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MAJOR ARTICLE

Gastroenteritis in Men Who Have Sex With Men in Seattle, Washington, 2017–2018

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Background. Men who have sex with men (MSM) are at risk for sexual transmission of enteric pathogens. The microbiology of gastroenteritis in MSM has not been examined since the advent of antiretroviral therapy and molecular diagnostics. Our objective was to assess the causes of gastroenteritis among MSM living with and without human immunodeficiency virus (HIV) coinfection in Seattle, Washington.

Methods. We conducted a retrospective cohort study of 235 MSM who underwent multiplex stool polymerase chain reaction (PCR) testing between 1 January 2017 and 1 June 2018. We abstracted clinical and laboratory data from electronic medical records. Parallel or reflexive culture and susceptibility testing were performed when PCR detected cultivable pathogens.

Results. Among 235 MSM tested (268 episodes), 131 had 151 episodes with positive test results. 148 (63.0%) individuals were living with HIV. Among positive tests, 88.7% detected a bacterial pathogen, 26% a virus, and 40% a parasite. Diarrheagenic *Escherichia coli* (enteroaggretative, enteropathogenic), *Shigella*, and *Campylobacter* were the most commonly detected bacteria (33.1%, 30.5%, and 17.2% of positive samples, respectively). Forty-three percent of positive specimens had ≥2 pathogens. Etiologies and clinical presentations were similar between men living with and without HIV. Cultured *Shigella* and *Campylobacter* isolates were frequently resistant to multiple antibiotics.

Conclusions. MSM present with gastroenteritis from varied pathogens, including some not detected by conventional stool culture. High levels of antibiotic resistance are consistent with frequent antibiotic exposure in this population and the transmission of multiresistant strains. New approaches are needed to detect, treat, and prevent enteric infections in MSM.

Keywords. acute gastroenteritis; infectious diarrhea; men who have sex with men; antimicrobial resistance; HIV.

Prior to the human immunodeficiency virus (HIV) epidemic, men who have sex with men (MSM) with multiple sexual partners were recognized to have a higher prevalence of intestinal pathogens, in particular, *Shigella*, *Campylobacter,* and *Giardia*, than the general population, [1–3]. This led to the recognition that enteric pathogens can be spread not only via traditional water- and foodborne routes but also through sexual activity [1]. Outbreaks of sexually transmitted *Shigella* infections have been increasingly documented throughout the world [4–10], and MSM and international travelers are recognized as high-risk groups for antibiotic-resistant *Shigella*. HIV infection compounds the risk of enteric infection by enhancing host susceptibility to opportunistic pathogens such as *Salmonella* and *Cryptosporidium* [11, 12].

Several studies have described the range of pathogens responsible for enteric infections in MSM. Such studies have focused largely on proctitis and proctocolitis [3, 13–15] and have mostly been conducted in sexually transmitted disease (STD) clinics with populations enriched for patients who present with classic sexually transmitted infections (eg, *Chlamydia*, gonorrhea, syphilis) using traditional diagnostic methods that predate the development of highly sensitive culture-independent molecular diagnostic tests [16, 17]. The present study was undertaken to examine the etiology of infectious diarrhea in MSM in the era of molecular diagnostics.

METHODS

Patient Population

Multiplex polymerase chain reaction (PCR) testing using a commercial panel was implemented for general stool pathogen testing in January 2017 across the University of Washington healthcare system including the University of Washington Medical Center, Seattle Cancer Care Alliance, Harborview Medical Center, and the University of Washington–affiliated outpatient clinics. A previously reported prospective multicenter observational study that involved these clinical sites was performed from 1 January 2017 to 30 September 2017 [18]. Based on the results of the initial analysis, the study was extended to focus on the subset of MSM patients with the study period extended until 1 June 2018.

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Laboratory Evaluation

Stool specimens submitted for diagnostic testing were transported in Cary-Blair transport medium and tested using the FilmArray GI Panel (BioFire Diagnostics, Salt Lake City, UT) upon receipt or on the following morning for specimens received between 11 pm and 7 am. From 1 January 2017 to 30 September 2017, stool cultures using blood, MacConkey, MacConkey-sorbitol, *Salmonella-Shigella* selective, cefsulodin-irgasan-novobiocin, and *Campylobacter* selective agar were performed in parallel. Thiosulfate-citrate-bile salt-sucrose agar to enhance the recovery of *Vibrio* spp. was added from July to September. Subsequently, targeted cultures were performed for specimens with cultivable pathogens detected using the GI Panel.

