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MAJOR ARTICLE

Comparison of Multiplex Gastrointestinal Pathogen Panel and Conventional Stool Testing for Evaluation of Patients With HIV Infection

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Background. Gastrointestinal pathogen panels (GPPs) are increasingly used to identify stool pathogens, but their impact in people with HIV (PWH) is unknown. We performed a retrospective cohort study comparing GPP and conventional stool evaluation in PWH.

Methods. We included all PWH who underwent GPP (Biofire Diagnostics; implemented September 15, 2015) or conventional testing, including stool culture, *Clostridium difficile* polymerase chain reaction testing, fluorescent smears for *Cryptosporidium* or *Giardia,* and ova and parasite exams (O&P) from 2013 to 2017. A total of 1941 specimens were tested, with 169 positive specimens detected in 144 patients. We compared result turnaround time, pathogen co-infection, antibiotic treatment, and treatment outcomes between positive specimens detected by conventional testing vs GPP.

Results. Overall, 124 patient samples tested positive by GPP, compared with 45 patient specimens by conventional testing. The GPP group demonstrated a higher co-infection rate (48.4% vs 13.3%; $P < .001$) and quicker turnaround time (23.4 vs 71.4 hours; $P < .001$). The GPP identified 29 potential viral infections that were undetectable by conventional stool tests. Unnecessary anti-infective therapy was avoided in 9 of 11 exclusively viral infections. Exclusively nonpathogenic parasites (n = 13) were detected by conventional stool tests, the majority of which were treated with metronidazole. There were no significant differences in clinical outcomes between groups.

Conclusions. In PWH, GPP implementation improved antibiotic stewardship through shorter turnaround times and detection of enteric viral pathogens.

Keywords. antibiotic stewardship; HIV; diarrhea; gastrointestinal pathogen panel.

Diarrhea is a prevalent gastrointestinal symptom in people with HIV (PWH), which may lead to increased morbidity and mortality [1, 2]. Rapid identification of potentially treatable causes of diarrhea is particularly important in immunocompromised persons. Deficient cellular immunity puts PWH at increased risk for opportunistic parasitic infections such as *Cryptosporidia* and *Microsporidia,* whereas high-risk sexual behaviors have been linked to *Shigella* and other relapsing infections [3, 4]. It is also important to identify potential causes of diarrhea in which antibiotic treatment is not indicated, such as Shiga-like toxin-producing *Escherichia coli* (STEC) or norovirus. In addition, persons with immunodeficiencies can have infectious gastroenteritis and not present with classical symptoms, making definitive diagnosis a challenge. The differential diagnosis in immunosuppressed persons is often broad and can require multiple tests that take days to result, including bacterial cultures and examinations for ova and parasites. A lengthy infectious work-up is required before noninfectious causes such as malabsorption (HIV enteropathy, lactose intolerance), medications, or supplements are considered [5].

Before the use of multiplex nucleic acid tests, ~80% of acute gastroenteritis cases (suspected foodborne) had no detected pathogen [6]. When compared with conventional methods, multiplex nucleic acid testing demonstrates faster turnaround times and thus more rapid diagnosis, treatment, and improved clinical sensitivity [7–16]. Although the use of multiplex gastrointestinal pathogen panels (GPPs) has increased over the past 5 years, the impact of these tests on PWH has not been investigated. To better understand the impact of GPP implementation, we compared the testing and treatment of diarrheal illnesses in PWH before and after the introduction of multiplex gastrointestinal (GI) panel testing.

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METHODS

Study Design

We performed a retrospective cohort study involving PWH presenting with gastrointestinal symptoms to the University of California, San Diego (UCSD). Patients were included if they had a diagnosis of HIV (based on documented HIV viral load polymerase chain reaction [PCR] and/or HIV 1/2 antibody enzyme-linked immunosorbent assay), were seen at UCSD between September 15, 2013, and September 15, 2017, and underwent stool testing for suspected symptoms of infectious gastroenteritis (diarrhea, blood in stool, fever, nausea/vomiting). UCSD implemented multiplex GI panel testing on September 15, 2015. This study was approved by the UCSD Institutional Review Board (IRB #181404).

