

# Outbreak of acute renal failure in Panama in 2006: a case-control study

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**Objective** In September 2006, a Panamanian physician reported an unusual number of patients with unexplained acute renal failure frequently accompanied by severe neurological dysfunction. Twelve (57%) of 21 patients had died of the illness. This paper describes the investigation into the cause of the illness and the source of the outbreak.

**Methods** Case-control and laboratory investigations were implemented. Case patients (with acute renal failure of unknown etiology and serum creatinine  $\geq 2$  mg/dl) were individually matched to hospitalized controls for age ( $\pm 5$  years), sex and admission date ( $\leq 2$  days before the case patient). Questionnaire and biological data were collected. The main outcome measure was the odds of ingesting prescription cough syrup in cases and controls.

**Findings** Forty-two case patients and 140 control patients participated. The median age of cases was 68 years (range: 25–91 years); 64% were male. After controlling for pre-existing hypertension and renal disease and the use of angiotensin-converting enzyme inhibitors, a significant association was found between ingestion of prescription cough syrup and illness onset (adjusted odds ratio: 31.0, 95% confidence interval: 6.93–138). Laboratory analyses confirmed the presence of diethylene glycol (DEG) in biological samples from case patients, 8% DEG contamination in cough syrup samples and 22% contamination in the glycerin used to prepare the cough syrup.

**Conclusion** The source of the outbreak was DEG-contaminated cough syrup. This investigation led to the recall of approximately 60 000 bottles of contaminated cough syrup, widespread screening of potentially exposed consumers and treatment of over 100 affected patients.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

## Introduction

Diethylene glycol (DEG) is a colourless and odourless liquid and a human toxicant. It is commonly used in industry and can be found in commercial products such as resins, antifreeze, inks and glues. In addition, DEG has also been found as a contaminant of raw materials used in the production of pharmaceuticals.<sup>1</sup> As a result, nine known poisoning epidemics associated with DEG-contaminated medications have occurred worldwide.<sup>2–10</sup> The first and largest outbreak, which resulted

in 105 deaths, occurred in the United States of America (USA) in 1937 and led to the passing of the 1938 Federal Food, Drug and Cosmetic Act requiring proof of safety before drugs were introduced into the marketplace.<sup>1</sup> Since that time, there have been no DEG mass poisonings in the USA but many have occurred in the developing world. Most recently, paediatric medicinal syrups contaminated with DEG have led to the deaths of 33 of 36 children known to be affected in India in 1998<sup>10</sup> and of 85 of 109 children known to be affected in Haiti in 1995–1996.<sup>9</sup> In both

outbreaks, patients had unexplained acute renal failure, a characteristic of moderate-to-severe DEG poisoning.<sup>11</sup>

In September 2006, a Panamanian physician reported an unusual number of patients with unexplained acute renal failure frequently accompanied by severe neurological dysfunction. Patients typically presented with abdominal symptoms, such as nausea, vomiting, epigastric discomfort and diarrhoea, followed several days later by oliguria or anuria, anorexia and fatigue. Many patients exhibited a spectrum of neurological effects, including cranial nerve

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palsies, acute flaccid extremity weakness and encephalopathy. All of the affected received health care through the Caja del Seguro Social (CSS) system. Despite dialysis, 12 out of 21 (57%) patients died.

When the Ministry of Health of Panama requested assistance from the Centers for Disease Control and Prevention (CDC) in the USA in early October 2006, it remained unclear whether the agent responsible for the outbreak was infectious or toxicological. Three leading hypotheses emerged. First, an infectious etiology was suspected but subsequently ruled out because there had been no known person-to-person transmission and because various bacterial cultures and viral tests for infectious causes of acute flaccid paralysis, such as enteroviruses, arboviruses, herpes viruses and *Campylobacter jejuni*, were negative. Second, an antihypertensive medication was suspected. Approximately 2 months before the outbreak, the CSS hospital system added lisinopril to its formulary as a first-line treatment for hypertension. Astute clinicians recognized that many of the affected patients were taking angiotensin-converting enzyme (ACE) inhibitors, such as lisinopril, which resulted in a concern that the formulary change was related to the outbreak. Finally, when two affected patients presented to a specific CSS hospital with bottles of a Panamanian-produced prescription liquid cough syrup, possible contamination of this medication was suspected.