Chart Review

A retrospective cohort analysis of the patient subset with a sex marker of male who were aged ≥18 years at the time of testing was performed. Chart review was used to identify patients who were MSM, defined as having documented sexual contact with male partners, a male intimate partner, or being described as "gay" or "homosexual" in the medical chart. For patients identified as MSM who underwent stool PCR testing with the FilmArray GI Panel, an in-depth chart review was performed to capture demographic information, presenting symptoms, HIV status, antiretroviral medication (ARV) use, additional diagnostic testing performed (white blood cell count; stool ova and parasite examination; testing for *Cryptosporidium*, *Cyclospora*, and *Cystoisospora* by modified acid-fast smear; *Chlamydia* and gonorrhea testing by PCR and culture; syphilis testing by serum rapid plasma reagin), antimicrobial treatment, and resolution of symptoms. All authors have doctoral-level training in clinical medicine or microbiology and participated in chart review.

Comparison Group

MSM data were compared to contemporaneous records from non-MSM individuals who underwent gastrointestinal pathogen testing using the same laboratory methods at the same institutions (previously published by Cybulski et al [18]). Individuals identified as MSM were excluded from the data from Cybulski et al to create Figure 1 and Supplementary Figure 1.

Data Analyses

Clinical variables between men living with and without HIV were compared, and significance was determined using the Student *t* test, χ^2 test, Fisher exact test, or Wilcoxon rank sum as appropriate. A *P* value of <.05 was considered significant. Statistical analyses were performed in R (R Core Team 2018, Vienna, Austria).

Ethics Statement

The University of Washington Institutional Review Board approved the study.

RESULTS

Demographics

A total of 235 MSM with symptoms of gastroenteritis were tested during the study period, of whom 130 (57.5%) had 1 or more clinical encounter for which they had a positive stool enteric pathogen test. A total of 151 clinical encounters had positive test results. The demographic features of individuals who underwent testing for diarrheal pathogens are described in Table 1. Overall, the majority (66%) of the population was non-Hispanic white, 11% were black, and 13% were Hispanic. While 64.6% of episodes involved individuals living with HIV, 70% of positive tests were from clinical encounters that involved individuals living with HIV, of which 82% were collected while the individual was on ARV therapy. Of positive tests from clinical encounters involving individuals living without HIV, more than 60% were collected while the individual was on preexposure prophylaxis (PrEP). Nearly 70% of testing occurred in the outpatient setting and an additional 15% in the emergency department. Concurrent testing for gonorrhea, chlamydia, and syphilis occurred less than one-third of the time.

Symptoms

Presenting symptoms and history are listed in Table 2. Overall, there was little difference observed in the clinical presentation of individuals living with and without HIV with gastroenteritis and positive test results. Individuals living with HIV were more likely to have diarrhea, especially watery diarrhea. Individuals living without HIV were significantly more likely to report a history of recent travel. For both groups, in nearly 14% of episodes with positive testing, the diarrhea was described as bloody, but tenesmus was rare (6%). Temperature >38°C (12.5%), subjective fever or chills (24.5%), or leukocytosis (14.5%) were reported in a minority of episodes with positive testing.

Microbiology

Overall, 65 (43%) samples were positive for 2 or more potential pathogens (Table 3). Twenty-nine percent of tests were positive for 2 pathogens, 9% for 3 pathogens, and 5% for 4 or more. Of all positive test results, 88.7% detected a bacterial pathogen, while 26% detected a virus and 40% detected a parasite. Of the bacterial causes, diarrheagenic *Escherichia coli*, in particular, enteroaggretative *E. coli* (EAEC) and enteropathogenic *E. coli* (EPEC), was most common, representing 33% of the pathogens detected (Figure 1, Supplementary Table 1). *Shigella* species comprised 30% and *Campylobacter* species 17%. Norovirus was the most common viral pathogen identified, representing 59% of viruses and 15% of pathogens overall. *Giardia* was the most common parasite identified, comprising 50% of parasitic pathogens and 20.5% of pathogens overall. Of samples in which more than 1 pathogen was found, diarrheagenic *E. coli* and *Shigella* predominated. Limited differences were observed between encounters that involved patients living with and without HIV.

