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MAJOR ARTICLE

Diagnosis of *Yersinia enterocolitica* Infection in Cancer Patients With Diarrhea in the Era of Molecular Diagnostics for Gastrointestinal Infections

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Background. *Yersinia enterocolitica* is an uncommon cause of diarrhea, mesenteric adenitis and bacteremia in the United States. There is limited information regarding the clinical course in immunocompromised patients. We describe the clinical presentations and outcomes in patients with cancer with *Y. enterocolitica* diagnosed at a US cancer center before and after introduction of gastrointestinal multiplex panel (GIMP) nucleic acid amplification tests (NAATs).

Methods. We reviewed medical records of all patients with *Y. enterocolitica* isolated from cultures or identified by means of NAATs from 2000 to 2018. We then extracted demographic information, clinical characteristics, treatment, and overall mortality rate at 30 days after the diagnosis of yersiniosis.

Results. We identified 17 cases: 6 cases by culture before April 2016 and 11 cases by NAATs after that; 4 of the latter were confirmed by means of culture (36%). This represented an 8-fold increase for overall detection and a 3-fold increase in culture-proved infections when adjusted per 1000 admissions. The most common presenting symptom was diarrhea (11 of 14 [79%]), followed by abdominal pain (9 of 14 [64%]) and nausea and vomiting (6 of 14 [43%]). In 1 patient, the infection resolved spontaneously; the other patients received antibiotic treatment, the majority with a fluoroquinolone. The 30-day mortality rate was 7.1%, and the cause of death was a complication of advanced cancer.

Conclusion. Since implementing use of the GIMP, we observed an increase in *Y. enterocolitica* cases, possibly related to increasing number of patients with cancer at our institution who are receiving intensive immunosuppression, increased testing due to ease and availability, and increased sensitivity of NAATs. GIMP NAATs are redefining the epidemiology of *Y. enterocolitica* infection in patients with cancer.

Keywords. Gastrointestinal multiplex panel (GIMP); immunocompromised host; molecular diagnostics; nucleic acid amplification testing (NAAT); *Yersinia enterocolitica*.

Yersinia enterocolitica, a facultative anaerobic, gram-negative coccoid bacillus belonging to the Enterobacteriaceae family, is frequently acquired by ingesting or handling undercooked pork products [1], and causes a clinical syndrome typically consisting of fever, abdominal pain, and diarrhea [2]. Although it is difficult to distinguish clinically from other causal agents of diarrheal syndromes, yersiniosis can mimic acute appendicitis, presenting with acute right lower abdominal pain, fever, and vomiting. At surgery, inflammation is not found in the appendix itself but surrounding the appendix, in the terminal ileum and the mesenteric lymph nodes, a phenomenon known as "pseudo-appendicitis." *Y. enterocolitica* will sometimes grow in cultures of the appendix and mesenteric lymph nodes, but they can be negative owing to the fastidious nature of the organism [3].

Acute yersiniosis can have serious complications, such as *Yersinia* septicemia, especially in immunocompromised hosts, infants, and those with iron overload states [4].

The diagnosis of yersiniosis can be made by culture of stool, appendix, mesenteric lymph node, throat, or blood [5]. The diagnosis is often missed, because stool cultures are rarely positive, and most laboratories do not specifically test for *Y. enterocolitica.*

With the advent of the nucleic acid amplification test (NAAT) gastrointestinal multiplex panel (GIMP) in recent years, clinicians can now detect gastrointestinal pathogens with high sensitivity and much faster turnaround time. As an example, Rand et al [6] showed that, among 158 patients with negative culture results, the BioFire FilmArray Gastrointestinal

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Panel was positive for ≥1 enteric pathogen in 35 of the patients (22.2%). In the immunocompromised population, such panels are especially useful, because infectious diarrhea is more prevalent and associated with increased disease. Rapid results are needed, because results affect decisions regarding treatment and infection control.