Enteric Pathogen Testing

At our institution, infectious evaluation for diarrhea was performed exclusively using conventional stool testing (stool culture, *Clostridium difficile* PCR, *Cryptosporidium* smear [auramine stain], *Giardia/Cryptosporidium* fecal direct fluorescent antigen, ova and parasite exam [O&P], and trichrome stain) until September 2015. The *C. difficile* PCR test at our institution (Simplexa, Focus Diagnostics) detects *C. difficile* toxin B gene (tcdB). In September 2015, our institution implemented the GPP BioFire FilmArray GI Panel (BioFire Diagnostics, Salt Lake City, UT, USA) for both inpatient and outpatient diarrhea evaluation. This test detects nucleic acid from 22 pathogens (13 bacteria, 5 viruses, and 4 parasites). All persons with a positive enteric pathogen test from September 2013 to September 2017 were included for the current analysis. Persons with >1 positive result over the 4-year period were considered separate events if a new pathogen was detected.

Data Abstraction

We abstracted the following information from the medical records: (a) demographics: age, sex, ethnicity; (b) gastrointestinal disease characteristics: fever, diarrhea, nausea/vomiting, hematochezia, other; (c) laboratory results: CD4 T-cell count, HIV viral load; (d) enteric pathogen testing: test type, pathogen(s) identified, turnaround time to result; (e) treatment characteristics: gastroenteritis treated with targeted anti-infective therapy (initiated in response to results), empiric anti-infective therapy (initiated before results were available), anti-infective therapy exposure in the past 30 days, antiretroviral therapy (ART) status; and (f) outcomes: symptom resolution at 7 days and 30 days, diagnostic interventions (imaging, endoscopy, biopsy/cytology), hospitalization, and surgery.

Statistical Analysis

We compared GPP and conventional testing using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. A P value of <.05 was considered statistically significant. All statistical analyses were performed in R (version 3.5.1).

RESULTS

Patient Characteristics

A total of 1941 specimens were tested in PWH (n = 1705 conventional stool tests; n = 236 GPP), with 169 positive specimens detected in 144 patients from September 2013 to September 2017 (n = 45 conventional stool testing; n = 124 GPP). Seventeen patients had 2 separate positive pathogen tests, and 4 patients had 3 positive pathogen tests over the 4-year time period. Of this group, 10 patients had repeat infection with a previously identified pathogen. The average time elapsed between test dates (range) was 344 (42–856) days, with 4 repeat infections in <3 months). Baseline patient demographics and clinical presentation characteristics are summarized (Table 1). PWH with positive pathogen testing at our institution consisted predominantly of males (97%). The majority of persons presented with diarrhea (90.5%); 4% presented with hematochezia, 7.1% presented with fever, and 10.7% presented with nausea and/or vomiting. The overall mean CD4 T-cell count (SD) was 520 (332) cells/mL. Persons with a positive conventional stool test had significantly lower CD4 T-cell counts at presentation compared with persons with a positive GPP (372 vs 574 cells/mL; $P < .001$); however, CD4 T-cell counts were overall much higher after 2015. Most people were taking ART (82.2% in the conventional stool test group vs 85.4% in the GPP group; $P = .634$), and there was no difference in HIV viral load ($P = .49$).

Enteric Pathogen Testing

Overall, 124 PWH tested positive using GPP. The most common enteric pathogens detected by GPP were *E. coli* species (Table 2). Coinfection was higher in the GPP group, with up to 4 pathogens detected in a single patient sample compared with standard stool testing (48.4% vs 13.3%; $P < .001$). The GPP positivity rate among PWH was 52.5% (124 positive GPPs/236 total GPPs), higher than the overall observed rates at our institution (37.1% ± 2.2%; BiofireTrend Reports). Among the 45 positive samples by conventional stool testing, *Clostridium difficile* was the most common enteric pathogen detected (26.6% of positive specimens; 2.2% of total specimens). Before 2015, conventional ova and parasite testing often reported nonpathogenic protozoa, including *Entamoeba coli* (n = 7), *Entamoeba hartmanni* (n = 2), *Endolimax nana* (n = 7), *Iodamoeba butchilii* (n = 2), and *Blastocytis hominis* (n = 6).