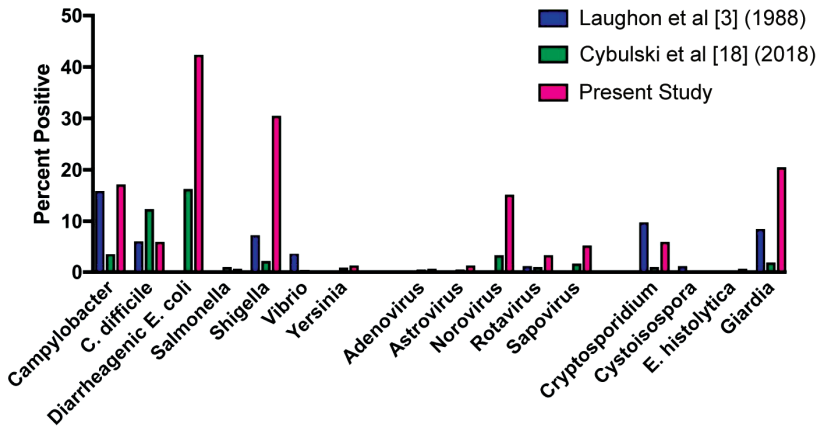

Figure 1. Pathogens detected by stool testing from episodes of gastroenteritis. The figure compares historical data from men who have sex with men in Baltimore, Maryland ([3]; n = 85, 85% living with human immunodeficiency virus [HIV]), contemporary data from the total University of Washington patient population in Seattle ([18]; n = 669), and this study (n = 151, 75% living with HIV).

Shigella was more common in patients living with HIV (36% vs 20% of detected pathogens, $P = .04$). In contrast, *Giardia* was more common in patients living without HIV than in patients living with HIV (33% vs 14%, respectively; $P < .01$). Among patients living with HIV, *Cryptosporidium* was identified more commonly in those with a CD4 count <200 (1% vs 17.8%, data not shown), although there was no significant difference between patients living with and without HIV in aggregate.

Response to Treatment

In encounters with positive testing, resolution of symptoms was documented in 112, with only 11 episodes resulting in

Table 1. Demographics and Clinical Characteristics of Men Who Have Sex With Men With Stool Pathogen Testing (N = 268 Episodes) and Comparisons for Differences Between Episodes Involving Individuals Living With and Without Human Immunodeficiency Virus With Positive Stool Pathogen Testing

		Pathogen-Positive Episode (n = 151)		
		HIV+	HIV−	
Characteristic	Overall (N = 268)	n = 100	n = 51	*P* Value
Age, mean (standard deviation), y	42.6 (13.5)	43.7 (11.6)	33.0 (12.9)	<.001
Race/ethnicity				.38
White non-Hispanic	178 (66.4)	70 (70.0)	34 (66.7)	
Black	30 (11.2)	11 (11.0)	6 (11.8)	
Hispanic	34 (12.7)	10 (10.0)	5 (9.8)	
Asian	14 (5.2)	3 (3.0)	5 (9.8)	
Other	12 (4.5)	6 (6.0)	1 (2.0)	
Location of testing[a]				.05
Inpatient	39 (14.6)	12 (12.0)	3 (5.9)	
Outpatient	186 (69.4)	63 (63.0)	42 (82.4)	
Emergency department	40 (14.9)	25 (25.0)	6 (11.8)	
Additional testing				
White blood cell count	149 (55.6)	63 (63.0)	26 (51.0)	.21
Stool ova and parasites exam	97 (36.2)	36 (36.0)	18 (35.3)	.99
Cryptosporidium, Cyclospora, and *Isospora* (*Cystoisospora*)	48 (17.9)	22 (22.0)	8 (15.7)	.35
Neisseria gonorrhoeae /*Chlamydia*	59 (22.0)	30 (30.0)	14 (27.5)	.89
Syphilis	54 (20.1)	28 (28.0)	13 (25.5)	.89
Preexposure prophylaxis	36 (13.4)	NA	31 (60.8)	…
Antiretroviral medications	139 (51.9)	82 (82.0)	NA	…
CD4, median (IQR)	375 (187–648)	444 (187–697.5)	NA	
Viral load				
Undetectable, n (%)	112 (41.8)	61 (61.0)	NA	…
Detectable, median (IQR)	50 220 (1262.5–209 350)	32 865 (554.5–359 000)	NA	…

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable.
[a]Three observations missing location of testing.

