Clinical Illnesses Associated with Isolation of Dysgonic Fermentor 3 from Stool Samples

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The clinical significance of the fastidious organism DF-3 isolated from stool cultures is unclear. We sought to improve our understanding of this organism and to further define its association with human disease. Stool cultures for DF-3 were obtained from three sources: an ongoing study of enteric pathogens in patients infected with the human immunodeficiency virus, a screening procedure in which all stool samples submitted for *Clostridium difficile* toxin assay were cultured for DF-3, and stool samples submitted specifically for DF-3 culture. Retrospective clinical data were obtained from chart reviews of patients with positive cultures. Antimicrobial susceptibility testing and cell wall fatty acid analysis were performed for each DF-3 isolated. Eight isolates of DF-3 were obtained over a period of 8 months. All patients either had severe underlying disease or were immunocompromised, including three patients coinfected with human immunodeficiency virus and two patients with inflammatory bowel disease. The spectrum of clinical disease ranged from chronic diarrhea with a well-defined response to therapy for DF-3 to an asymptomatic carrier state. Cell wall fatty acid analysis of these isolates demonstrated a consistent pattern with a large peak of 12-methyltetradecanoate. DF-3, a fastidious gram-negative coccobacillus, can be recovered from stool cultures of immunocompromised patients by using selective media. The presence of 12-methyltetradecanoate in cell wall fatty acid analysis assists in identification. The increased use of a selective medium-(cefoperazone-vancomycin-amphotericin B) in the evaluation of diarrhea in immunocompromised hosts, including persons with inflammatory bowel disease, may better define the association of DF-3 with human gastrointestinal disease.

DF-3 is the designation given by the Special Bacterial Pathogens Laboratory of the Centers for Disease Control for a fastidious, small, coccobacillary gram-negative organism (4). Wagner et al. (12) reported on 53 DF-3 isolates from a variety of sources that were referred to the Centers for Disease Control through 1987; 10 of the isolates had been recovered from blood cultures. The organism has been associated with human disease, including soft-tissue infection (2), bacteremia (1), and diarrhea (12). The role of this organism as a cause of diarrhea has been suggested by Wagner et al. (12), although the mechanisms remain unclear.

DF-3 does not grow well on standard enteric isolation media such as MacConkey, Salmonella Shigella, xylose-lysine-deoxycholate agars or most selective Campylobacter media incubated at 42°C. It is best recovered from stool specimens through the use of selective culture media containing antimicrobial agents, such as cefoperazone and vancomycin, that inhibit the overgrowth of normal stool flora. An example of this medium is cefoperazone-vancomycin-amphotericin (Remel Laboratories, Lenexa, Kans.) blood agar incubated at 35°C. Thus, the organism will not be recovered from routine stool cultures in most laboratories unless a specific search is made.

The agents of diarrhea in immunocompromised patients include common bacterial pathogens, mycobacteria, protozoa, fungi, and viruses (3, 11, 14), although a definable etiology is present in only 60% of cases (10). The linkage between DF-3 and diarrhea in the few reported cases is based on clinical recovery following antimicrobial therapy and elimination of the organism from follow-up stool specimens. We sought to improve our understanding of the role of DF-3 in diarrheal disease by prospective screening of stool samples submitted for culture. As a result, we report eight cases of enteric DF-3 in immunocompromised patients.

CASE REPORTS

Patient 1. A 38-year-old white female with steroid-dependent asthma noted 20 to 30 watery, nonbloody stools per day associated with crampy abdominal pain but no fever. Initial cultures for typical enteric pathogens, *Clostridium difficile* toxin assay, and parasite examination revealed only *Blastocystis hominis*. Metronidazole therapy for 2 weeks had no effect on the diarrhea. Quantitative immunoglobulins showed an immunoglobulin G (IgG) level of 531 mg/dl (normal range, 600 to 1,480 mg/dl). Sigmoidoscopy with biopsy revealed normal colonic mucosa. Following 3 months of symptoms, selective media culture revealed DF-3. A repeat culture confirmed a moderate growth of DF-3. Clindamycin at 300 mg four times a day (q.i.d.) orally (p.o.) for 2 weeks resulted in rapid improvement of her symptoms and clearance of DF-3. She has remained asymptomatic at 6 months.

Patient 2. A 31-year-old white female developed acute, profuse watery diarrhea accompanied by crampy abdominal pain and bloating. She had a 25-lb weight loss. Initial
evaluation, not including a culture for DF-3, showed no evidence of an infectious etiology. Treatment with courses of metronidazole, tetracycline, and cholestyramine yielded no improvement. A small bowel biopsy suggested nontropical sprue and a 2-month trial of a gluten-free diet had no effect on her symptoms. A barium contrast study showed mild irregularity of her terminal ileum. Colonoscopy revealed several aphthous ulcers with a biopsy showing inflammation. An abdominal computerized tomography scan demonstrated mesenteric and retroperitoneal lymph node enlargement, and biopsy of these lymph nodes showed reactive hyperplasia. A diagnosis of possible inflammatory bowel disease was made and prednisone at 40 mg/day for 2 months resulted in improvement in her stool frequency, though some diarrhea persisted. Her symptoms had persisted for 9 months when stool was submitted specifically for DF-3 isolation. The culture was positive on two occasions for DF-3. Immunologic evaluation demonstrated a serum IgG level of 696 mg/dl (normal range, 706 to 1,451 mg/dl), an IgG level of 7 mg/dl (normal range, 10 to 190 mg/dl), negative human immunodeficiency virus (HIV) serology, and normal T-cell subsets. Therapy with tetracycline at 500 mg p.o. q.i.d. for 2 weeks did not affect her symptoms, and a follow-up culture showed persistence of DF-3. Susceptibility testing of her isolate showed only intermediate susceptibility to tetracycline with clindamycin showing a large zone of inhibition. Clindamycin at 300 mg p.o. q.i.d. was given for 2 weeks and follow-up culture 4 weeks later was negative for DF-3. Her symptoms had improved but not resolved. Follow-up at 6 months found her to be minimally symptomatic with an episode of diarrhea every 3 to 4 weeks.

