Enhanced Surveillance of Norovirus Outbreaks of Gastroenteritis in Georgia

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SYNOPSIS

Objectives. The role of noroviruses in both foodborne and person-to-person outbreaks of acute gastroenteritis (AGE) has been difficult to determine in the U.S. because of lack of routine norovirus testing and of national reporting of person-to-person outbreaks. We conducted a prospective study in one state in which enhanced testing for noroviruses was performed to better understand the relative contribution of all gastroenteric pathogens.

Methods. During the two-year period, 2000–2001, we took all fecal specimens from AGE outbreaks reported in Georgia that were negative for bacteria and tested these for norovirus.

Results. We investigated 78 AGE outbreaks, from which suitable fecal samples were collected from 57 of them. Norovirus was identified in 25 (44%) outbreaks, bacteria in 20 (35%) outbreaks, and parasites in one (2%) outbreak. Forty-three (75%) of the outbreaks tested were foodborne, of which 17 (40%) were attributable to norovirus and 18 (42%) were attributable to bacteria. Adjusting for incomplete testing, we estimated that 53% of all AGE outbreaks were attributable to norovirus. A total of 2,674 people were reported ill in the 57 outbreaks, and norovirus infections accounted for 1,735 (65%) of these cases. Norovirus outbreaks tended to be larger than bacterial outbreaks, with a median number of 30 vs. 16 cases per outbreak, respectively (p=0.057).

Conclusions. This study provides further evidence that noroviruses are, overall, the most common cause of AGE outbreaks in the U.S. Improved specimen collection, reporting person-to-person outbreaks, and access to molecular assays are needed to further understand the role of these viruses and methods for their prevention.

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Noroviruses are a major cause of acute gastroenteritis (AGE) among people of all ages, and are estimated to cause 23 million cases of gastroenteritis annually in the United States.¹ Norovirus disease often presents as large outbreaks of vomiting and diarrhea among people of all ages and in diverse settings, such as cruise ships, nursing homes, and the food industry.²⁻⁵ These viruses are highly infectious and are transmitted by multiple modes: directly, from person to person; via contaminated food or water; and via airborne droplets of vomitus. Environmental contamination has also been well documented as a source of continuing infection in outbreaks.⁶⁻⁸

While noroviruses have long been suspected to be the most frequent infectious cause of epidemic and endemic gastroenteritis, this has been hard to confirm as virus detection relies on molecular methods that are usually not routine and are available only in public health laboratories. Consequently, few outbreaks of suspected viral illness are investigated with the collection of proper specimens (e.g., bulk fecal specimens rather than rectal swabs) for application of molecular tests.⁸ Moreover, because outbreaks other than those clearly transmitted by food or water are not routinely reported to the Centers for Disease Control and Prevention (CDC), efforts are rarely made to obtain an etiology in outbreaks of AGE apparently transmitted from person to person in settings such as hospitals and nursing homes, the majority of which are suspected to be norovirus.9 Historically, therefore, norovirus outbreaks have been both underdiagnosed and underreported, which has limited a full appreciation of the disease burden attributable to this virus.

From 1993 through 1997, for example, only 65 (2%) of 3,257 foodborne outbreaks reported to CDC were confirmed to be due to norovirus, and 2,182 (67%) outbreaks remained of unknown etiology.¹⁰ In two studies in which molecular diagnostics for norovirus were applied to stool specimens from nonbacterial outbreaks submitted to CDC between 1997-2000 and 2000-2004, noroviruses were detected in 81% and 93% of these outbreaks, respectively.^{2,11} This selection of outbreaks is likely to be biased toward those outbreaks exhibiting clinical and epidemiologic characteristics typical of viral infection; nonetheless, these data clearly point to norovirus as a major cause of outbreaks of unknown etiology. More recent studies have suggested that 30%-50% of foodborne outbreaks in the U.S. may be attributed to noroviruses.^{5,12} Sequencing of detected noroviruses is also rarely performed, yet molecular typing is crucial to better understand if outbreaks are linked, for instance, by a common, contaminated food.

Since 1995, Georgia (population 9.5 million) has

participated in the Foodborne Disease Active Surveillance Network of CDC, which, along with state sources, has provided increased funding for improved investigation and reporting of outbreaks of gastroenteritis, including better collection and routine testing of specimens for both norovirus and bacterial pathogens and sequencing of any detected noroviruses. We turned to outbreak data collected in 2000 and 2001 in Georgia to validate national estimates of the role of norovirus in foodborne outbreaks of AGE and also to better understand the burden and etiology of all outbreaks of AGE, including those propagated from person to person.

