angiograms were obtained within 12 months (in 56 patients in the CABG group and in 151 patients in the PCI group). The primary indications leading to angiography were angina in 29 patients in the CABG group (14.0%) and 95 patients in the PCI group (45.9%), myocardial infarction in 10 patients in the CABG group (4.8%) and 19 patients in the PCI group (9.2%), an abnormal stress test in 5 patients in the CABG group (2.4%) and 2 patients in the PCI group (1.0%), and myocardial ischemia in 1 patient in the CABG group (0.5%) and 12 patients in the PCI group (5.8%).

Patrick W. Serruys, M.D., Ph.D.
Erasmus University Medical Center Rotterdam
3015 GD Rotterdam, the Netherlands
p.w.j.c.serruys@erasmusmc.nl
Friedrich W. Mohr, M.D., Ph.D.
Herzzentrum Universität Leipzig
4289 Leipzig, Germany
for the SYNTAX Investigators

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Melamine-Contaminated Powdered Formula and Urolithiasis

TO THE EDITOR: The article by Guan et al.,[1] the accompanying editorial by Langman,[2] and the letter to the Editor by Wang et al.[3] (all in the March 12 issue) provide information about the epidemiology of pediatric nephrolithiasis caused by melamine poisoning. Here we supplement those data and commentary with information regarding diagnosis and treatment on the basis of our clinical experience and the advice of the Chinese Ministry of Health.[4,5]

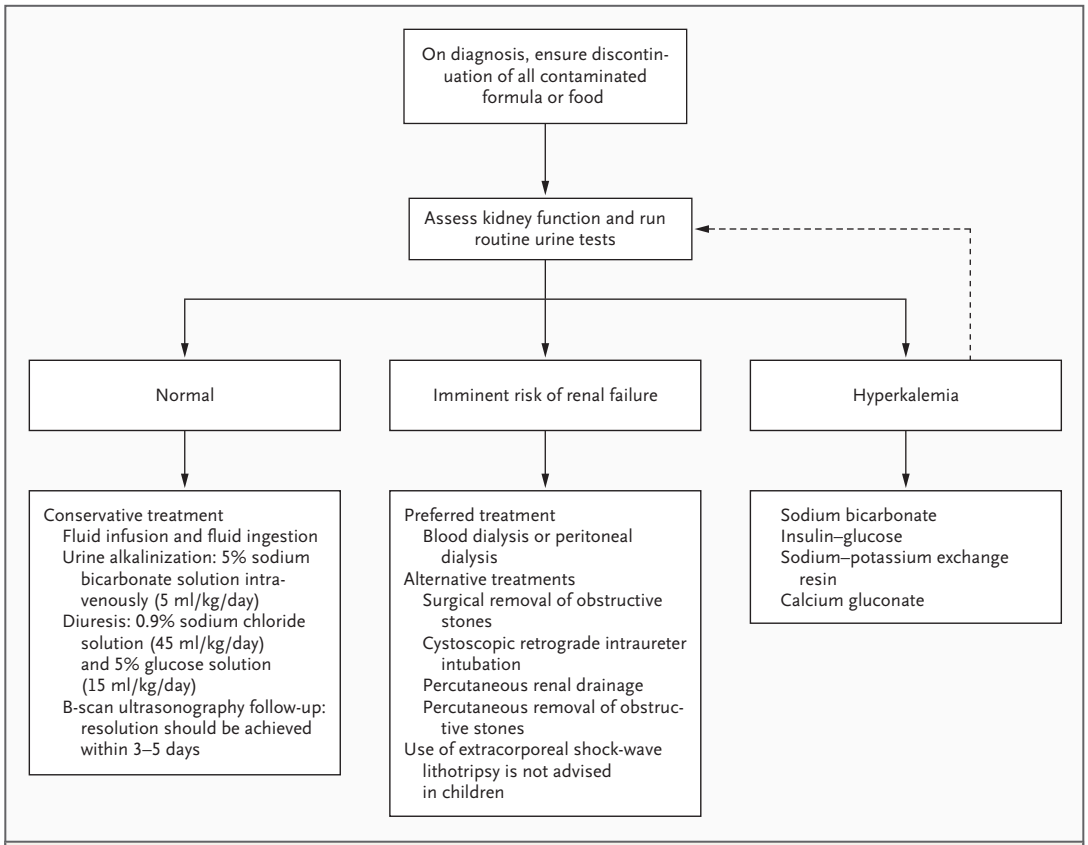

Figure 1. Treatments for Pediatric Nephrolithiasis Caused by Melamine Poisoning as Recommended by the Chinese Ministry of Health.