Although features of the clinical presentation were consistent with DEG toxicity, the etiology was not confirmed and the source remained unknown. In October 2006, a case-control investigation was conducted to confirm the etiology and to identify the source of the outbreak.

## Methods

### Case and control patient selection

Case patients were those admitted to a specific CSS hospital (Hospital A) on or after 15 August 2006 with acute renal failure of unknown etiology characterized by oliguria or anuria and a serum creatinine level  $\geq 2$  mg/dl or with an acute worsening of pre-existing chronic renal failure. Control patients were those admitted to Hospital A for any cause other than renal failure. For

every case patient we attempted to enrol five matched hospitalized patients as controls. Controls were randomly selected from a daily hospital census and individually matched to cases on the basis of sex, age ( $\pm 5$  years) and date of hospital admission, which had to be no more than 2 days before the admission date of the matched case patient or any time thereafter.

### Data collection

A study questionnaire was designed to collect demographic and health information and to assess potential exposures. When a hospitalized case or control patient was unable to give consent and respond, the closest relative gave consent and completed the questionnaire. Questionnaires were administered in Spanish by health-care providers on the study team. Blood and urine samples were collected and analysed for a variety of potential nephrotoxic and neurotoxic substances, including metals, paraquat, organophosphate metabolites that reflected potential exposure to organophosphorous parent pesticides and carbamate metabolites that reflected potential exposure to carbamate parent pesticides.

### DEG exposure

While data collection for the case-control study was ongoing, investigators sent medications linked to the case patients, including samples of cough syrup and lisinopril, to CDC in Atlanta, GA, USA. The laboratory of the United States National Center for Environmental Health analysed the cough syrup samples and identified DEG. The United States Food and Drug Administration confirmed the presence of DEG in the cough syrup and determined that the lisinopril samples were within expected pharmaceutical parameters.

On the basis of the positive laboratory results, the main exposure of interest was the consumption of prescription cough syrup in a specified time period before hospital admission. This information was captured by the study questionnaire in two ways. First, in an open-ended question, case patients (or their proxies) were asked to list prescription medications taken in the 3 months before hospitalization. The 3-month interval was selected to cover the period when the first suspected case

was reported (Fig. 1). Control patients were also asked to list prescription medications but, to cover the same exposure window, the timeframe used was dependent on the admission date of the matched case patient. Second, in a direct question, both case and control patients were asked about their consumption of any liquid syrup in the 3 months before hospitalization (using the same timeframe described above). If they had consumed liquid syrup, they were asked about the type of syrup taken and whether it was a prescription, non-prescription or traditional (e.g. homemade) product. Exposed case and control patients were those who listed prescription liquid cough syrup in the open-ended question or who responded affirmatively to the direct question by saying they had consumed prescription liquid syrup for a cough.

### Laboratory analysis

Medication and urine samples collected from case and control patients were analysed for the presence of DEG. Eleven liquid medications in their original containers were received by the CDC laboratory for analysis, including five labelled as an antihistamine and expectorant, two as expectorants, three as antacids and one as a vitamin preparation. As part of an environmental assessment of the CSS production laboratory, samples of medications and raw ingredients were also obtained and shipped to the CDC for analysis.

The pharmaceutical products were diluted to 1:100 with water and analysed using high-performance liquid chromatography–tandem mass spectrometry. Three precursor-to-product ion transitions were monitored for both native DEG and the isotopically labelled internal standard. Quantification was achieved using isotope dilution calibration. Detailed descriptions of these methods can be found in a separate publication.<sup>12</sup> To assess urinary DEG, samples were extracted using immobilized sorbent liquid–liquid extraction with acetonitrile and diethyl ether as the eluent. The DEG in the eluate was then chemically derivatized to form the heptafluorobutyric diester of DEG. Samples were analysed using gas chromatography–tandem mass spectrometry, in which three precursor-to-product ion transitions were monitored for DEG and only one for its labelled

analogue. Quantification was achieved using isotope dilution calibration in which extraction recoveries were automatically corrected to 100% for each individual sample. Using these methods, the minimum detection level for urinary DEG was 10 parts per billion. A more detailed description of this procedure and the validation parameters will be reported elsewhere.