Based on surveillance data collected by the Foodborne Diseases Active Surveillance Network (FoodNet) operated by the Centers for Disease Control and Prevention (CDC), the incidence of *Y. enterocolitica* has been increasing steadily in the past 3 years, from 139 cases in 2015 to 302 in 2016 and 489 in 2017 [7]. The increase has been shown by culture methods as well as culture-independent diagnostic testing, such as the NAAT GIMP. FoodNet reports that the use of a GIMP to detect gastrointestinal pathogens increased from 2 per 460 laboratories (<1%) in 2013 to 59 per 421 laboratories (14%) in 2016. The CDC postulates that the increase in incidence is multifactorial, including increased ordering of testing owing to the ease and availability of NAATs, increased detection owing to increased sensitivity of NAATs compared with culture-based methods, and increased number of infections.

Although most cases of uncomplicated yersiniosis in the immunocompetent host are self-limited and do not require treatment with antimicrobials, the course of infection in immunocompromised hosts has not been well studied, and whether it should be treated with antimicrobials is open to question. Before the molecular diagnostic era, *Y. enterocolitica* infections at The University of Texas MD Anderson Cancer Center (MDACC) were diagnosed very infrequently. However, since introduction of the GIMP, we have seen a surge of *Y. enterocolitica* infections. Because this organism has not been studied in the immunocompromised host in the past, we set out to study the epidemiology, clinical characteristics, clinical course, coinfections, risk factors, mortality rate, and antimicrobial treatment in this patient population.

METHODS

We queried the microbiology laboratory database at MDACC and identified a total of 17 patients who had *Y. enterocolitica* infections from the year 2000 to May 2018. Eleven patients were identified using the GIMP from April 2016 to May 2018, and 6 were identified by means of culture only, before the molecular diagnostics era. Three of the 6 with positive cultures were early enough in the database to have only paper medical records; a thorough review of their records could not identify all the information necessary for this case series, so these 3 patients were excluded. As a result, we report herein findings in a total of 14 patients in whom demographic information, comorbid conditions, coinfections, clinical characteristics, treatment, and overall mortality rate 30 days after diagnosis were evaluated. This retrospective study was approved by the institutional review board, with a waiver for consent.

RESULTS

Demographic data, underlying cancer, clinical presentation, imaging findings, degree of immunosuppression, coinfections, and antimicrobial treatment for all 14 patients are shown in Table 1. The patients' mean age (standard deviation) was 54 (14) years, and they included 7 men and 7 women. Race was predominantly white, followed by Asian; almost a third of the white patients were Latino. Solid tumor comprised 64% of the cancer cases, with hematologic cancer making up 36%; a third of the patients had undergone hematopoietic stem cell transplantation (HSCT). Ten of the infections were community acquired. In 4 patients, infections were diagnosed >48 hours after admission, in 2 after HSCT. The patients who had undergone HSCT did not seem to have worse outcomes from *Y. enterocolitica* than those patients with solid tumors. The most common presenting symptom was diarrhea, followed by abdominal pain, nausea/vomiting, and fever. One patient had bacteremia along with pseudoappendicitis.

From the introduction of the GIMP at MDACC, in April 2016, through May 2018, a total of 11 cases of *Y. enterocolitica* infection were identified at our institution. In contrast, only 6 cases were identified from 2000 to 2016 by culture-based methods. Four of the 11 cases (36%) detected using the GIMP were confirmed by culture. Overall, 2.5 cases of yersiniosis were identified for every 1000 NAATs performed at our institution. When adjusted for the number of admissions for each of the study periods, the incidence of *Y. enterocolitica* infection was 0.13 infections per 1000 inpatient admissions after the introduction of NAATs, compared with 0.016 per 1000 inpatient admissions in the culture-only period, which amounts to an 8-fold increase. In the NAAT period, when all positive results are reflexed to a stool culture, the number of culture-proved infections was 0.047 infections per 1000 patient admissions, translating to a 3-fold increase compared with the culture-only period.

Three (19%) patients had coinfection with *Clostridioides* (formerly *Clostridium*) *difficile* and 4 (25%) patients had previous *C. difficile* infection (CDI). Treatment varied greatly. Clinicians elected to treat all but 1 patient with antimicrobials; the antimicrobial of choice was a fluoroquinolone (55%), followed by cephalosporin (25%) and β-lactam (13%). Tetracyclines, trimethoprim-sulfamethoxazole, and carbapenem were each used in 1 patient (Table 2). All of these patients recovered from their infections. The 30-day mortality rate in these patients was 7.1%. The death all occurred as a result of advanced cancer.