Kidney stones that have formed as a result of melamine poisoning differ from the more commonly encountered radiopaque stones containing calcium oxalate and phosphate in that they are radiolucent and not revealed by standard radiography.[4] In light of these distinctions, B-scan ultrasonography should be used to detect kidney stones in children who have consumed milk that is suspected of being contaminated with melamine.[4] Kidney stones that are associated with melamine poisoning commonly affect the collecting system and ureters bilaterally, predominantly at the ureteropelvic and ureter–bladder junctions.[4] The urinary tract may be extensively obstructed.[4] The stones can affect large areas and produce a light background echo.[4] Our recommended courses of action, depending on the degree of severity of nephrolithiasis, are summarized in Figure 1.

Kunmei Ji, Ph.D.
Shenzhen University
Shenzhen 518060, China

Shenglang Zhu, M.D.
Shenzhen Nanshan Hospital
Shenzhen 518052, China

Zhigang Liu, M.D.
Shenzhen University
Shenzhen 518060, China
lzg@szu.edu.cn

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TO THE EDITOR: The report by Guan et al. regarding infants who consumed melamine-contaminated formula states that the increase in the relative risk of stones was lower in preterm infants (odds ratio, 4.5) than in term infants (odds ratio, 7.0). As noted in the accompanying editorial, preterm infants generally have a higher risk of stones, in part because of a decreased rate of excretion of urinary inhibitors of stone formation. If we assume there was an equal likelihood of ingesting the tainted formula and an equal duration of exposure among all infants, preterm infants in this study should have been at higher risk than term infants. Were the preterm infants seen at a younger age than term infants, when they might still be under a gestational age of 40 weeks? At that stage of development, with lower urine-concentrating capacity, their ability to exceed solubility products in urine might be poor. Alternatively, among preterm infants, the duration of exposure, a factor in the study by Wang et al., might have been less. It would also be interesting to know whether preterm infants made up a greater proportion of those with glomerular dysfunction, since these infants might have had reversible glomerular albuminuria from prematurity itself.[1]

Vikas R. Dharnidharka, M.D., M.P.H.
University of Florida
Gainesville, FL 32610-0296
vikasmd@peds.ufl.edu

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TO THE EDITOR: In his editorial, Langman discusses the three reports of renal injury from melamine. Other health effects may be worth considering in light of the molecular composition of melamine (Fig. 1). Melamine is a triazine (1,3,5-triazine–2,4,6-triamine). Atrazine is a chlorinated triazine (2-chloro-4-[ethylamine]-6-[isopropylamine]-s-triazine) and is used extensively as a broadleaf herbicide in the Midwest and elsewhere in the world, although its use is banned in Europe. Atrazine has been associated with reproductive

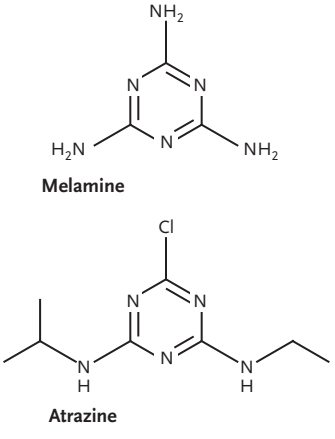

Figure 1. Molecular Structures of Melamine and Atrazine.

malformations, such as hermaphroditism in amphibians.[1,2] Long-term screening for reproductive ill effects in babies who have been exposed to melamine-adulterated formula may be warranted. Conversely, studies on the health of agricultural workers using atrazine should include an assessment of renal colic and kidney failure.

Bruce Hocking, M.B., B.S.
9 Tyrone St.
Camberwell, VIC 3124, Australia
bruhoc@connexus.net.au

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THE AUTHORS REPLY: Ji et al. state that kidney stones that are associated with melamine contamination are usually radiolucent, which was the case in our study. We emphasized that melamine-associated urolithiasis should be diagnosed by ultrasonography rather than by radiographic studies. Because ureteropelvic and ureterovesical junctions are relatively narrow, obstruction occurred more easily in these regions.[1] We believe that this is characteristic of all types of stones, not just those associated with the ingestion of melamine. For diagnostic purposes, since laboratory investigation often occurred after obstruction, we believe that imaging with ultrasonography is the most important technique for diagnosis and for making clinical decisions. For the children with renal failure induced by obstruction, the most important action is to relieve the obstruction.[2]

Dharnidharka notes that preterm infants are generally more prone to all types of stones than are term infants. In our study, 7 preterm infants and 29 full-term infants had urinary stones. The average ages were 1.56±0.84 years for preterm infants and 1.74±0.72 years for full-term infants. There was no significant difference between the ages of the two groups. However, the percentage of preterm infants who were less than 40 weeks old was higher than that of full-term infants (28.6% vs. 3.4%, P=0.09). There was no significant difference between preterm infants and full-term infants in the time of exposure to melamine-contaminated formula. There was also no significant difference in the rate of glomerular dysfunction between the preterm infants (4%) and the full-term infants (9%), which suggests that glomerular dysfunction was not associated with the immaturity of the preterm infants.