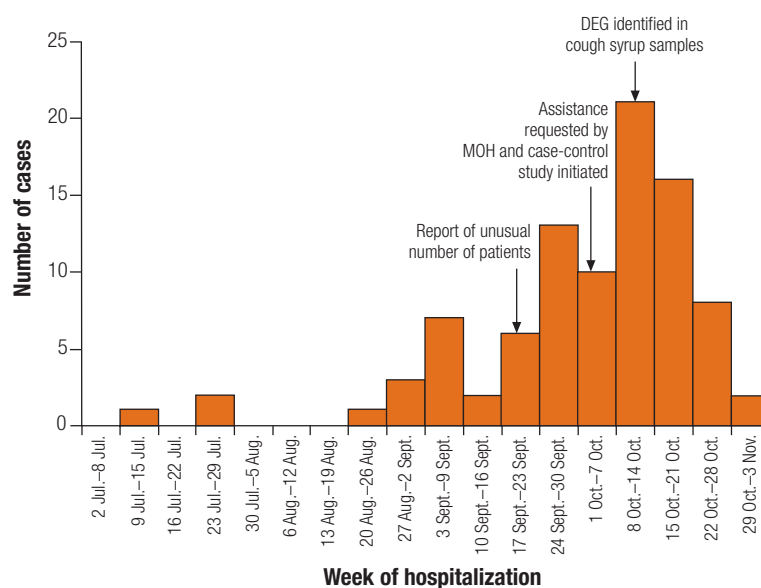
### Statistical analysis

Questionnaire data were analysed using SAS, version 9.1, statistical software (SAS Institute Inc., Cary, NC, USA). For categorical covariates, the distributions of descriptive statistics were compared between cases and controls; for continuous covariates, the means were compared. Crude and adjusted odds ratios were estimated using two sets of exact conditional logistic regression models, which represented both the open-ended and direct questions about the main exposure. Crude odds ratios (ORs) and their associated 95% confidence intervals (CIs) were calculated for exposure-related outcomes, as well as for potential risk factors. Adjusted odds ratios (AORs) and 95% CIs were calculated to control for confounding by risk factors that were significantly associated with the exposure.

### Results

Forty-two case patients and 140 control patients were enrolled in the study. Overall, 76.2% of case interviews and 12.1% of control interviews were conducted using proxies. Some patients presented to Hospital A with acute renal failure as early as July 2006, but the peak time for admission was in mid October 2006 (Fig. 1). Table 1 lists the descriptive characteristics of case and control patients. The majority of cases and controls were male (64.3% and 58.6%, respectively) and aged 55 years or older (80.9% and 82.1%, respectively). Most case and control patients resided in the Metropolitana region (38.0% and 49.3%, respectively). Case patients, in comparison with control patients, more often self-reported general (81.0% versus 71.4%), gastrointestinal (85.7% versus 38.6%), respiratory (64.3% versus 40.0%), urinary (81.0% versus 10.0%) or neurological (83.3% versus 51.4%) signs and symptoms. Control patients self-reported twice as many symptoms in the 3 months be-

Fig. 1. Number of patients admitted with acute renal failure due to DEG poisoning in Panama, from 2 July 2006 to 3 November 2006



DEG, diethylene glycol; MOH, Ministry of Health.

fore hospitalization as did case patients (mean: 8.5 versus 4.0). The mean serum creatinine level was much higher in case patients than in control patients (11.1 mg/dl versus 1.4 mg/dl).

Table 2 presents the frequency of potential risk factors in case and control patients. Case patients, compared with control patients, more often self-reported diabetes (35.7% versus 28.6%), hypertension (71.4% versus 54.3%), renal disease (28.6% versus 13.6%) and cardiovascular disease (33.3% versus 27.9%). Hypertension was the most common self-reported pre-existing condition among case and control patients. Case patients were significantly more likely than controls to have taken prescribed ACE inhibitors (OR: 5.39, 95% CI: 2.39–12.2) and to have reported pre-existing hypertension (OR: 2.75, 95% CI: 1.13–6.71) or renal disease (OR: 2.49, 95% CI: 1.04–5.99).