METHODS

Data collection and analysis

We collected epidemiologic and microbiologic information on all outbreaks of AGE reported to the Georgia Division of Public Health for a two-year period, from January 1, 2000, to December 31, 2001. Samples from outbreak cases were tested routinely at the Georgia Public Health Laboratory for bacteria and occasionally for parasites. If specimens remained available, those testing negative with this initial screen were additionally tested for norovirus at CDC and detected strains were sequenced. Information was compiled on all outbreaks and included suspected mode of transmission, setting, number of people ill, whether or not a food handler was implicated, number of specimens collected, and all test results. We analyzed data using SAS® version 8.1,13 and we compared medians using the Wilcoxon Rank Sum test.

Laboratory methods

All fecal specimens, collected irrespective of suspected outbreak etiology, were first sent to the Georgia Public Health Laboratory for testing by culture for bacteria including Salmonella subspecies (spp.), Shigella spp., Campylobacter spp., Escherichia coli O157:H7 (E. coli), Aeromonas spp., Staphylococcus aureus (S. aureus), Clostridium perfringens (C. perfringens), and Yersinia enterocolitica (Y. enterocolitica). If E. coli were identified, the colonies were further tested for Shiga-like toxin. Implicated food items or food-handler hands were tested for S. aureus or its enterotoxin. Those specimens testing negative for bacterial pathogens were analyzed by electron microscopy for small round structured viruses (SRSVs), and specimens from selected outbreaks were also tested for parasites. If SRSVs were determined to be present or if the outbreak was negative for other pathogens yet suspected to be viral in etiology, samples were sent to CDC for norovirus testing with reverse transcriptionpolymerase chain reaction, targeted to a region of the polymerase gene (region B), and previously described methods.¹⁴ For further characterization of strains, a more variable region of the capsid gene (region C) was amplified.¹⁵ Amplified products were sequenced, and we analyzed all sequences using GCG[®].¹⁶

We attributed an outbreak to a pathogen if two or more stool specimens tested positive. For attribution of *S. aureus* outbreaks, either (1) two affected people had stool isolates with matching pulsed-field gel electropheretic patterns or (2) at least one stool and the implicated food tested positive for *S. aureus* or its enterotoxin.

RESULTS

From January 1, 2000, to December 31, 2001, a total of 78 outbreaks of AGE were reported (42 in 2000 and 36 in 2001). We collected a median of six rectal swabs or stool samples (range: 1–20) per outbreak from patients involved in 57 (73%) of the 78 outbreaks.

Of the 57 outbreaks with specimens, 56 (98%) were tested for routine enteric bacteria and 34 (60%) for noroviruses, almost all of which initially tested negative for bacteria. Overall, noroviruses were detected in 25 (74%) of 34 outbreaks tested, while bacteria were detected in 20 (36%) of 56 outbreaks tested. Of four outbreaks tested for parasites, one (25%) was positive (for *Cyclospora* spp.). Of the 11 outbreaks with specimens that remained without an etiology, seven were not tested for noroviruses and 11 were not tested for parasites (Table 1).

If the 11 outbreaks that remained with no etiology had been fully tested for viruses and parasites, and assuming the same detection rates as those outbreaks testing negative for bacteria that were tested, we estimate that an additional five outbreaks would be attributable to norovirus for a total of 30 (53%), three outbreaks would be attributable to parasites for a total of four (7%), while three outbreaks would remain of unknown etiology (Table 2).

Overall, noroviruses were the most common cause of outbreaks of AGE in Georgia during the study period, detected in 44% of the 57 outbreaks for which specimens were available, and could be attributed to 53% of all outbreaks with specimens if testing had been complete. Altogether, bacterial agents were attributed to 35% of outbreaks with specimens and included *S. aureus* (n=11), *C. perfringens* (n=3), *Salmonella* spp. (n=3), and *E. coli* (n=1). One outbreak tested positive for both *Salmonella* spp. and *Y. enterocolitica*, and another was positive for both *S. aureus* and *C. perfringens* (Figure 1).

Of 57 outbreaks, foodborne transmission was implicated in 43 (75%), person-to-person transmission was implicated in seven (12%), and mode of transmission could not be determined in seven (12%) of the outbreaks. Of the 43 foodborne outbreaks, 17 (40%) were associated with norovirus, 18 (42%) were associated with bacteria, one (2%) was associated with *Cyclospora* spp., and seven (16%) remained of unknown etiology. Of the seven outbreaks transmitted from person to person, five (71%) were associated with norovirus, none with bacteria, and two (29%) with unknown etiology (Table 3).