Table 2. Clinical Characteristics of Men Who Have Sex With Men During Episodes of Gastroenteritis With Stool Pathogen Testing (N = 268 Episodes) and Comparisons for Differences Between Episodes Involving Individuals Living With and Without Human Immunodeficiency Virus With Positive Stool Pathogen Testing (all n, % Unless Otherwise Noted)

		Pathogen-Positive Episode (n = 151)		
	Overall	HIV+	HIV−	
Characteristic	N = 268	n = 100	n = 51	*P* Value
Diarrhea	239 (89.2)	98 (98.0)	41 (80.4)	<.001
Watery	120 (44.8)	54 (54.0)	16 (31.3)	.01
Bloody	29 (10.8)	14 (14.0)	7 (13.7)	.99
Nausea	83 (31.0)	35 (35.0)	17 (33.3)	.99
Vomiting	46 (17.2)	22 (22.0)	7 (13.7)	.28
Abdominal pain	142 (53.0)	63 (63.0)	32 (62.7)	.99
Tenesmus	13 (4.9)	7 (7.0)	2 (3.9)	.78
Headache	18 (6.7)	8 (8.0)	5 (9.8)	.76
Fever/chills	56 (20.9)	25 (25.0)	12 (23.5)	.99
Fatigue	55 (20.5)	24 (24.0)	9 (17.6)	.53
Symptom duration, median (interquartile range), days	10 (4–30)	7 (3–18)	7 (4–21)	.20
Sick contact	20 (7.5)	11 (11.0)	5 (9.8)	.99
Travel	27 (10.0)	6 (6.0)	12 (23.5)	<.01
Fever (>38°C)	37 (13.8)	15 (15.0)	6 (11.8)	.99
Leukocytosis (>10K white blood cells)	27 (10.0)	13 (13.0)	7 (13.7)	.99

Abbreviation: HIV, human immunodeficiency virus.

unchanged symptoms (Table 3). Overall, antibiotics were given in 75% of episodes with positive testing. The most common antibiotics prescribed were ciprofloxacin and azithromycin, which were prescribed in 40.9% and 21.7%, respectively, of cases in which antibiotics were prescribed. The mean duration of antibiotic treatment was 5 days. Fourteen patients (13%) did not receive antibiotics despite the detection of a bacterial pathogen, and 11 (79%) of them experienced spontaneous resolution of

Table 3. Incidence of Multiple Pathogen Detection on Stool Testing, Ancillary Testing, Antibiotic Use, and Clinical Outcomes of Men Who Have Sex With Men With Gastroenteritis and Positive Pathogen Stool Testing (N = 151 Episodes)

	Overall	HIV+	HIV−	
Characteristic	N = 151	n = 100	n = 51	*P* Value
Pathogens detected by multiplex polymerase chain reaction, mean (standard deviation)	1.6 (0.9)	1.7 (0.9)	1.6 (0.9)	.61
Number of pathogens detected (%)				.74
1	86 (57.0)	56 (56.0)	30 (58.8)	
2	44 (29.1)	29 (29.0)	15 (29.4)	
3	14 (9.3)	9 (9.0)	5 (9.8)	
>4	8 (5.3)	6 (6.0)	1 (2.0)	
Additional pathogens detected, n (%)				
Gonorrhea	6 (4.0)	4 (4.0)	2 (3.9)	.99
Chlamydia	9 (6.0)	7 (7.0)	2 (3.9)	.71
Acute syphilis	4 (2.6)	4 (4.0)	0 (0.0)	.30
Received antimicrobial, n (%)	115 (75.7)	75 (75.0)	40 (76.9)	.84
Duration of treatment, median (IQR), days	5 (3–7)	5 (3–7)	3 (3–7)	.07
Length of stay,[a] median (IQR), days	4 (2–5.25)	4 (2–6)	3 (3-3)	.31
Clinical change, n (%)				.09
Resolved	112 (73.7)	74 (74.0)	38 (73.1)	
Improved	18 (11.9)	16 (16.0)	2 (3.8)	
Unchanged	11 (7.2)	7 (7.0)	4 (7.7)	
Unknown	8 (5.3)	3 (3.0)	5 (9.6)	
Other[b]	2 (1.3)	0 (0.0)	2 (3.8)	

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

[a]n = 25 admitted to the hospital overall, 19 HIV+, 6 HIV−.