DISCUSSION

Clinical presentations of *Y. enterocolitica* infection in patients with cancer are varied and can include typical and atypical presentations. Onset of diarrhea and positive cultures >48 hours after admission suggest healthcare acquisition or possibly asymptomatic carriage with reactivation of infection

Table 1. Characteristics of Patients With *Yersinia enterocolitica* Infections in the Case Series

Patient Age, y/Sex/ Race/ Ethnicity	Underlying Cancer	Recent Cancer Therapy	Presenting Symptoms	Absolute Neutrophil/ Lymphocyte Count, × 10^3 Cells/μL	Imaging	Acquisition	Culture/Co-infection	Treatment
63/M/white	Maxillary sinus SCC	None	Abdominal pain, diarrhea	7.14/0.99	No imaging performed	Community	Stool: *Y. enterocolitica,* Resistant to amoxicillin-clavulanate	None
79/M/Asian	Pancreatic cancer, CVA	None	Change in mental status, abdominal pain, diarrhea	20.6/0.67	Thickened sigmoid, rectum	Transfer from rehabilitation facility >7 days	*C. difficile*	Oral vancomycin, metronidazole, cefepime
63/F/Asian	DLBC lymphoma, autologous HSCT, MRD HSCT days 162, GVHD	Steroids tacrolimus	Abdominal pain, nausea and vomiting, diarrhea for 2 days	5.62/0.85	Ileus	Community	Negative	Decrease Steroids, trimethoprim-sulfamethoxazole
25/F/Latino	Aplastic anemia, MUD HSCT days 63, GI GVHD	CSA, steroids, ATG, tacrolimus	Nausea, abdominal pain, diarrhea for 2 days	6.93/2.84	No imaging performed	Community	Negative	Levofloxacin
64/FLatino	AML, MRD HSCT days 168, GVHD	Steroids	Upper GI tract ulcers with bleeding, diarrhea for 2 days, abdominal pain	4.66/0.57	Bleeding from upper GI tract	Ate Spam from home as inpatient on days 54	Negative	Ciprofloxacin, ceftriaxone
49/M/white	Adenocarcinoma of rectum, pelvic exenteration	None	Nausea, vomiting for 2 wk, fever, increased colostomy output for 2 days	5.06/1.00	Fluid collection in pelvis	Community	Negative	Piperacillin-tazobactam, IV vancomycin, ciprofloxacin
46/M/white	AML, MUD HSCT days 93, BK virus cystitis, CTL infusion, HHV-6, EBV reactivation	Steroids, tacrolimus	Diarrhea for 2 days, profuse, diffuse abdominal pain,	2.31/0.43	No imaging performed	Inpatient days 110	Stool: *Y. enterocolitica* R amoxicillin-clavulanate	Ciprofloxacin
62/M/Asian	Poorly differentiated metastatic lung cancer, anti-HBc positive	Carboplatin, etoposide	Fever, malaise, chills, abdominal pain	25.93/3.87	Ileocecal thickening, mesenteric adenopathy	Community	Stool: *C. difficile*, ETEC; |blood: *Y. enterocolitica,* R amoxicillin-clavulanate	Piperacillin-tazobactam, IV vancomycin de-escalated to oral vancomycin, ceftriaxone
58/F/white	DLBC lymphoma, autologous HSCT	Carmustine, etoposide, cytarabine, melphalan, rituximab	Fever, chills, diarrhea, abdominal pain	1.46/0.09	No imaging performed	Community, eating pork sandwich	*C. difficile*	IV vancomycin, cefepime, oral vancomycin, fidaxomicin
68/F/white	Metastatic NSCLC	Poziotinib	Nausea, diarrhea	13.14/0.6	No imaging performed	Community	Stool: *Y. enterocolitica*	Doxycycline
49/Mwhite	Metastatic tonsillar SCC	Ipilimumab	Diarrhea	6.66/0.49	No imaging performed	Community	Stool: *Y. enterocolitica*	Ciprofloxacin
53/M/white	Metastatic colon cancer	Regorafenib	Fever, rectal pain, vomiting	Not available	Small perianal abscess	Community vs hospital?	Perianal wound: *Y. enterocolitica, Citrobacter, Enterococcus*	Ciprofloxacin
46/F/Latino	Pancreatic cancer	Cisplatin, interferon alfa, 5-FU	Abdominal wall abscess	Not available	Abdominal wall abscess near scar from Whipple procedure	Community	Abscess culture: *Y. enterocolitica, Enterococcus,* CoNS, α-hemolytic *Streptococcus*	IV vancomycin, imipenem, de-escalated to moxifloxacin
31/F/white/ Middle Eastern	Metastatic melanoma	Dabrafanib/ trametinib, IL-2, prednisone	Diarrhea, acute on chronic RLQ pain, nausea, vomiting	3.52/1.32	None	Community, sushi	Stool: *Y. enterocolitica* R amoxicillin-clavulanate	Ciprofloxacin