The 57 outbreaks with specimens reported in Georgia occurred in a variety of settings, but predominantly in food outlets, schools, and daycare centers. Norovirus outbreaks were more frequent than bacterial outbreaks in closed (e.g., nursing homes) or semi-closed (e.g., schools and workplaces) settings (15 vs. 10, respectively). A total of 2,674 people were reported ill in the

Table 1. Laboratory results of testing stool samples collected from57 outbreaks of gastroenteritis, Georgia, 2000–2001

Pathogens tested	Number of outbreaks tested	Nun	Number of			
		Bacteria N (percent)	Norovirus N (percent)	Parasites N (percent)	Total N (percent)	outbreaks of unknown etiology
Bacteria, parasites,	4	0/4 (0)	3/4 (75)	1/4 (25)	4/4 (100)	0
Bacteria, norovirus	29	4/29 (14)	21/29 (72)	NA	25/29 (86)	4
Norovirus	1	NA	1/1 (100)	NA	1/1 (100)	0
Bacteria	23	16/23 (70)	NA	NA	16/23 (70)	7
Total	57	20/56 (36)	25/34 (74)	1/4 (25)	46/57 (81)	11

NA = not applicable

	Number of outbreaks tested	Number of positive outbreaks N (percent)	Number of positive outbreaks of unknown etiology not tested for each pathogen group	Number of additional outbreaks assuming complete testing ^a	Total number of positive outbreaks	Percent of each pathogen group attributed to all outbreaks (n=57)
Bacteria	56	20 (36)	0	0	20	35
Norovirus	34	25 (74)	7	5	30	53
Parasites	4	1 (25)	11	3	4	7

Table 2.	Estimate	ed number	of norovi	rus outbre	aks attri	buted to	bacteria,
noroviru	ises, and	parasites,	assuming	complete	testina,	Georgia,	2000-2001

^aDerived by multiplying the number of unknown outbreaks not tested for each etiology (bacteria = 0, norovirus = 7, parasites = 11) by the percent positive for each etiology

57 outbreaks, and norovirus infections accounted for 1,735 (65%) of these cases. Outbreaks associated with norovirus were larger than those attributed to bacterial agents, with a median number of 30 vs. 16 cases per outbreak, respectively (Wilcoxon Rank Sum test, p=0.057). Outbreaks of unknown etiology accounted for 414 (15%) of all the cases, with a median of 25 cases per outbreak, comparable in size to outbreaks associated with norovirus (Table 3).

The 17 foodborne norovirus outbreaks were linked to a variety of food types, but cold foods (e.g., sandwiches and salads) predominated. Bacterial outbreaks were linked to the consumption of foods of animal origin (i.e., meat and egg products) in 11 of 18 (61%) outbreaks compared with no such foods associated with norovirus outbreaks. In 30% of outbreaks, an implicated food item could not be determined by the investigators. Food handlers were identified as the source of infection in 13 (30%) of 43 foodborne outbreaks. Norovirus was associated with seven (53%) and bacterial agents with five (38%) of the 13 outbreaks; the etiology could not be determined in one outbreak. In 10 of 17 (59%) foodborne norovirus outbreaks, no food handler was implicated. Food handlers admitted to working while ill during five of the 17 norovirus outbreaks, but only during one of 18 bacterial outbreaks (Table 4).

Sequence data were available for strains from 20 of the 25 norovirus outbreaks, and these comprised 20 unique outbreak strains that belonged either to one of the main human norovirus groups, genogroup1 (GI) (n=7) or genogroup 2 (GII) (n=13). These genogroups were further divided into clusters. The seven unique GI strains from seven different outbreaks belonged to four clusters. Of the 13 unique GII strains, two were classified into GII, cluster 2 (Melksham virus), but the remaining 11 could not be classified correctly using the Region B primers. Two outbreaks (A and K) were associated with a mixed infection and norovirus strains of two different sequences. Three outbreaks were associated with noroviruses sharing identical region B sequences (outbreaks G, H, and K) (Figure 2).

To better discriminate, further sequence analysis in the more variable capsid region of the norovirus strains from two of the outbreaks with identical region B sequences (H and K) found that they were different from one another, suggesting unrelated sources of virus. In addition, no epidemiologic link could be found among the three outbreaks, as they occurred during a six-month period (September 2000 to April 2001) in separate parts of the state. Two were associated with ill food handlers—one at a catered workplace event and the second in a nursing home. The third outbreak occurred in a school, and this outbreak was attributed to person-to-person transmission.