[b]Includes an individual who died (n = 1) individual who was asymptomatic when diagnosed (n = 1).

their symptoms. For 27 patients with *Campylobacter* or *Shigella* with available resistance testing, 2 did not receive antibiotics and 4 received antibiotics to which their isolate was resistant. Despite this, all experienced resolution or improvement of their symptoms.

Antimicrobial Resistance

Of 19 *Shigella* isolates tested, all were resistant to ampicillin and trimethoprim-sulfamethoxazole, and all but 2 were resistant to azithromycin (Supplementary Figure 1). *Shigella* isolates were generally sensitive to ciprofloxacin based on Clinical and Laboratory Standards Institute criteria of minimum inhibitory concentration (MIC) <1 μg/mL, with only 1 of 19 tested demonstrating high-level resistance (MIC >2 μg/mL). The *Shigella* isolate that was resistant to ciprofloxacin remained sensitive to azithromycin. However, only 2 of 10 *Shigella flexneri* isolates had a ciprofloxacin MIC ≤0.12 μg/mL. In contrast, all but 1 of 9 isolates of *Shigella sonnei* had ciprofloxacin MIC <0.12 μg/mL. Nine *Campylobacter* isolates were tested for antimicrobial susceptibility. Seven (78%) were resistant to ciprofloxacin (MICs 8 to >256 μg/mL), and 8 (89%) were resistant to erythromycin (MIC >256 μg/mL). Resistance testing was not performed for azithromycin, and the single isolate that was tested against doxycycline was resistant (MIC 64 μg/mL).

DISCUSSION

This is the largest study of the causes of gastroenteritis in MSM and the first such study in the HIV era to use comprehensive molecular diagnostic testing. Specific pathogens were detected in 56.3% of cases, a substantially higher diagnostic yield than the 33.5% yield observed in the general population [18]. Our observations confirm earlier studies that indicated that MSM are at higher risk for infectious diarrhea caused by *Campylobacter*, *Shigella*, and *Giardia* and extend the known microbial spectrum of gastroenteritis in MSM to include diarrheagenic *E. coli*, in particular, EAEC and EPEC, and norovirus. *Clostridium difficile* was detected less frequently in MSM than in the general population.

Shigella or diarrheagenic *E. coli* were detected in more than one-half of the positive fecal specimens. This stands in contrast to studies of the etiology of acute gastroenteritis in the general population in high-resource settings. Among patients who presented to 9 emergency departments in the United States, norovirus was the most common pathogen (26%), and bacteria collectively were responsible for only 17% of cases [19]. Studies in Austria, the Netherlands, and Germany similarly found bacterial pathogens to account for a minority of cases of acute gastroenteritis [20–22]. While these studies were completed prior to the advent of culture-independent diagnostics and thus had lower sensitivity, they remain the only studies of the etiology of gastroenteritis in large, primary care populations. At our institutions over the same time period as the present study, MSM had higher rates of diarrheagenic *E. coli* (42.4 vs 16.3%), *Shigella* (30.5% vs 2.2%), *Giardia* (20.5% vs 1.9%), and *Campylobacter* (17.2% vs 3.6%) in comparison to the general population [18] (Figure 1).

The increased risk of *Shigella* in MSM [1, 3, 23] and the sexual transmission of *Shigella* in outbreaks [4–9, 24–27] has been well documented. Recent studies in Australia that used whole-genome sequencing have provided evidence of ongoing transmission of related clusters of *S. flexneri* and *S. sonnei* among MSM [28]. The prevention of sexually transmitted enteric pathogens may require different considerations than the control of foodborne outbreaks that involve the same pathogens. Although antibiotic therapy is selectively administered to patients with foodborne gastroenteritis depending on the severity of symptoms [29], it may play a more prominent role in arresting transmission via sexual exposure. The potential utility of screening asymptomatic high-risk individuals for enteric pathogen colonization must also be considered. The high proportion of individuals with *Shigella* who were using PrEP correlates with increasing rates of bacterial sexually transmitted infections in persons using PrEP [30] and underscores emerging evidence that risk compensation by PrEP users may be leading to more high-risk sexual practices [31]. Although living with HIV is a risk factor for severity and complications of bacterial enteritis [11, 12, 32], we did not observe significant differences in the clinical presentations of MSM living with and without HIV, which likely reflects the effectiveness of contemporary antiretroviral therapy.

