubular Dysfunction
Children with stones	2/34 (5.9)	1/34 (2.9)	0/34	4/41 (9.8)	0/41
Children with suspected stones	0/76	1/76 (1.3)	1/76 (1.3)	12/88 (13.6)	4/88 (4.5)
Children without stones	4/262 (1.5)	4/262 (1.5)	2/262 (0.8)	15/269 (5.6)	8/269 (3.0)
All children	6/372 (1.6)	6/372 (1.6)	3/372 (0.8)	31/398 (7.8)	12/398 (3.0)
P value*	0.10	0.63	0.65	0.04	0.42

* P values were calculated for the comparisons among the three subgroups of children with the use of Fisher's exact test, except in the case of glomerular dysfunction, for which Pearson's chi-square test was used.

the diagnosis of melamine-related urinary stones requires an ultrasonographic examination.

Unlike typical urinary tract stones, most of the melamine-associated stones we detected were not characterized by shadowing on ultrasonography. Sun et al.⁴ analyzed specimens of melamine-associated stones from 13 children with renal failure by using liquid chromatography–mass spectrophotometry and found that the stones were composed primarily of uric acid and melamine. Before the announcement of formula contamination, a 3-month-old boy was admitted to our hospital after presenting with a 2-week history of diarrhea. On ultrasonography, multiple tiny stones, the largest of which was 0.3 cm by 0.4 cm, were observed bilaterally in the renal pelvis, without shadowing or obstruction of the urinary tract system. After the announcement of melamine contamination, we inquired about exposure to melamine; the boy had received formula containing 150 ppm of melamine for 3 months. After treatment for 9 days, which included hydration and urine alkalinization, ultrasonography was repeated. Only one stone (0.5 cm in diameter) was detected in his left renal pelvis. This case suggests that melamine-related stones may not be dense and may be easily passed after hydration and alkalinization, findings that are consistent with a urate component.

Most melamine-associated stones in our series were small and sand-like, especially those in the renal pelvis. A previous study showed renal tubular degeneration in dogs exposed to melamine-contaminated pet food.¹ However, it is not known whether melamine or uric acid mixed with melamine forms microcrystals that could cause tubulointerstitial injury in humans.

In our analysis of biomarkers of early renal injury in 398 children, the incidence of glomerular dysfunction, but not renal tubular dysfunction, differed significantly among children who had stones, those who were suspected to have stones, and those who did not have stones. More children suspected to have stones had apparent glomerular dysfunction than those who did not have stones (13.6% vs. 5.6%, $P=0.01$), yet there were no significant differences in the incidence of glomerular dysfunction between children with stones and those without stones (9.8% and 5.6%, $P=0.37$). It is unclear whether there were other factors at play, such as other renal diseases, among the children suspected to have stones.

Whether melamine can cause injury of other tissues and organs in humans is unknown. In our study, serum alanine aminotransferase levels were normal in all but two children, both under 1 year of age; one of the two children was suspected to have stones and the other did not have them. Neither child had received high-melamine formula, and neither had symptoms of urinary tract infection. The reasons for the increased serum alanine aminotransferase levels were not determined.

In our study, 121 children were exposed to high-melamine formula, but only 23 of these children had urinary stones. Thus, urinary stones developed in a minority of children exposed to high-melamine formula. Multivariate logistic-regression analysis with the use of two models indicated that preterm infants were 3.7 to 4.5 times as likely as term infants to have stones. Gilsanz et al.⁵ reported that preterm infants were more susceptible than term infants to the development of urinary stones not related to melamine,

Table 4. Predisposing Factors and Odds Ratios for the Development of Urinary Tract Stones.

Predisposing Factor	Model 1				Model 2			
	Children with Stones		Children with Suspected Stones		Children with Stones		Children with Suspected Stones	
	odds ratio (95% CI)	P value	odds ratio (95% CI)	P value	odds ratio (95% CI)	P value	odds ratio (95% CI)	P value
Increasing age — per yr	1.2 (0.7–1.9)	0.50	1.3 (0.9–1.8)	0.13	1.1 (0.7–1.6)	0.77	1.2 (0.9–1.6)	0.15
Sex								
Male	0.8 (0.4–1.8)	0.66	1.0 (0.6–1.6)	0.99	0.9 (0.5–1.7)	0.83	0.9 (0.6–1.5)	0.79
Female	1.0		1.0		1.0		1.0	
Birth type								
Preterm	4.5 (1.6–12.4)	0.003	0.9 (0.3–2.6)	0.88	3.7 (1.4–9.7)	0.009	1.2 (0.5–3.0)	0.66
Unknown					1.9 (0.9–3.9)	0.07	0.8 (0.5–1.4)	0.47
Term	1.0		1.0		1.0		1.0	
Melamine content in formula								
High	7.0 (2.1–23.0)	0.001	2.6 (1.2–5.4)	0.01	5.4 (2.2–12.9)	<0.001	2.3 (1.2–4.4)	0.008
Moderate	2.0 (0.6–6.2)	0.25	1.7 (0.9–3.2)	0.10	1.4 (0.6–3.3)	0.44	1.5 (0.9–2.5)	0.15
None	1.0		1.0		1.0		1.0	
Formula alone or with breast milk								
Formula with breast milk	1.4 (0.7–3.0)	0.39	1.3 (0.8–2.2)	0.26	1.0 (0.5–1.9)	0.10	1.4 (0.9–2.2)	0.16
Unknown					0.3 (0.1–1.0)	0.05	0.4 (0.2–0.9)	0.03
Formula alone	1.0		1.0		1.0		1.0	

possibly owing to a combination of immature renal function and differences in the regulation of mineral homeostasis.

Our study has certain limitations, in part because it focused on an accidental outbreak of renal disease. First, some data were missing among responses to the questionnaire. Second, the geographic location of our hospital, in the center of Beijing, a city in northern China, might have led to enrollment bias for two reasons: screened children mainly came from nearby provinces, such as Hebei and Henan, in which the melamine contamination was reported as being more serious than elsewhere. In addition, children screened in other hospitals, especially those who had urinary stones or were suspected of having stones, may have been sent for further evaluation to our hospital, a well-known referral hospital for children, resulting in referral bias and an overestimate of the incidence of urinary stones. Third, since for some children, morning urine samples were not collected before the visit to the hospital, ran-

dom, untimed urine specimens were obtained in our study, which may have influenced the urinary findings.

A fourth limitation is the lack of data on renal pathological characteristics, since it was not feasible in this situation to perform renal biopsies in children with urolithiasis. Therefore, we could not assess the direct injury of renal tissue by melamine. To date, we have information about changes in renal pathological characteristics in only one case, involving an 8-month-old boy with melamine-associated urinary stones who was hospitalized after prolonged anuria caused by bilateral urethral stones.⁴ His renal-biopsy specimen revealed sclerosis in 6 of 26 glomeruli, partial tubular epithelial-cell degeneration, lymphocyte infiltration in the renal interstitium, and focal fibrosis; the results of immunofluorescence analysis were normal. However, it is unclear whether the renal histopathological changes were caused by melamine itself or by the acute obstructive uropathy that ensued. Finally, we were unable to test the

melamine concentration of milk formulas ourselves; instead, we relied on reported values of the melamine content.

In conclusion, we suggest that children with urinary stones induced by melamine-tainted formula require careful ongoing and long-term follow-up.

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No potential conflict of interest relevant to this article was reported.

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