Abbreviations: 5-FU, fluorouracil; anti-HBc, antibody to hepatitis B core antigen; ATG, antithymocyte globulin; CoNS, coagulase-negative *Staphylococcus* species; CSA, cyclosporine; CTL, cytotoxic lymphocyte; CVA, cerebrovascular accident; DLBC, diffuse large B cell; EBV, Epstein-Barr virus; ETEC, enterotoxigenic *Escherichia coli*; GI, gastrointestinal; GVHD, graft-vs-host disease; HHV, human herpesvirus; HSCT, hematopoietic stem cell transplantation; IL-2, interleukin 2; MRD, matched related donor; MUD, matched unrelated donor; NSCLC, non–small cell lung cancer; RLQ, right lower quadrant; SCC, squamous cell carcinoma.

Table 2. Characteristics, Treatment, and Mortality Rate in Patients With *Yersinia enterocolitica* Infections in the Case Series

Characteristics, Treatment, and Outcome	Patients, No. (%)[a] (n = 14)
Age, mean (SD), y	54 (14)
Sex	
Male	7 (50)
Female	7 (50)
Race/ethnicity	
White	11 (79)
Black	0
Asian	3 (21)
Other	0
Latino	3 (21)
Underlying cancer	
Solid	9 (64)
Hematologic	5 (36)
HSCT performed	5 (36)
Clinical presentation	
Fever	4 (29)
Nausea/vomiting	6 (43)
Abdominal pain	9 (64)
Diarrhea	11 (79)
Bacteremia	1 (7)
Pseudoappendicitis	1 (7)
Absolute cell count, median, × 10^3 cells/μL	
Neutrophils	6.14
Lymphocytes	0.76
Imaging findings	
Colitis	2 (14)
Adenitis	1 (7)
C. difficile infection	
Coinfection	3 (21)
Previous infection	4 (29)
Treatment used for infection	
None	1 (7)
Tetracycline	1 (7)
Sulfa	1 (7)
Fluoroquinolone	8 (57)
Cephalosporin	4 (29)
β-Lactam	2 (14)
Carbapenem	1 (7)
30-d Mortality rate, %	7.1

Abbreviations: HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
[a]Data represent no. (%) of patients unless otherwise specified.

during immunosuppression. In a patient in our series with acute myeloid leukemia after HSCT, *Y. enterocolitica* infection developed on hospital day 110, raising the question of a healthcare-associated infection. However, it was unlikely for him to have eaten contaminated food in the hospital environment unless food was brought in from home. No other cases of yersiniosis were found at the hospital at that time to suggest an outbreak. His clinical picture posed the possibility that he could have been colonized by the organism in the past, and severe immunosuppression caused the infection to become clinically apparent.

In the setting of HSCT, a number of infections can reactivate, such as herpesviruses, hepatitis B, bacteria such as *Mycobacterium tuberculosis*, and parasites such as *Toxoplasma* and *Strongyloides*. Another possibility would be acquiring yersiniosis from blood transfusion; the CDC has reported a case series of transfusion-associated *Y. enterocolitica* sepsis [8]. The patient described above did receive packed red blood cells daily for weeks before the onset of diarrhea. However, blood products undergo rigorous testing before being released for transfusion, with testing for bacterial contamination as a major step, so the likelihood that this patient received blood contaminated with *Y. enterocolitica* is low.