When asked to recall all prescription medications consumed, 40.5% of cases and 2.9% of controls listed prescription liquid cough syrup. However, when asked directly about the consumption of liquid syrups, 90.2% of cases and 20.9% of controls reported the use of prescription liquid cough syrup (Table 3). Consumption of prescription liquid cough syrup was significantly associated with the onset of acute renal failure for both open-ended (OR: 13.1, 95% CI: 3.92–43.6) and

direct (OR: 37.3, 95% CI: 8.82–158) questioning. These estimates changed little after controlling for pre-existing hypertension, pre-existing renal disease and the use of ACE inhibitors.

The mean concentration of DEG in cough syrup samples from a single lot of Panamanian-produced prescription liquid cough syrup obtained from patients was  $8.1\% \pm 1.0\%$ . Cough syrup samples that had the same lot number as the contaminated medications obtained from the manufacturer and found to have a DEG content of  $7.6\% \pm 0.2\%$ . Raw material labelled as glycerin and obtained from the pharmaceutical manufacturer, and purportedly used in the formulation of the cough syrup, contained  $22.2\% \pm 0.8\%$  DEG.

In addition, there was a significant difference in urinary DEG level between cases and controls ( $P < 0.001$ ). The urinary DEG level ranged from 50–4000 ng/ml in cases, whereas DEG was undetectable in controls.

### Discussion

This case-control study investigated the largest known DEG mass poisoning of adults in the past 70 years. Epidemiological and laboratory findings implicated a prescription liquid cough syrup, produced by a CSS hospital pharmaceutical manufacturing facility, as the cause of the outbreak in

Panama. The presence of DEG was finally confirmed in a single lot number of a product that was labelled as glycerin and that was imported to Panama from China via a European broker. The contaminated glycerin identified in the implicated cough syrup had also been used in the production of at least one other prescription liquid medication and two prescription topical creams. These findings led to the recall of over 60 000 medications presumed to be contaminated by DEG and to wide-spread screening for renal dysfunction in potentially exposed consumers. By April 2007, 119 official case patients had been identified, of who 78 died despite haemodialysis and supportive care (case fatality rate 65.5%). Cardiac arrest, shock and cardiac arrhythmia were the most common causes listed for these deaths.

In addition, 20% of control patients reported consuming the prescription liquid cough syrup. However, these patients did not develop symptoms consistent with our case definition. There are several possible explanations for this finding. First, because liquid syrups are ubiquitous in Panamanian culture and used for a variety of ailments, those who reportedly consumed liquid cough syrup could have actually consumed a different type of liquid syrup. Second, control patients might have consumed prescription liquid cough syrup from a different lot, which was not contaminated with DEG. These potential misclassifications of exposure and outcome would bias our results towards an acceptance of the null hypothesis.<sup>13</sup> Finally, it is plausible that these individuals did consume contaminated syrup but did not consume a large enough dose to develop acute renal failure or were not compromised by having an existing illnesses. Although data were collected from case and control patients on the frequency and quantity of contaminated syrup consumption, the data were not complete and did not allow us to calculate a minimum toxic dose in this study.

It is difficult to determine the magnitude of this outbreak. The Ministry of Health of Panama reported that over 60 000 bottles of the prescription cough syrup had been distributed, yet only 119 official cases were identified. Given the severity of the illness and the case fatality rate among the

Table 1. Descriptive characteristics of case patients with acute renal failure and control patients, Panama 2006

