Risk of hypertension and reduced kidney function after acute gastroenteritis from bacteria-contaminated drinking water

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Abstract

Background: The long-term health consequences of acute bacterial gastroenteritis remain uncertain. We studied the risk of hypertension and reduced kidney function after an outbreak of acute gastroenteritis due to contamination of a regional drinking water supply with *Escherichia coli* O157:H7 and *Campylobacter* species.

Methods: A total of 1958 adults with no known history of hypertension or kidney disease before the outbreak participated in a long-term follow-up study. Of the participants, 675 had been asymptomatic during the outbreak, 909 had had moderate symptoms of acute self-limited gastroenteritis, and 374 had had severe symptoms that necessitated medical attention. The outcomes of interest were a diagnosis of hypertension or the presence of reduced kidney function and albuminuria during the follow-up period.

Results: After a mean follow-up of 3.7 years after the outbreak, hypertension was diagnosed in 27.0% of participants who had been asymptomatic during the outbreak and in 32.3% and 35.9% of those who had had moderate and severe symptoms of acute gastroenteritis respectively (trend $p = 0.009$). Compared with the asymptomatic participants, those with moderate and severe symptoms of gastroenteritis had an adjusted relative risk of hypertension of 1.15 (95% confidence interval [CI] 0.97–1.35) and 1.28 (95% CI 1.04–1.56) respectively. A similar graded association was seen for reduced kidney function, defined as the presence of an estimated glomerular filtration rate below 60 mL/min per 1.73 m^2 (trend $p = 0.03$). No association was observed between gastroenteritis and the subsequent risk of albuminuria.

Interpretation: Acute bacterial gastroenteritis necessitating medical attention was associated with an increased risk of hypertension and reduced kidney function 4 years after infection. Maintaining safe drinking water remains essential to human health, as transient bacterial contaminations may have implications well beyond a period of acute self-limited illness.

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Acute bacterial dysentery is a global health concern, particularly in developing countries.[1] *Escherichia coli* O157:H7 and *Campylobacter jejuni* infections may have long-term health consequences beyond the period of acute illness.[2–5] Receptors for *E. coli* O157:H7 Shiga toxin are found in the kidney. Exposure to this pathogen may result in substantial loss of nephrons and subsequent hyperfiltration, which can lead to long-term systemic hypertension and reduced kidney function.[6–8] The most toxic form of *E. coli* O157:H7 infection is hemolytic uremic syndrome, and the potential for long-term renal dysfunction and hypertension after this condition is well described.[2] It is unknown whether bacterial gastroenteritis in the absence of recognized hemolytic uremic syndrome may lead to clinically important long-term renal sequelae. We evaluated the long-term risk of hypertension and reduced kidney function among previously healthy adults following an outbreak of acute gastroenteritis due to the bacterial contamination of a regional water supply in Ontario.

Methods

The methods of this follow-up study have been described elsewhere,[9,10] and a full description is available at www.cmaj.ca/cgi/content/full/172/3/261.

In brief, the municipal water supply in Walkerton, a small rural town in Ontario, became contaminated with bacteria, predominantly *E. coli* O157:H7 and *Campylobacter* species, in May 2000. Heavy rainfall had contributed to the surface transport of livestock fecal contaminants into inadequately chlorinated drinking water, supplied from a shallow well.[11] Over 2300 people became ill with acute gastroenteritis, 27 cases of hemolytic uremic syndrome were identified, and there were 6 deaths.[12] Being the most serious case of water contamination in recent North American history, this event attracted world-wide media attention and sparked public concern about the safety of drinking water.[13]

Following the outbreak, we invited all people who either lived in the Walkerton area or who had consumed municipal water at the time of the outbreak to attend a clinic and participate in a long-term follow-up study. We asked each of the participants to attend an annual clinic visit 2, 3 and 4 years after the initial outbreak, to complete a standardized questionnaire, undergo a physical examination and provide blood and urine specimens.

Of the 4496 participants, we excluded those less than 18 years of age (n = 1073), because thresholds for hypertension in children differ from those in adults.[14] In addition, we excluded adults with a history of chronic gastrointestinal symptoms (n = 298), hypertension (n = 919), kidney disease (n = 752) or diabetes mellitus (n = 251) present before the outbreak (these conditions were not mutually exclusive; see Appendix 1 in the full-text online version of the article [at www.cmaj.ca/cgi/content/full/173/3/261] for the method of assessment of these conditions). Thus, 1958 adults were included in our analysis.