Na Guan, M.D., Ph.D.
Jie Ding, M.D., Ph.D.
Peking University First Hospital
Beijing 100034, China
djnc_5855@126.com

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THE EDITORIALIST REPLIES: We do not have substantial epidemiologic data and mechanistic explanations regarding melamine-associated kidney stones in infants caused by tainted powdered formula. Only very recently has it been feasible to measure urinary melamine and its metabolites easily; such capability may help define the risk of stones from dietary exposure.[1]

With respect to the recommendations of Ji and colleagues, I have several concerns. I do not expect that a fully obstructed urinary tract with stones would be asymptomatic in young infants. Such affected infants would probably show a lack of normal health, appetite, and growth, with symptoms such as irritability, urinary infection, gross hematuria, and stone colic. Certainly, no infants should continue to receive tainted formula, and without additional exposure, newly diagnosed cases will cease, since melamine is not stored in or released from body tissues.

What then should the medical community do about the infants who were exposed? Without evidence of an ongoing epidemic of new kidney stones or new cases of melamine-related acute kidney failure, a conservative approach to care has been supported by pediatric nephrologists internationally.[2]

With respect to Hocking's comments: although there are reports of urinary epithelial neoplasia in rats that receive dietary melamine in high doses and of its modulation by dietary polyunsaturated fatty acid,[3] we do not have a clear understanding of these relationships. Simple chemical similarities of structure may not predict similar actions (e.g., retinoid compounds in skin disorders).[4] A melamine-like triazine compound may be antineoplastic, and cyanuric acid salts are nonmutagenic. Atrazine has not been linked to nephrolithiasis. However, experimental studies have shown that atrazine induces insulin re-

sistance and alters mitochondrial functions,[5] which may be associated with an increased risk of kidney stones. Agricultural workers may have additional environmental risk factors for kidney stones, including chronic volume depletion and high levels of dietary fructose.

Craig B. Langman, M.D.
Children's Memorial Hospital
Chicago, IL 60614

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Pulmonary Rehabilitation

TO THE EDITOR: In their Clinical Therapeutics article, Casaburi and ZuWallack (March 26 issue)[1] do not discuss the BODE index and its role in evaluating the effect of pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD). The BODE index incorporates the body-mass index (BMI), the severity of airflow obstruction and dyspnea, and exercise tolerance in a 10-point scale in which higher scores indicate a higher risk of death. This index has been shown to be a better predictor of mortality than Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging, which classifies only the severity of obstruction.[2] Changes in the BODE index correlate with favorable outcomes after surgery for lung-volume reduction[3] and after pulmonary rehabilitation. In a controlled study, patients with COPD undergoing pulmonary rehabilitation had improved BODE scores and outcomes.[4] The authors found that mortality due to respiratory disease at 2 years after pulmonary rehabilitation was 7%, as compared with 39% in the control group. Furthermore, their analysis showed that BODE scores returned to baseline after 2 years of follow-up, confirming what most of us already know about pulmonary rehabilitation: its benefits wane over time.

Luis M. Seijo, M.D.
Clínica Universitaria de Navarra
31008 Pamplona, Spain
lmseijo@unav.es

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THE AUTHORS REPLY: The BODE index was designed as an easily measured predictor of death in patients with COPD. It predicts mortality better than the forced expiratory volume in 1 second (FEV_1), but this is virtually a mathematical imperative, since the BODE index incorporates FEV_1 as one of its predicting variables. Studies have examined the BODE's usefulness in assessing outcome after therapeutic interventions. Cote and Celli found that patients with COPD undergoing pulmonary rehabilitation have improvements in their BODE score[1] — as would be expected from well-described improvements in exercise tolerance and dyspnea.[2] However, we cannot agree with Seijo's inference that the observed difference in mortality between patients who completed rehabilitation and patients who either declined to participate in or did not complete the intervention (the "control" group, although the study's authors did not designate it as such) demonstrates a survival benefit of pulmonary rehabilitation. Potential selection biases notwithstanding, patients who decline to participate in or do not complete rehabilitation have characteristics that are likely to lead to a poor prognosis[3]; Cote and Celli acknowledged this in their discussion. A randomized trial of pulmonary rehabilitation which is adequately powered for an outcome of survival remains a high priority.[4]

Richard Casaburi, Ph.D., M.D.
Los Angeles Biomedical Research Institute
Torrance, CA 90502
casaburi@ucla.edu