Characteristic	Cases (N = 42)		Controls (N = 140)	
	n	%	n	%
<b>Sex</b>				
Female	15	35.7	58	41.4
Male	27	64.3	82	58.6
<b>Age (years)</b>				
18–24	0	–	2	1.4
25–34	4	9.5	8	5.7
35–44	1	2.4	2	1.4
45–54	3	7.1	13	9.3
55–64	8	19.0	45	32.1
65–74	14	33.3	36	25.7
≥ 75	12	28.6	34	24.3
<b>Region of residence</b>				
Cocle	7	16.7	4	2.9
Colon	1	2.4	5	3.6
Herrera	1	2.4	6	4.3
Los Santos	0	–	3	2.1
Metropolitana	16	38.0	69	49.3
Panama Este	0	–	2	1.4
Panama Oeste	5	11.9	21	15.0
San Miguelito	10	23.8	28	20.0
Veraguas	2	4.8	2	1.4
<b>Symptoms<sup>a</sup></b>				
General	34	81.0	100	71.4
Gastrointestinal	36	85.7	54	38.6
Respiratory	27	64.3	56	40.0
Urinary	34	81.0	14	10.0
Neurological	35	83.3	72	51.4
<b>Proxy interview</b>	32	76.2	17	12.1
<b>Variable</b>				
	<b>Mean</b>	<b>Standard deviation</b>	<b>Mean</b>	<b>Standard deviation</b>
Age (years)	65.2	16.6	63.6	14.7
Number of symptoms	4.0	3.9	8.5	5.0
Serum creatinine level (mg/dl)	11.1	5.2	1.4	1.8

<sup>a</sup> General symptoms included self-reported fever, headache, loss of appetite, tiredness, dizziness, muscle pain and joint pain. Gastrointestinal symptoms included self-reported vomiting, nausea, diarrhoea, stomach pain and epigastric discomfort. Respiratory symptoms included self-reported cough, shortness of breath and expectoration. Urinary symptoms included self-reported oliguria and anuria. Neurological symptoms included self-reported difficulty in speaking, numbness, paralysis, weakness, loss of tactile sensation, loss of consciousness, convulsion, difficulty in swallowing and facial muscle weakness.

case patients in this investigation, it is surprising that more cases were not discovered. There is concern that there may have been a number of seriously ill exposed individuals who did not come into contact with the medical system. It is also hypothesized that some DEG-related deaths may have occurred before recognition of the outbreak. To address this issue, retrospective case-finding is now being carried out by the Panama-

nian government to identify individuals who were diagnosed with Guillain-Barré syndrome or acute renal failure within a timeframe that coincides with the distribution of the contaminated lot of cough syrup. Another consideration is that the minimum toxic dose of DEG is not well established. Therefore, there may be thousands of people who were exposed to the contaminated syrup but who displayed only minor symptoms

and did not develop acute renal failure or even seek medical care.

Little is known about the pathophysiology of DEG toxicity. However, the underlying mechanisms are thought to be similar to those involved in ethylene glycol (EG) poisoning. Ethylene glycol is a primary ingredient in antifreeze and the pathophysiology of EG poisoning is well documented.

Consumption of products containing either DEG or EG can produce increased serum osmolality, metabolic acidosis and acute renal failure.<sup>9,14–19</sup> Increased serum osmolality and an elevated osmolal gap are observed within hours after acute ingestion, when blood concentrations of these compounds are high. Serum osmolality typically decreases as the parent compound is quickly metabolized or eliminated, or both. Diethylene glycol has a less pronounced effect on serum osmolality due to its higher molecular weight and typically smaller ingested dose.

In EG ingestion, metabolic acidosis can result from the formation of intermediary acid metabolites (i.e. glycolate and oxalate) by metabolism of the parent compound and also from lactate acidosis.<sup>20</sup> Therapeutic interventions for EG poisoning, such as fomepizole, work by blocking metabolism of the parent compound.<sup>18</sup> Acute renal failure in EG poisoning is due to the precipitation of calcium oxalate crystals in the tubular lumen. Understanding of these pathways is considerably less

Table 2. Frequency of potential risk factors and odds ratios for the onset of acute renal failure for these risk factors in case and control patients, Panama 2006

Potential risk factor	Cases (N = 42)		Controls (N = 140)		Odds ratio <sup>a</sup> (95% CI)
	n	%	n	%	
<b>Any pre-existing condition</b>					
Diabetes	15	35.7	40	28.6	1.62 (0.75–3.50)
Hypertension	30	71.4	76	54.3	<b>2.75 (1.13–6.71)</b>
Renal disease	12	28.6	19	13.6	<b>2.49 (1.04–5.99)</b>
Cardiovascular	14	33.3	39	27.9	1.23 (0.56–2.70)
Other	13	31.0	51	36.4	0.76 (0.36–1.61)
<b>Any ACE inhibitor<sup>b</sup></b>					
Yes	26	61.9	34	24.3	<b>5.39 (2.39–12.2)</b>
No	16	38.1	106	75.7	Referent

ACE, angiotensin-converting enzyme; CI, confidence interval.