We divided the participants into 3 groups according to the presence and severity of acute gastroenteritis at the time of the outbreak: (a) "none" included participants who had been asymptomatic during the outbreak; (b) "moderate symptoms" included those who had had moderate symptoms of acute self-limited gastroenteritis, which could neither be confirmed nor refuted by prior health records because the participant had not sought medical attention; and (c) "severe symptoms" included those who had had severe symptoms of acute gastroenteritis that necessitated medical attention. Participants with severe symptoms were more likely than those with moderate symptoms to describe bloody diarrhea (40% v. 18%, $p < 0.001$), prolonged diarrhea (70% v. 53%, $p < 0.001$) and fever (50% v. 33%, $p < 0.001$) (Table 1). Forty-nine percent of the participants with severe symptoms had visited an emergency department, where cases of gastroenteritis had been treated conservatively (Table 1).

Table 1: Characteristics of study participants before and during an outbreak of acute gastroenteritis from bacteria-contaminated drinking water

Characteristic	Acute gastroenteritis during outbreak; % of participants*		
	None *n = 675*	Moderate symptoms *n = 909*	Severe symptoms *n = 374*
White	99	99	98
Female	54	51	58
Age at time of outbreak, mean (SD), yr	40 (16)	38 (16)	37 (15)
Before outbreak			
Medical history			
Arthritis	15	16	18
Gallstones	4	5	8
Tobacco smoking	22	29	30
Elevated cholesterol level	9	7	8
Prior myocardial infarction	0.7	0.3	0.3
Prior stroke	0.3	0.4	0.3
First-degree relative with hypertension	36	37	37
Medical check-up during year before outbreak	59	57	64
Body mass index, mean (SD), kg/m^2	27 (6)	27 (6)	27 (6)
Serum creatinine level, mean (SD), µmol/L†	79 (15)	77 (15)	77 (15)
Fasting blood glucose level, mean (SD), mmol/L†	5.1 (0.6)	5.1 (0.4)	5.1 (0.5)
During outbreak			
Drank from contaminated water source	98	100	100
Self-reported symptoms‡			
Diarrhea			
Duration, median, d	–	4–5	6–7
≥ 4 stools per day for ≥ 3 d	–	53	70
Bloody diarrhea	–	18	40
Abdominal pain	–	87	92
Fever	–	33	50
Documented use of health care services			
Visited an emergency department	–	0	49
Admitted to hospital	–	0	5
Stool culture performed§	0.3	0.3	40
Positive for *Escherichia coli* O157:H7 only	0	0	14
Positive for *Campylobacter* only	0	0	17
Positive for both bacteria	0	0	2

Note: SD = standard deviation.
*Unless stated otherwise.
†Complete data were available for all participants except serum creatinine and fasting blood glucose levels before the outbreak, which were available for 30% and 23% of the participants respectively.
‡Symptoms were recalled by participants over 2 years after the outbreak.
§Positive culture results were reported as a percentage of participants who had a culture performed.

The primary study outcome was a diagnosis of hypertension. Blood pressure was measured by trained study personnel at a single clinic, using a validated method.[14] The mean of 3 measurements was obtained for each visit. In the absence of diabetes mellitus or renal impairment, hypertension was defined by a mean systolic blood pressure of 140 mm Hg or a mean diastolic blood pressure of 90 mm Hg at any follow-up visit.[14] For participants with an estimated GFR below 60 mL/min per 1.73 m^2, a level of protein in a 24-hour collection of urine of 300 mg/d, a random urine albumin:creatinine ratio of 22.6 mg/mmol (200 mg/g) or diabetes mellitus, hypertension was defined by a mean systolic blood pressure of 130 mm Hg or a mean diastolic blood pressure of 80 mm Hg.[14] During the course of follow-up, a participant was also considered to have hypertension if he or she received a prescription for antihypertensive therapy from a physician not involved in the study.

The secondary study outcomes included the presence of reduced kidney function and micro- or macroalbuminuria.

All participants provided written informed consent. In 2002, both the University of Western Ontario Research Ethics Board and the Kidney Foundation of Canada Scientific Committee approved the current study protocol.

Results

The characteristics of the study participants before and during the outbreak are presented in Table 1. Of the 1958 participants, 675 had no acute symptoms, 909 had moderate symptoms of gastroenteritis and 374 had severe symptoms. The characteristics of the participants before the outbreak were similar across the 3 groups except for smoking status: fewer asymptomatic participants were smokers (22% v. 29% and 30%, $p = 0.003$) (Table 1).