The multiplex panel allowed for the identification of potential pathogens that could not be diagnosed with conventional testing. These included enteroaggregative *E. coli* (EAEC; n = 34), enterotoxigenic *E. coli* (ETEC; n = 5), and enteropathogenic *E. coli* (EPEC; n = 40). Twenty-nine potential viral etiologies were detected in 28 different persons (adenovirus, n = 2; astrovirus, n = 2; norovirus, n = 22; rotavirus, n = 1; sapovirus,

Table 1. Characteristics of Patients With HIV Infection With Positive Enteric Pathogen Testing Using Either Conventional Stool Evaluation or Multiplex Gastrointestinal Pathogen Panel

Characteristic	Conventional Stool Tests (n = 45)	GPP (n = 124)	*P*
Male, No. (%)	45 (100)	119 (96.0)	.326
Mean age (SD)	47.2 (9.2)	48.4 (10.2)	.523
Ethnicity, No. (%)			.171
White	22 (48.9)	72 (58.1)	
Black	4 (8.9)	10 (8.1)	
Hispanic	18 (40)	31 (25)	
Other	1 (2.2)	11 (8.9)	
Symptoms at presentation, No. (%)			
Diarrhea	41 (91.1)	112 (90.3)	>.999
Blood in stool	1 (2.2)	6 (4.8)	.676
Fever	1 (2.2)	11 (8.9)	.185
Nausea &/or vomiting	4 (8.9)	14 (11.3)	.783
Labs at presentation			
CD4 count, mean (SD)	371.8 (264.8)	574.3 (337.7)	<.001
Viral load copies/mL, No. (%)			.486
<50	31 (70.5)	93 (75)	
50–200	2 (4.6)	10 (8.1)	
≥200	11 (25)	21 (16.9)	
Receiving ART, No. (%)	37 (82.2)	105 (85.4)	.634

Abbreviations: ART, antiretroviral therapy; GPP, gastrointestinal pathogen panel.

n = 2), which would not have been identified before 2015. Not surprisingly, the implementation of the GPP at our institution decreased the utilization of conventional stool cultures by 66% (158 to 56 total cultures upon GPP implementation). Utilization of *Cryptosporidium* smear and ova and parasite exam were also dramatically decreased upon GPP implementation (262 vs 96 *Cryptosporidium* smears and 273 vs 91 O&P exams).

The overall mean turnaround time for positive results was significantly decreased with the institution of multiplex testing compared with conventional testing (23.4 vs 71.4 hours; $P < .001$) (Table 3). Detection of *Giardia* was decreased to an average of 22.4 hours with GPP, as opposed to 74.8 hours with conventional stool studies ($P < .001$). *Campylobacter* and *Salmonella*, 2 highly infectious bacterial species, were detected within 22.4 hours vs 56.5 hours for conventional testing ($P = .038$) and 10.7 hours vs 68 hours, respectively. The mean turnaround time for *Shigella*/enteroinvasive *E. coli* (SD) was 19.3 (11.4) hours. Twelve of the 22 *Shigella*/enteroinvasive *E. coli* EIEC were confirmed with culture. No *Shigella* sp. were detected by conventional stool tests.

Anti-infective Therapy

A summary of anti-infective therapy characteristics is included in Table 4. Of the positive specimens, a total of 134 of 169 (79.3%) patients received anti-infective therapy (75.6% of conventional stool tests and 80.7% of GPPs; $P = .5$). Of patients who received antibiotics, 21.3% were empirically treated, whereas 58.0% received targeted treatment once the test results were known. Of the patients who were empirically treated, 12 (34.3%) were continued on the same treatment once results were known. There were no differences between groups for antibiotic exposure or patients on prophylactic anti-infective therapy. CD4 T-cell count, HIV viral load, and ART status did not impact receipt of empiric antibiotic treatment. Empiric treatment between the positive-GPP and negative-GPP groups demonstrated no significant difference (21.3% of positive GPPs receiving empiric treatment vs 18.1% of negative GPPs receiving empiric treatment; $P = .549$).