<sup>a</sup> Statistically significant findings are in **boldface** type.

<sup>b</sup> ACE inhibitors examined included enalapril, ramipril and lisinopril.

clear in DEG poisoning,<sup>21</sup> although data from animal studies indicate that there exist metabolic pathways similar to those observed with EG.<sup>22–24</sup> Calcium oxalate crystalluria has not been reported in human DEG poisoning; however, it has variably been induced experimentally.<sup>25,26</sup> Although oxalate is produced in a lower proportion in DEG poisoning, it is not the obvious cause of renal toxicity.<sup>25</sup> Though information is limited, experience with a few experimental and therapeutic interventions suggests that blocking the formation of metabolites, as is done in cases of EG poisoning, could be helpful in treating DEG poisoning.<sup>24,27,28</sup>

Despite DEG being chemically similar to EG, there are some notable differences in the neurological manifestations of poisoning. Peripheral neuropathy is unusual in EG poisoning,<sup>29</sup> but both cranial and somatic peripheral neuropathies have been described following DEG poisoning.<sup>9,15,16</sup> These findings have been attributed to, alternatively, a predominantly axonal or demyelinating process.<sup>15,16,30</sup> Of note, peripheral neuropathy and cranial neuropathies, and specifically bilateral facial nerve involvement, were particularly prominent in the majority of the Panamanian case patients. As these neuropathies are often delayed by several days,<sup>15</sup> the longer survival period of these patients probably allowed these delayed-onset neurological features to become clinically apparent. Encephalopathy has also been reported in both EG and DEG toxicity and was observed in several of the Panamanian case patients. Initial but limited histopathological assessment of central nervous system tissue from DEG patients with encephalopathy was notable for the lack of evidence of inflammation or significant demyelination.<sup>16</sup> The mechanism of neurological toxicity in encephalopathy and peripheral neuropathy associated with DEG remains unclear.<sup>9,15,16</sup>

Epidemiological data identified a predominance of older case patients with co-morbidities such as pre-existing renal insufficiency, hypertension or diabetes. Individuals with baseline renal insufficiency or a chronic disease

Table 3. Responses to open-ended and direct questions about the ingestion of prescription liquid cough syrup and odds ratios for the onset of acute renal failure for affirmative responses in case and control patients, Panama 2006

Response	Cases (N = 42)		Controls (N = 140)		Crude odds ratio <sup>a</sup> (95% CI)	Adjusted odds ratio <sup>a,b</sup> (95% CI)
	n	%	n	%		
<b>Open-ended question</b>						
Yes	17	40.5	4	2.9	<b>13.1 (3.92–43.6)</b>	<b>11.1 (3.17–39.0)</b>
No	25	59.5	136	97.1	Referent	Referent
<b>Direct question<sup>c</sup></b>						
Yes	37	90.2	29	20.9	<b>37.3 (8.82–158)</b>	<b>31.0 (6.93–139)</b>
No	4	7.3	110	79.1	Referent	Referent

CI, confidence interval.

<sup>a</sup> Statistically significant findings are in **boldface** type.

<sup>b</sup> Adjusted model controlled for pre-existing hypertension, pre-existing renal disease and the use of angiotensin-converting enzyme inhibitors, including enalapril, lisinopril and ramipril.

<sup>c</sup> One case patient who was unsure about the consumption of liquid syrups was coded as missing.

that has an impact on intrinsic renal dysfunction may be more susceptible to the nephrotoxic effect of DEG. These individuals are probably more likely to develop clinical symptoms when exposed. It is also plausible that seemingly vulnerable subpopulations with pre-existing renal disease or hypertension would also be more likely to take lisinopril or another ACE inhibitor. Lisinopril was a first-line antihypertensive medication prescribed within the CSS hospital system. Moreover, ACE inhibitors are indicated for hypertensive patients at risk of renal disease. These factors may help to explain the statistically significant relationship between taking an ACE inhibitor and the development of renal failure. In addition, ACE inhibitors are known to cause a dry irritating cough.<sup>31</sup> Therefore, it is possible that CSS patients taking lisinopril or another ACE inhibitor were more likely to be prescribed the implicated cough syrup.