Participants were followed for a mean of 3.7 (standard deviation 0.7) years after the outbreak. Overall, 86%, 72% and 75% of the participants returned for annual clinic visits 2, 3 and 4 years after the outbreak, respectively, with no difference in these rates across the 3 symptom groups ($p = 0.64$).

Hypertension

A total of 492 participants received a diagnosis of hypertension after the outbreak, for an age- and sex-standardized rate of 31.1% over the 3.7 years of follow-up. In most cases (83%), the hypertension was diagnosed only on the basis of blood pressure measurements taken by the study personnel; in 13% of cases, the participant had elevated blood pressure measurements recorded at the study clinic despite having been prescribed antihypertensive therapy after the outbreak; and in the remaining 4% of cases, the participant had normal blood pressure measurements recorded at the study clinic after having begun antihypertensive therapy by their primary physician.

A new diagnosis of hypertension was made more frequently among patients who had moderate or severe symptoms than among those who were asymptomatic (Fig. 1). Compared with the asymptomatic participants, those with moderate and severe symptoms of gastroenteritis had an adjusted relative risk of a new diagnosis of hypertension of 1.15 (95% confidence interval [CI] 0.97–1.35) and 1.28 (95% CI 1.04–1.56) respectively (see Table 2 in the full-text online version of the article at www.cmaj.ca/cgi/content/full/173/3/261).

Among the 1535 participants who attended at least 2 annual study clinic visits, where evidence of hypertension was required on 2 separate occasions, we found that newly diagnosed hypertension was diagnosed in 234 of them, for an age- and sex-standardized rate of 19.4%. The rates were 17.6%, 18.7% and 25.4% among those with no symptoms, moderate gastroenteritis and severe gastroenteritis, respectively ($p = 0.01$). Compared with the asymptomatic participants, those with moderate and severe symptoms had an adjusted relative risk of a subsequent diagnosis of hypertension of 1.02 (95% CI 0.79–1.32) and 1.49 (95% CI 1.12–1.98) respectively.

Among the 1049 participants who attended all 3 annual clinic visits and who were normotensive at their first visit, 11 were found to have hypertension at both subsequent visits. The respective rates of newly diagnosed hypertension were 0.16%, 1.26% and 1.86% among those with no symptoms, moderate symptoms and severe symptoms of gastroenteritis respectively ($p = 0.04$).

Among the participants who had no symptoms of gastroenteritis at the time of the outbreak, the mean systolic blood pressure at their last visit, adjusted for age and sex, was 123 mm Hg; the values were significantly higher among those with moderate gastroenteritis (126 mm Hg) and severe gastroenteritis (127 mm Hg) ($p = 0.009$). The respective diastolic blood pressures were 72, 74 and 74 mm Hg ($p = 0.03$).

Reduced kidney function and albuminuria

At the last follow-up visit, 38 of the participants were found to have reduced kidney function, of whom 37 had a GFR between 30 and 60 mL/min per 1.73 m^2 and 1 had a GFR below 30 mL/min per 1.73 m^2. None had end-stage kidney failure. The age- and sex-standardized rate of newly diagnosed reduced kidney function was 4.3% over the 3.7 years of follow-up and was more frequent among patients with symptoms than among those who were asymptomatic (Fig. 2). However, there was no statistical difference between the groups in the mean GFR ($p = 0.19$), the mean random urine albumin:creatinine ratio ($p = 0.57$) or the age- and sex-standardized rates of newly diagnosed micro- or macroalbuminuria ($p = 0.71$) (see Table 3 in the full-text online version of the article at www.cmaj.ca/cgi/content/full/173/3/261).