DISCUSSION

In the U.S., data on outbreaks of AGE not caused by foodborne transmission are not routinely collected nationally. This study in one state extends our understanding of the transmission of norovirus in foodborne settings and its role in all outbreaks of AGE, and supports the conclusion that norovirus is the single most common cause of all AGE outbreaks in Georgia, and likely in the U.S.

From 2000 to 2001 in Georgia, we estimated that up to 53% of all outbreaks with available specimens would have been norovirus confirmed if specimens tested only for bacteria had also been tested for norovirus. All bacterial pathogens together accounted for 35% of outbreaks and parasitic agents for 2% of outbreaks. Norovirus was the main cause of AGE outbreaks in most



Figure 1. Etiology of 57 outbreaks of gastroenteritis with specimens collected, Georgia, 2000–2001

^aEstimated additional outbreaks if specimens negative for bacteria had been fully tested for viruses and parasites spp. = subspecies

E. coli = Escherichia coli

S. aureus = Staphylococcus aureus

settings and was associated with as many foodborne outbreaks as all bacterial agents combined. Moreover, norovirus outbreaks affected almost twice as many people as bacterial outbreaks and accounted for the large majority of all illnesses associated with outbreaks of a known etiology. Almost 25% of foodborne outbreaks were associated with ill food handlers, and in half of these cases, the worker admitted to working while ill. One possible explanation of the fact that those ill with norovirus were more likely to continue working is because vomiting—often a predominant norovirus symptom—may not have been considered infectious compared with diarrhea.

Sequence information on the norovirus strains provided interesting insights into the molecular epidemiology of norovirus. For one, outbreaks in Georgia were caused by strains commonly circulating in the U.S. at the time, with a predominance of GII/4 strains.^{11,17} Second, the study highlighted the potential of genetic sequences to link or discriminate between outbreaks. Three of the outbreaks were attributed to strains with identical sequences in the polymerase region (region B), suggesting a common source, but further sequence analysis of the capsid region found two of these outbreaks to be caused by viruses of distinct, rather than the same, sequences. Lastly, the finding of two different sequences in each of two outbreaks suggests several sources of infection or a possible role of sewage-contaminated water, perhaps coming in contact with oysters on the seabed or used to irrigate produce.^{18,19}

Our reported rate of detection of norovirus in specimens from outbreaks in Georgia was consistent with several recent studies documenting the relatively high frequency of foodborne norovirus outbreaks. A U.S. national study that extrapolated laboratory data correcting for incomplete testing⁵ and a multisite study that used stool kits to enhance the collection and testing of specimens for norovirus both found that norovirus may be a cause of up to 50% of foodborne outbreaks.²⁰ By use of epidemiologic criteria elaborated by Kaplan et al.,²¹ one study in Minnesota attributed norovirus to

Characteristic	Norovirus (n=25) N (percent of row)	Bacterial (n=20) N (percent of row)	Unknown (n=11) N (percent of row)	Total (n=57)ª N (percent)
Mode of transmission				
Foodª	17 (40)	18 (42)	7 (16)	43 ^b (75)
Person to person	5 (71)	0(0)	2 (29)	7 (12)
Unknown	3 (43)	2 (29)	2 (29)	7 (12)
Setting				
Food outlet ^c	7 (39)	7 (39)	3 (17)	18 (32)
School or daycare	5 (42)	4 (33)	3 (25)	12 (21)
Nursing home or retirement center	2 (100)	0(0)	0 (0)	2 (4)
Workplace	4 (57)	2 (29)	1 (14)	7 (12)
Private residence	3 (43)	4 (57)	0 (0)	7 (12)
Hotel or club	1 (33)	0 (0)	2 (67)	3 (5)
Other	3 (38)	3 (38)	2 (24)	8 (14)
Number of cases				
Total	1,735 (65)	525 (20)	414 (15)	2,674 (100)
Median (range)	30 (4–485)	16 (2–125)	25 (5–105)	

Table 3. Epidemiologic characteristics of 57 outbreaks of gastroenteritiswith specimens reported in Georgia, 2000–2001

^aIncludes two outbreaks attributable to ice—one of norovirus etiology and the other of unknown etiology

^bIncludes one outbreak attributable to cyclospora

^cIncludes restaurants, cafeterias, and catered events

41% of foodborne outbreaks from 1981 to 1998.⁴ Other work found these clinical and epidemiologic criteria for norovirus outbreaks to be very specific and used them to estimate that 28% of foodborne outbreaks would be attributable to norovirus.¹²