The results of this investigation reinforce the lesson that DEG toxicity remains a global health threat and

should be an early consideration when an unusual number of people seek treatment for unexplained acute renal failure. During this investigation, analytical methods for detecting DEG in urine samples were developed. These methods enable DEG to be identified rapidly in instances where specific pharmaceuticals are not clearly implicated. This investigation also re-emphasized the fact that outbreaks of DEG-related illness are not limited to the paediatric population. Though the largest outbreaks have been among children,<sup>2,6,7,9,10</sup> half of DEG-related outbreaks have occurred among adults.<sup>2,4,5,8</sup> Finally, despite efforts to raise public awareness, mass poisoning by DEG will remain a public health threat unless individual countries are willing to develop and adhere to regulations governing the manufacturing of pharmaceuticals and the chemicals used in their production. ■

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## Résumé

### Flambée d'insuffisance rénale aiguë au Panama en 2006: étude cas-témoin

**Objectif** En septembre 2006, un médecin panaméen a signalé un nombre inhabituel d'insuffisances rénales aiguës inexpliquées, s'accompagnant fréquemment d'un dysfonctionnement neurologique sévère. Douze (57 %) des 21 malades sont morts de cette insuffisance. Le présent article décrit l'enquête réalisée sur les causes de la maladie et l'origine de la flambée épidémique.

**Méthodes** Une étude cas-témoin et des investigations en laboratoire ont été menées. Les cas (personnes présentant une insuffisance rénale aiguë d'étiologie inconnue et un taux de créatinine sérique  $\geq 2$  mg/dl) ont été appariés individuellement à des témoins hospitalisés en fonction de l'âge ( $\pm 5$  ans), du sexe et de la date d'admission (2 jours au plus avant la déclaration du cas ou plus tard). Un questionnaire et des données biologiques ont été recueillis. La principale mesure de résultat était l'odds ratio de la prise de sirop antitussif sur prescription par les cas et les témoins.

**Résultats** Quarante-deux cas et 140 témoins ont été inclus dans l'étude. L'âge médian des cas était de 68 ans (plage de

variation : 25-91 ans) et 64 % d'entre eux étaient des hommes. Après ajustement pour une hypertension ou une pathologie rénale préexistante et pour l'utilisation d'inhibiteurs de l'enzyme de conversion de l'angiotensine, une association importante a été relevée entre la prise de sirop antitussif soumis à prescription et l'apparition de la maladie (odds ratio ajusté : 31,0, intervalle de confiance à 95 % : 6,93 - 138). Les analyses de laboratoire ont confirmé la présence de diéthylène glycol (DEG) dans les échantillons biologiques provenant des cas, un taux de contamination par le DEG de 8 % des échantillons de sirop pour la toux et un taux de contamination de 22 % de la glycérine ayant servi à préparer ce sirop.

**Conclusion** L'origine de la flambée était un sirop antitussif contaminé par du DEG. Les investigations ont conduit au rappel d'environ 60 000 flacons de sirop contaminé, à un dépistage à grande échelle des consommateurs potentiellement exposés et au traitement de plus de 100 patients touchés.

## Resumen

### Brote de insuficiencia renal aguda en Panamá en 2006: estudio de casos y controles

**Objetivo** En septiembre de 2006, un médico panameño notificó un número inhabitual de pacientes aquejados de insuficiencia renal aguda idiopática, asociada con frecuencia a disfunción neurológica grave. Doce (57%) de 21 pacientes habían muerto a causa de la enfermedad. Se describe aquí la investigación

realizada para determinar la causa de la enfermedad y la fuente del brote.

**Métodos** Se llevaron a cabo estudios de casos y controles e investigaciones de laboratorio. Los pacientes objeto de estudio (con insuficiencia renal aguda de origen desconocido y creatinina

sérica  $\geq 2$  mg/dl) fueron apareados individualmente con pacientes control hospitalizados considerando la edad ( $\pm 5$  años), el sexo y la fecha de ingreso ( $\leq 2$  días antes o después del ingreso del paciente estudiado). Se recopilaron datos de cuestionarios y datos biológicos. El criterio principal de valoración fueron las posibilidades de casos y controles de haber tomado jarabe contra la tos de venta con receta.