To identify the impact of the GPP on antibiotic stewardship, we evaluated the treatment of viral infections, EAEC and EPEC, and nonpathogenic parasites (ie, *Entamoeba coli, Entamoeba hartmanni, Endolimax nana, Iodamoeba butchilii,* and *Blastocystis hominis*). Exclusive viral infections (not including viruses co-identified with bacteria or pathogenic parasites) were detected in 11 persons, only 2 of whom (18.2%) received antibiotics. EPEC was detected in 40 of 124 (32.3%) specimens, and 60% of those received treatment with ciprofloxacin (mono-infection 50%; co-infection 65.4%) (Table 4). EAEC was detected in 34 of 124 (27.4%) specimens, 76.5% of whom received treatment with ciprofloxacin, TMP-SMX, or azithromycin (mono-infection 71.4%; co-infection 77.8%) (Table 4). Nonpathogenic protozoa were exclusively detected in 13 persons, with 10 (76.9%) receiving anti-infective therapy (metronidazole n = 7; mebendazole/albendazole n = 1; ciprofloxacin n = 1; ceftriaxone n = 1). Three of 7 (42.9%) with *Entamoeba coli*, 0 of 1 (0%) with *E. harmanni,* 2 of 4 (50%) with *E. nana,* 2 of 2 (100%) with *I. butchilii,* and 4 of 5 (80%) with *Blastocystis hominis* were treated.

Table 2. Identification of Enteric Pathogens in Patients With HIV Detected by Gastrointestinal Pathogen Panel or Conventional Stool Testing

	Conventional Stool Evaluation (n = 45)	Gastrointestinal Pathogen Panel (n = 124)
Bacteria, No.		
CDI	11	29
Escherichia coli species		
EAEC	-	34
EPEC	-	40
ETEC	-	5
Campylobacter sp.	2	13
Salmonella sp.	1	1
Yersinia sp.	0	1
Shigella/enteroinvasive *E. coli*	0*	22*
Shigella sp. (confirmed)	0*	12*
Aeromonas sp.	1	0
Mycobacterium sp.	1	0
Viral, No.	0	29
Adenovirus	-	2
Astrovirus	-	2
Norovirus	-	22
Rotavirus	-	1
Sapovirus	-	2
Parasites, No.		
Cryptosporidium	5	3
Giardia lamblia	9	13
Nonpathogenic parasites, No.		
Entamoeba coli	7	0
Entamoeba hartmanni	2	0
Endolimax nana	7	0
Iodamoeba butchilii	2	0
Blastocytis hominis	6	0
Co-infections, No. (%)	6 (13.3)*	60 (48.4)*

Abbreviations: CDI, *Clostridium difficile* infection; EAEC, enteroaggregative *Escherichia coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*.

*Indicates a significant difference in detection between GPP and conventional stool testing; *Shigella*/enteroinvasive *E. coli* $P = .001$; *Shigella* sp. (confirmed) $P = .037$; co-infections $P < .001$.

Impact of Enteric Pathogen Testing on Clinical Outcomes

We compared the clinical outcomes (symptom resolution at 7 and 30 days, respectively) and interventions (imaging, endoscopy, pathologic tissue evaluation, and surgery) between subjects with a positive conventional stool test and subjects with a positive gastrointestinal pathogen panel. There were no significant differences in clinical outcomes or interventions between groups (Table 5).