Another patient with widely metastatic lung cancer presented with septic shock and was found to have *Y. enterocolitica* bacteremia as well as pseudo-appendicitis at imaging, a classic presentation of this pathogen. Finally, watery diarrhea occurred in a patient with maxillary sinus squamous cell cancer who had undergone resection, chemotherapy, and radiation and had recurrent CDI. GIMP results were positive for *Y. enterocolitica,* but by the time antibiotics were prescribed, the patient's symptoms had completely resolved. It is important to note that he was not receiving immunosuppressive medications like most of the other patients in the case series, which may have made a difference in the spontaneous and rapid resolution. The other patients in this case series were receiving chemotherapy for cancer or immunosuppression for graft-vs-host disease, in addition to their preexisting compromised state due to cancer, which made it difficult for the clinician not to prescribe antibiotics.

Historically, *Y. enterocolitica* is known to affect countries with colder climates and is seen more frequently in the wintertime. In our cohort of patients, spring seems to be the common season.

The significance of *Y. enterocolitica* in wound cultures in our case series was difficult to discern: 1 wound culture was from a small, perianal abscess—*Y. enterocolitica*, along with a number of other enteric organisms, grew from the same culture—and the other was an abdominal wall abscess near the incision of Whipple procedure for pancreatic adenocarcinoma. It was also a polymicrobial infection with a number of other enteric organisms (Table 1). In these cases, it may be more plausible that the polymicrobial abscess is the cause of the infection rather than *Y. enterocolitica* alone.

The 8-fold increased *Y. enterocolitica* infection rate among immunocompromised patients at our institution since the introduction of the GIMP could be related to the increasing number of patients with cancer at our institution who are receiving intensive immunosuppression, increased testing due to ease and availability, and the increased sensitivity of NAATs. In a personal communication (Rodriguez-Barradas M, 7 November 2018) with an infectious disease provider at another tertiary facility in the Houston area that has also used GIMP testing for the past 2 years, we learned that they have detected no cases of *Y. enterocolitica* thus far, suggesting that

the increased prevalence of *Y. enterocolitica* at our facility is be more likely to result from intensive immunosuppression in our patient population, rather than from increased testing. Positive NAAT results with negative cultures probably reflect prior antibiotic therapy and carriage of low enteropathogen numbers, but we cannot exclude the possibility of false-positive results.

More than half of the patients had either concomitant or previous CDI, suggesting some shared risk factors. For patients in whom both were detected using the GIMP, it was difficult to discern which was the true pathogen. After *C. difficile* was detected with the GIMP, a reflex toxin assay was done, with positive results for all 3 patients, suggesting true infection. Nevertheless, both organisms were treated with antimicrobials, but it is crucial to be cognizant that antimicrobials used for *Y. enterocolitica* may further disrupt native bowel flora and place patients at risk for recurrent CDI.

The only other copathogen identified was enterotoxigenic *Escherichia coli* in the patient who had septic shock with *Y. enterocolitica* bacteremia as well as CDI. None of the other patients had coinfections with other organisms other than *C. difficile*.

In immunocompetent patients, *Y. enterocolitica* infection is most often a self-limiting condition. There are no case-control trials supporting antimicrobial treatment of uncomplicated yersiniosis, such as *Y. enterocolitica* enterocolitis. In a prospective, placebo-controlled Canadian study with 34 children, no clinical benefit was demonstrated with treatment with trimethoprim-sulfamethoxazole [9]. A Norwegian study also concluded that the duration of illness did not differ between patients who were treated and those who were untreated, although bacterial shedding in stool did decrease after treatment [10]. The initiation of therapy was quite late (12 and 21 days after the onset of illness, respectively) in the clinical course in both trials, so it is unclear whether early treatment could have made a difference.

Of the 14 immunocompromised patients in our series, 13 were treated with antibiotics, a decision that was guided by clinical judgment, and 1 infection resolved spontaneously. The 13 patients who received antibiotics all recovered from their infection. GIMP NAATs are redefining the epidemiology of *Y. enterocolitica* infections in patients with cancer.

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