The Centers for Disease Control and Prevention (CDC) and the World Health Organization have declared antimicrobial-resistant *Shigella* to represent a major public health threat [33, 34]. A 2017 CDC advisory suggested that *Shigella* spp. with ciprofloxacin MIC of 0.12–1.0 μg/mL may not be suitable for treatment with ciprofloxacin [35], despite being categorized as susceptible by current interpretive criteria. We observed generally higher rates of antimicrobial resistance in bacterial isolates from MSM compared to men who do not have sex with men (Supplementary Figure 1). *Shigella flexneri* and *S. sonnei* isolates from MSM were almost uniformly resistant to azithromycin and also resistant to ampicillin and trimethoprim-sulfamethoxazole. Along with other reports, this suggests the rapid emergence of azithromycin resistance in *Shigella* spp. from MSM [28, 36–38]. Of 15 *S. flexneri* isolates from MSM, 12 had a ciprofloxacin MIC of 0.12–1.0 μg/mL. All of these patients had resolution of their symptoms after receipt of ciprofloxacin, suggesting that fluoroquinolones may still be clinically effective for strains with MICs in this range. Antibiotic-resistant *Campylobacter* is also a global health priority [33]. Although the number of *Campylobacter* isolates available for susceptibility testing in our study was limited, high rates of resistance to macrolides and/or fluoroquinolones in *Campylobacter coli* and *Campylobacter jejuni* are of concern and have been previously noted in MSM-related outbreaks [39, 40]. High rates of

resistance in enteric pathogens from MSM may reflect both the transmission of multidrug-resistant outbreak strains and selective pressure from frequent antibiotic exposure. Oral treatment options for *Shigella* and *Campylobacter* spp. that are resistant to both fluoroquinolones and macrolides are limited.

Furthering concerns about antibiotic resistance is the high rate of prescription of antibiotics in our study regardless of detected etiology. Clinicians in our study prescribed antibiotics in 75.7% of visits with positive testing. Infectious Disease Society of America (IDSA) guidelines recommend empiric antibiotics in immunocompetent adults who show signs and symptoms of bacillary dysentery in order to treat presumptive shigellosis [41]. However, *Shigella* was detected in only 30% of positive tests. Furthermore, IDSA guidelines recommend testing only in cases of suspected bacillary dysentery or moderate to severe watery diarrhea. We suspect that the high rate of testing and treatment in our study is due to 2 factors. First, many consider people living with HIV to be immunocompromised regardless of CD4 count and may therefore test and treat people living with HIV based on immunocompromised guideline recommendations. Second, there is active discussion in the STD community regarding testing and treating of gastroenteritis in MSM [42], with some advocating for increased testing and treatment in MSM to prevent further transmission.

The strengths of our study include the use of sensitive molecular microbiological diagnostic testing, a relatively large cohort for which detailed clinical information was available, a study population who presented for routine medical care, and the availability of susceptibility testing for *Shigella* and *Campylobacter* isolates. Limitations include a patient population from a single healthcare system that may not necessarily be representative of MSM populations elsewhere, the lack of susceptibility testing for uncultured bacterial isolates, and a reliance on retrospective clinical data from chart review. An important limitation of our study is inherent to PCR-based testing, which is highly sensitive and able to detect both colonized and infected individuals. This may be particularly important for diarrheagenic *E. coli*, which is commonly found in asymptomatic carriers, but *Campylobacter* and *Shigella* may also be carried asymptomatically [43–45]. This underscores the importance of appropriate patient selection for testing and treatment [41, 46]; most patients in our study had symptoms consistent with acute gastroenteritis. It is possible that some of the organisms in patients with multiple targets detected were not responsible for the patients' symptoms.

In conclusion, MSM are at increased risk for gastroenteritis from a broad range of pathogens including diarrheagenic *E. coli*, *Giardia*, norovirus, and multidrug-resistant *Shigella* and *Campylobacter* spp. In the era of effective antiretroviral therapy, the clinical presentation and outcomes of enteric infections in individuals living with and without HIV appears to be comparable. However, antimicrobial treatment options are becoming limited, and persistent evidence of transmission through sexual contact suggests that current prevention strategies are ineffective. New approaches are needed to detect, treat, and prevent enteric infections in MSM.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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