DISCUSSION

In this retrospective cohort study of 169 PWH who tested positive by either conventional stool testing or multiplex GPP for symptoms suggestive of infectious gastroenteritis, we made several fundamental observations. Of interest, co-infection rates of 48.4% among the GPP-positive samples were higher than what has been reported in the literature for HIV-seronegative persons (12%–33%), as well as the rate of co-infection overall observed at our institution (24.3%; BioFire Trend Reports) [7, 8, 11–14]. The significance of co-infection is uncertain and warrants further investigation, particularly in PWH. The immunosuppression associated with HIV may result in prolonged shedding that potentially contributes to the increased detection of multiple pathogens. Prior studies have shown that multiple pathogens are more likely to be detected in children <5 years of age [12–14]. Different co-infections have also been described in other studies [7, 13]. One multinational study reported *Campylobacter* and EPEC as the most common co-infections, whereas EAEC, *Yersinia enterocolitica*, and norovirus were detected most frequently by FilmArray in a separate study [7, 13]. The role and impact of these specific pathogen combinations is not well established or understood. Interestingly, EPEC, an organism classically associated with developing countries and diarrhea in children, was the most frequently detected pathogen in our GPP group, and in 43.3% (26 of 60) of co-infections.

Consistent with previous studies comparing multiplex PCR pathogen panels with conventional stool studies, turnaround time was significantly decreased by PCR methods [7–16]. Faster turnaround times in the GPP group (23.4 vs 71.4 hours; $P < .001$) allowed decisions based on results within 24 hours in most patients. Rapid turnaround time may also allow faster implementation of infection prevention and isolation to decrease the risk of person-to-person transmission among hospitalized patients. Before the widespread use of nucleic acid testing, the detection of enteric viruses in PWH with diarrhea ranged from

Table 3. Turnaround Time From Collection to Reporting of the Key Bacterial (*Campylobacter* sp., *Salmonella* sp., *Shigella*/EIEC) and Parasitic (*Cryptosporidium, Giardia lamblia*) Pathogens

Turnaround Time, h	Conventional Stool Tests, Mean ± SD, h	Conventional Stool Tests, No.	GPP, Mean ± SD, h	GPP, No.	*P*
Overall	71.4 + 59.7	44	23.4 ± 16.9	124	<.001
Campylobacter sp.	56.5 ± 17.7	2	22.4 + 9.2	13	.038
Salmonella sp.	68.0	1	10.7	1	-
Shigella/EIEC	-	0	19.3 ± 11.4	22	-
Cryptosporidium	77.0 ± 60.7	5	27.9 ± 17.0	3	.393
Giardia lamblia	74.8 ± 47.5	9	22.4 ± 6.1	13	<.001

Abbreviations: EIEC, enteroinvasive Escherichia coli; GPP, gastrointestinal pathogen panel.

Table 4. Treatment Characteristics of HIV Patients With Positive Enteric Pathogen Testing Using Either Conventional Stool Evaluation or Multiplex Gastrointestinal Pathogen Panels

Characteristic	Conventional Stool Tests (n = 45), No. (%)	GPP (n = 124), No. (%)	*P*
Empiric therapy	11 (24.4)	25 (20.2)	.532
Retrospective targeted therapy	3 (27.3)	9 (37.5)	.709
Switched to targeted therapy	4 (36.4)	7 (28)	.703
Targeted therapy	23 (51.1)	75 (60.5)	.294
Pathogens of interest treated with anti-infective therapy			
EAEC mono-infection with targeted therapy		5/7 (71.4)	
EAEC co-infection with targeted therapy		21/27 (77.8)	
EPEC mono-infection with targeted therapy		7/14 (50)	
EPEC co-infection with targeted therapy		17/26 (65.4)	
Viral infection		2/11 (18.2)	
History of anti-infective therapy in past 30 d	15 (33.3)	30 (24.2)	.243
Receiving anti-infective prophylaxis	7 (15.6)	10 (8.1)	.159

Abbreviations: EAEC, enteroaggregative *Escherichia coli*; EPEC, enteropathogenic *E. coli*; GPP, gastrointestinal pathogen panel.