**Resultados** Participaron en el estudio 42 casos y 140 controles. La mediana de la edad de los casos fue de 68 años (intervalo: 25–91 años); el 64% eran varones. Tras determinar si los pacientes presentaban una historia previa de hipertensión y nefropatía y de uso de inhibidores de la enzima convertidora de la angiotensina, se detectó una relación significativa entre la

ingestión de jarabe antitusígeno y la aparición de la enfermedad (razón de posibilidades (OR) ajustada: 31,0, intervalo de confianza del 95%: 6,93–138). Los análisis de laboratorio confirmaron la presencia de dietilenglicol (DEG) en las muestras biológicas de los pacientes estudiados, con una contaminación por DEG del 8% en las muestras de jarabe y del 22% en la glicerina utilizada para preparar dicho jarabe.

**Conclusión** La fuente del brote fue el jarabe antitusígeno contaminado por DEG. Esta investigación llevó a retirar aproximadamente 60 000 frascos del jarabe contaminado, realizar un amplio cribado de los consumidores potencialmente expuestos, y tratar a más de cien pacientes afectados.

## ملخص

### نفشي الفشل الكلوي الحاد في بنما عام 2006: دراسة للحالات والشواهد

وكان متوسط أعمار ذوي الحالات 68 عاماً (المدى: 25 – 91 عاماً)، 64% منهم من الذكور. وبعد التضييق من حيث فرط الضغط الموجود قبلياً، والإصابة بمرض كلوي، واستخدام مثبطات للإنزيم المحول للأنجيوتنسين، تبين وجود ارتباط يعتقد به إحصائياً بين تناول شراب السعال الموصوف، وبدء ظهور العلة (نسبة الأرجحية المعدلة 31.0، بفواصل ثقة 6.93-139). وأكدت التحاليل المختبرية وجود غليكول ثنائي الإيثيلين في العينات البيولوجية المأخوذة من المرضى ذوي الحالات، ووجد تلوث بغليكول ثنائي الإيثيلين في 8% من عينات شراب السعال، وتلوث في الغليسرين المستخدم في تحضير هذا الشراب، في 22% من العينات.

**الاستنتاج:** كان شراب السعال الملوث بغليكول ثنائي الإيثيلين هو مصدر الفاشية. وقد أدى هذا الاستقصاء إلى استدعاء حوالي 60 000 زجاجة من شراب السعال الملوث، وإجراء تحر واسع النطاق للأشخاص الذين يحتمل استهلاكهم لهذا الدواء ومعالجة أكثر من 100 من المرضى المصابين.

**الغرض:** أبلغ طبيب بنمي، في أيلول/سبتمبر 2006، عن إصابة عدد غير عادي من المرضى بفشل كلوي حاد غير معروف السبب، صحبه، على نحو متكرر، خلل عصبي وخيم، حيث توفي اثنا عشر مريضاً (57%) من بين 21 مريضاً، جراء هذه العلة. ويقدم هذا البحث وصفا للاستقصاء الذي جرى للتعرف على سبب هذه العلة، ومصدر الفاشية.

**الطريقة:** أجريت استقصاءات على المرضى ذوي الحالات، والشواهد، واستقصاءات أخرى مختبرية. وتمت مضاهاة المرضى ذوي الحالات (المصابين بالفشل الكلوي الحاد الغير معروف السبب، ولديهم نسبة كرياتينين في المصل مقدارها 2 مغم/ديسيلتر أو أكثر)، كل على حدة، مع الشواهد الذين أدخلوا إلى المستشفى، من حيث العمر ( $\pm$  خمس سنوات)، والجنس، وتاريخ الدخول للمستشفى (قبل مريض الحالة بيومين أو أقل)، كما أجري استبيان وجمعت بيانات بيولوجية حول ذلك. وكان المقياس الرئيسي للنتائج هو أرجحية تناول كل من المرضى ذوي الحالات، والشواهد، لشراب موصوف للسعال.

**النتائج:** اشترك في هذه الدراسة 42 من ذوي الحالات و140 من الشواهد.

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