Non-foodborne outbreaks of gastroenteritis, particularly those involving person-to-person transmission that are often of viral etiology,⁹ were likely underestimated in this study. Funding that the state of Georgia received has been used to improve foodborne outbreak investigation, but outbreaks transmitted from person to person, often in closed settings (e.g., nursing homes), remain poorly reported and investigated in states, and are not nationally notifiable. States that have more developed surveillance for outbreaks of AGE in nursing homes generally report more viral-like outbreaks in such settings.²² Outbreaks in nursing homes and hospitals are more often reported in the United Kingdom and Europe,²³⁻²⁵ and in the last five to 10 years, these have been associated with variants of noroviruses in the GII/4 cluster also found in this study.26,27 No hospital outbreaks were reported in this study, which is in contrast to European countries, especially the United Kingdom, where hospitals are one of the most common settings for norovirus outbreaks. It remains possible that characteristics of private hospitals in the U.S., such as fewer patients per room and dedicated bathroom

facilities, may result in less nosocomial transmission than in publicly funded hospitals in Europe, where large wards and shared facilities are the norm.

Limitations

Our study had several limitations. First, we collected data on relatively few outbreaks during the two-year period. The frequency of norovirus infections varied from year to year in part because of the emergence of new strains, and may also have differed from state to state.^{26,27} For this reason, the impact of norovirus in these two years may not be generalizable to other years or states.

Second, although 79 outbreaks occurred in the time period, specimens were only collected and tested from 57 outbreaks, and this subset of outbreaks may have been different from those with no testing performed. We were unable to test specimens from all outbreaks for all pathogens because collection of rectal swabs in some outbreaks allowed bacterial but not norovirus testing. It remains possible that outbreaks testing positive for bacteria and not further tested for norovirus were mixed infections with viruses, leading us to underestimate the role of norovirus. Conversely, the outbreaks testing negative for bacteria and not tested from norovirus may not have been so tested because the outbreaks did not present with epidemiologic



Figure 2. Phylogram of 22 different sequence types associated with 20 different outbreaks of acute gastroenteritis that occurred in Georgia, 2000–2001^a

^aIncludes 27 reference sequences from Genbank. The tree is based on a 172-base pair region of the ribonucleic acid polymerase gene (Region B) created using the DISTANCES program with uncorrected distances, followed by GROWTREE analysis. The length of arms in the tree denote relative nucleotide difference in Region B and, therefore, genetic relatedness of strains.

GI = genogroup 1

GII = genogroup 2

characteristics of norovirus infection. Incomplete data prevented us from applying epidemiologic criteria to attribute a viral etiology to these outbreaks for which specimens were not collected or the seven outbreaks for which specimens were not tested for norovirus.

CONCLUSIONS

Noroviruses are the predominant etiology of both foodborne and non-foodborne outbreaks of gastroenteritis; efforts to collect and test fecal specimens from outbreaks of AGE for noroviruses should be supported in all states to better characterize the burden of these viruses nationwide. Reporting and investigation of outbreaks propagated from person to person in nursing homes should be a priority, as these institutions house vulnerable populations where morbidity may be higher.⁹ Further development of sequencing capabilities in states will also allow for the use of sequence comparisons to provide additional insights into the transmission of noroviruses. A better understanding of the burden and transmission of noroviruses will lead to increasingly specific control measures, including appropriate isolation, work furlough, and development

Table 4. Role of different foods and food					
handlers in 43 foodborne outbreaks with					
specimens in Georgia, 2000–2001					

Variable	Norovirus (n=17)	Bacterial (n=18)	Unknown (n=8)	Total (n=43)
Implicated food				
Salad and fruit	3	0	0	3ª
Shellfish ^b	2	0	1	3
Sandwich ^c	2	2	2	6
Meat dish	0	9	2	11
Egg dish	0	2	0	2
lce	1	0	1	2
Other	3	0	0	3
Unknown	6	5	2	13
Food handler				
Suspected sour	ce 7	5	1	13
Working while i	II 5	1	0	6

^aThe number includes one berry-associated outbreak attributed to *Cyclospora* subspecies. No food handler was implicated.

^bIncludes raw oysters, crab, and shrimp

 $^{\rm c}$ Includes chicken quesadillas and burritos, roast beef sandwich, chicken sandwich, turkey sandwich, and tacos

and use of effective disinfectants and, moreover, should stimulate the research and development of potential vaccines.

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