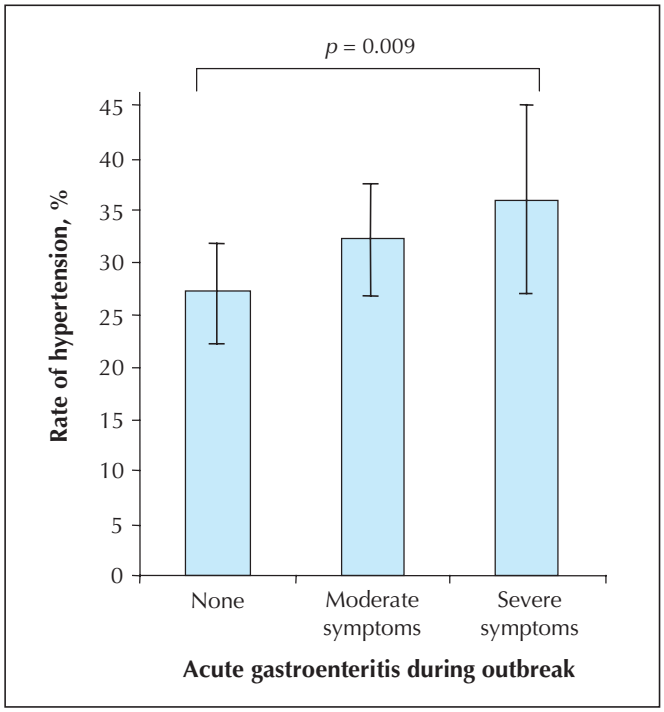

Fig. 1: Age- and sex-standardized rates of newly diagnosed hypertension a mean of 3.7 years after an outbreak of acute gastroenteritis from bacteria-contaminated drinking water. Error bars represent 95% confidence intervals.

Interpretation

Nearly 4 years after a major outbreak of acute gastroenteritis from drinking water contaminated with *E. coli* O157:H7 and *Campylobacter* bacteria, we observed a relative increase of 33%, or an absolute increase of 9%, in the rate of newly diagnosed hypertension among participants who had experienced severe gastroenteritis during the outbreak. Those who had had acute gastroenteritis had systolic and diastolic blood pressures that were 2 to 4 mm Hg higher than the measurements of participants who had remained asymptomatic during the outbreak. Increased rates of hypertension after bacterial gastroenteritis were also accompanied by evidence of reduced kidney function.

In the general population, the cause of hypertension is multifactorial, influenced by genetic predisposition, diet and lifestyle choices, in addition to any predilection from early kidney damage. We hypothesize that acute enteropathic *E. coli* and *Campylobacter* infection may establish a state of chronic inflammation in some people, which could have a number of long-term health consequences.[15,16] In addition, those who were acutely ill during the outbreak may have been under the most duress, and detailed psychological assessment may help elucidate the importance of stress as a hypertension mediator.[17,18] Biological experiments and human observational studies emphasize the risk of long-term renal sequelae after recovery from hemolytic uremic syndrome, the most toxic form of acute *E. coli* O157 infection.[2,6,8,19–22] In the current study, we examined the incidence of long-term renal complications after *E. coli* O157:H7 gastroenteritis, which in some people could be the result of subclinical or unrecognized hemolytic uremic syndrome.[23]

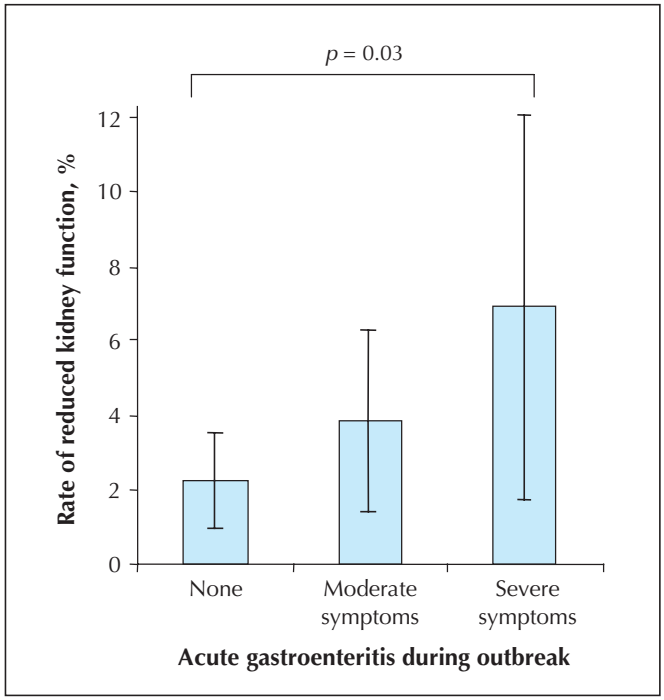

Fig. 2: Age- and sex-standardized rates of newly diagnosed reduced kidney function (defined as glomerular filtration rate < 60 mL/min per 1.73 m^2) a mean of 3.7 years after an outbreak of acute gastroenteritis from bacteria-contaminated drinking water. Error bars represent 95% confidence intervals.

Large outbreaks of water-borne infections are extremely rare in Western nations. The willingness of the residents in the local community to participate in our study enabled us to obtain detailed information and measurements about their previous and current health. There may never again be an opportunity to systematically study the long-term effects of such a potentially serious widespread outbreak. However, the circumstances surrounding this unique outbreak require the results to be interpreted judiciously.