7.4% to 45% [17–19]. This study demonstrates that clinicians are appropriately deferring antibiotics in PWH with viral causes of infectious gastroenteritis (only 18.2% treated). Two areas we identified to improve antibiotic stewardship were the treatment of noninvasive *E. coli* in adults and nonpathogenic parasites. Although EAEC and EPEC are major causes of diarrhea in children, their importance in adults, even in PWH, is less clear [20–22]. Yet, 60% of persons with EPEC and 76.5% with EAEC received treatment with ciprofloxacin or azithromycin. Most persons with exclusive nonpathogenic protozoa (76.9%) received metronidazole, despite a reporting disclaimer as "nonpathogenic protozoan." Increased training in appropriate antibiotic use is warranted.

Another interesting finding was the importance of rapid diagnosis of *Shigella* infection by GPP during an outbreak that occurred during the study period. A large multistate outbreak of *Shigella* infection in men who have sex with men was reported in 2015–2016 [23]. We detected 12 cases of culture-confirmed *Shigella* sp. from 2015 to 2017, with none in the previous 2 years in this population. Reflex culture confirmation of *Shigella* sp. in *Shigella*/EIEC PCR–positive stools is important both for recovery of isolates to send to Public Health Laboratories [24] and for sensitivity testing, as increasing resistance to ciprofloxacin, trimethoprim-sulfamethoxazole, and azithromycin has been detected in *Shigella* sp. [25]. Another example of rapid outbreak detection occurred in Iowa and Nebraska during evaluation of the FilmArray GPP. An outbreak of *Cyclospora* was detected by the FilmArray GPP 1 week before detection by conventional testing [26]. Biofire Trend was implemented to provide BioFire users with an up-to-date view of GI pathogens circulating at their institution compared with nationally [27]. This is achieved by providing de-identified test results to a cloud database that is available in real time on the Syndromic Trends public website [27]. Utilization of Biofire Trend could potentially help detect the beginning of GI pathogen outbreaks specifically in PWH presenting with symptoms of infectious gastroenteritis.

The cost-effectiveness of multiplex PCR GPP has not definitively been established [28]. A study performed in the United Kingdom showed that GPP assay use resulted in $34 800 in laboratory expense while reducing overall health care costs by $69 500 (when accounting for hospital days, isolation costs, etc.) [29]. Beal et al. demonstrated a similar trend with increased laboratory expenses, with net savings of $293.61 per patient when hospital stay and radiology costs are taken into account [30]. Unfortunately, this question was beyond the scope of this study,

Table 5. Comparisons of Clinical Outcomes and Interventions Between Subjects With a Positive Conventional Stool Test and Subjects With a Positive Gastrointestinal Pathogen Panel

Clinical Outcomes and Interventions	Conventional Stool Tests (n = 45), No. (%)	GPP (n = 124), No. (%)	*P*
Symptom resolution at 7 d	2/32 (6.3)	13/63 (20.6)	.081
Symptom resolution at 30 d	10/42 (23.8)	34/111 (30.6)	.433
Interventions	2 (4.4)	8 (6.5)	>.999
Imaging	0 (0)	1 (0.8)	>.999
Endoscopy	2 (4.4)	6 (4.8)	>.999
Biopsy &/or cytology	1 (2.2)	3 (2.4)	>.999
Surgery	0 (0)	1 (0.8)	>.999

Abbreviation: GPP, gastrointestinal pathogen panel.

but it should continue to be evaluated, specifically considering the potential cost savings of appropriate anti-infective therapy.

We were unable to find any differences in clinical outcomes and interventions between conventional stool testing and GPP. This can be attributed to the subjectivity of symptom resolution in addition to persons being lost to follow-up.

In conclusion, based on this retrospective cohort study, the utilization of GPP in PWH is highly advantageous for the rapid turnaround time, the identification of viral infections that do not warrant antibiotic treatment, and the early identification of potential outbreaks. Future studies should be performed to evaluate the significance of multiple pathogens detected by GPP in HIV patients. In addition, the use of GPP to detect outbreaks in PWH warrants further investigation. The cost-effectiveness of multiplex PCR also warrants further investigation, particularly in the outpatient setting when hospital stay and isolation cost savings are noncontributory.

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