The number of participants in our study who subsequently had reduced kidney function was small, which limited our ability to conduct relevant multivariate and sensitivity analyses. In addition, the mean estimated GFR and mean random urine albumin:creatinine ratio were not appreciably different after the bacterial gastroenteritis, which suggests that the risk of overt renal disease is not clear. Given the protracted course of most cases of progressive renal disease, a longer follow-up of this cohort could clarify the risk of nephropathy after gastroenteritis due to *E. coli* O157.[24–26]

Both *E. coli* O157 and *Campylobacter* bacteria were present in the drinking water supply, and objective evidence of coinfection was present in some stool cultures. We considered gastroenteritis as a single entity attributable to both pathogens. Although additional analyses may have discerned the rate of hypertension according to stool culture results, the small number of routinely collected specimens at the time of the outbreak limited our ability to do so.

The cohort was assembled 2 years after the outbreak. Selection bias may have influenced the study results, although a previous analysis suggested that any such selection would bias toward demonstrating no association between acute gastroenteritis and long-term sequelae.[9]

Our data collection after the outbreak depended in part on each participant's ability to recall their health status at the time of the outbreak, which may have been more than 2 years earlier. People seeking financial compensation may be prone to recall acute symptoms that in truth were absent.[27] Such misclassification would minimize any true association between acute gastroenteritis and biologically plausible long-term health sequelae. To guard against such a bias, we established a group with self-reported symptoms that were confirmed by medical records: in this group, the observed association with hypertension remained consistent in all of our analyses.

Alternatively, some participants seeking financial compensation who were truly acutely ill during the outbreak may have exaggerated their current symptoms for the purpose of monetary gain. This would exaggerate any true association between bacterial gastroenteritis and long-term sequelae. Although a major concern for self-reported long-term symptoms, we believe this did not influence the observed association with hypertension. We used a standardized and ac-

cepted definition of hypertension[14] to avoid incorrectly labelling a person as having hypertension. Furthermore, the majority of participants who were found to have hypertension were unaware of its presence at the time of diagnosis.

The outbreak resulted in subsequent detailed surveillance of the health of Walkerton's residents. Although we excluded all people with previously recognized hypertension or risk factors for renal impairment, some participants with newly identified hypertension or reduced kidney function may have had these conditions before the outbreak. Up to 30% of adults may have unrecognized hypertension,[14] while others have undiagnosed reduced kidney function.[28] As such, the incidence of newly diagnosed hypertension and reduced kidney function probably does not solely represent de novo events arising after the outbreak. Some residents with borderline hypertension or silent renal dysfunction before the outbreak may have been more susceptible to gastrointestinal infection and subsequently had high rates of new diagnoses during follow-up. This would exaggerate any true association between gastroenteritis and these sequelae. However, the equal distribution of relevant health conditions across the 3 exposure groups before the outbreak makes this less likely. The risk of hypertension remained significantly associated with documented symptoms of gastroenteritis even after adjustment for other measured prognostic factors, including health care surveillance before the outbreak. Finally, acute bacterial gastroenteritis was associated with an increased risk of hypertension 4 years after the outbreak among participants who were confirmed to be normotensive by detailed assessment at their first study visit.

In conclusion, acute self-limited bacterial gastroenteritis necessitating medical attention may be an independent risk factor for long-term hypertension and reduced kidney function. Taken together, our findings will help guide future studies assessing the utility of screening and follow-up of patients who recover from acute bacterial gastroenteritis. More importantly, maintaining safe drinking water remains essential to human health,[29–33] as transient bacterial contaminations may have implications well beyond a period of acute self-limited illness.[34]

Main findings

Adults with symptomatic bacterial gastroenteritis from drinking contaminated water were more likely than asymptomatic adults to have newly diagnosed hypertension and reduced renal function during the follow-up period of almost 4 years after infection.

Implications

Acute self-limited bacterial gastroenteritis may be an important causal factor in the pathogenesis of long-term serious health effects such as hypertension and renal impairment.

This article has been peer reviewed.

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Contributors: Amit Garg was the principal author. Amit Garg, Douglas Matsell, Brian Haynes, Marina Salvadori and William Clark all contributed to the conception and design of the study and to the acquisition of data. Amit Garg and Heather Thiessen-Philbrook performed the statistical analysis. All of the authors revised the manuscript for intellectual content and gave their final approval of the version to be published.

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