Patient 3. A 43-year-old white male with a history of Hodgkin's disease 14 years prior, colon cancer requiring colectomy and ileostomy 2 years prior, and recent chemotherapy was admitted for surgical correction of acute ureteral obstruction. Seven days following his surgical procedure, during which he received ampicillin and gentamicin, the ostomy output increased and a diarrheal evaluation was done. Stool studies were negative for routine enteric pathogens, including C. difficile. A selective stool culture after 2 weeks of diarrhea grew DF-3. Although the isolate was resistant to ciprofloxacin, the patient received this agent for a concomitant urinary tract infection and had gradual decrease in stool output over 2 weeks. A repeat stool culture for DF-3 6 months later was still positive.

Patient 4. A 43-year-old white male with HIV infection (CD4* = 16/mm3) and Pneumocystis carinii pneumonia was diagnosed with cryptosporidium 8 months prior to the documentation of DF-3 from abnormal stool. He had experienced 8 months of intermittent, painless, watery diarrhea. Medications included clotrimazole, amitryptiline, probanthine, diphenoxylate hydrochloride, and codeine. Therapy with doxycycline at 100 mg p.o. twice daily for 2 weeks resulted in mild improvement in his stool output. Follow-up cultures on two occasions were negative for DF-3. Retreatment with tetracycline at 500 mg q.i.d. resulted in no further improvement in his persistent intermittent diarrhea.

Patient 5. A 59-year-old white female diabetic with chronic renal failure was admitted with a 3-day history of nausea, vomiting, and diarrhea, characterized by passage of four to five loose to watery stools each day. There was no history of fever, chills, or abdominal pain. DF-3 was isolated from one of the diarrheal stool specimens. A barium enema showed the diarrhea spontaneously cleared after 3 days without specific therapy. Follow-up stool examinations were not done.

Patient 6. A 42-year-old HIV-infected white male (CD4* = 638/mm3) developed intermittent crampy abdominal pain associated with intermittent bloody diarrhea 7 months prior to evaluation. Following a colonoscopic biopsy a diagnosis of inflammatory bowel disease was made. Treatment with sulfasalazine, metronidazole, and prednisone resulted in modest improvement. Stool culture for enteric pathogens, including DF-3, and examination for parasites were negative 3 months prior to evaluation. Because of persistent symptoms, a colonoscopic evaluation and biopsy were performed and showed severe acute and chronic inflammation. Stool examination at this time was remarkable for B. hominis, and cultures grew DF-3. Tetracycline therapy at 500 mg q.i.d. was given for 2 weeks. A follow-up culture for DF-3 4 weeks after completing therapy was negative. Although there seemed to be some clinical improvement, intermittent crampy abdominal pain and bloody diarrhea continued.

Patient 7. A 45-year-old Hispanic male with alcoholic liver disease, Reiter's syndrome, and a poorly defined vasculitis was maintained on prednisone and azathioprine. Quantitative immunoglobulins showed a polyclonal increase in IgG. He presented with 2 weeks of bloody diarrhea and decompression of his liver disease. A sigmoidoscopy demonstrated normal mucosa, and a biopsy revealed nonspecific chronic inflammation. A culture of stool demonstrated growth of DF-3 and was otherwise negative. No antimicrobial therapy for DF-3 was prescribed. Death followed upper gastrointestinal bleeding, encephalopathy, and the development of hepatoportal syndrome.

Patient 8. A 49-year-old black male with a HIV infection, remote splenectomy, CD8 lymphocytosis syndrome (sicca syndrome, chronic pulmonary infiltrates; CD8* = 9,000/ mm3, CD4* = 900/mm3), and on tuberculosis suppression had his stool screened as part of the HIV enteric study. DF-3 was isolated in the absence of gastrointestinal symptoms from formed stool. Medications included isoniazid and ranitidine and both amoxicillin and ciprofloxacin in the preceding 3 months for sinusitis. Complete microbiologic analysis of stool revealed no typical enteric pathogens (bacteria, mycobacteria, viruses, or parasites). A follow-up culture 6 months later revealed no evidence of DF-3 and the patient has remained without gastrointestinal symptoms.

MATERIALS AND METHODS

DF-3 isolates were obtained from the clinical microbiology laboratories at the National Jewish Center for Immunologic and Respiratory Diseases (two cases), the Denver Veterans Affairs Medical Center (five cases), and the Denver Presbyterian-St. Lukes Medical Center (one case). The isolates were recovered from stool specimens submitted from three sources: patients with undiagnosed diarrhea who had stool submitted specifically for DF-3, patients who underwent a screening procedure in which all stool specimens submitted for the evaluation of C. difficile over a specific period were simultaneously cultured for DF-3, and from an ongoing study of HIV enteric pathogens. This HIV study is a prospective investigation of the microbiology of the stool of HIV-infected persons. Persons entering this study have stool samples examined for ova and parasites and cultures for typical bacterial pathogens as well as viral, fungal, and mycobacterial cultures. These stool samples are screened regardless of the presence of symptoms.

The results of the culture identifications and susceptibility testing data were reported to the caregiver who made the decision to treat. Several patients underwent endoscopy, and histology results have been noted.
TABLE 1. Clinical characteristics of patients from whom DF-3 was isolated from stool culture

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Underlying disease</th>
<th>Duration of symptoms (wk)</th>
<th>Stool character</th>
<th>Presence of Cramps</th>
<th>Presence of Fecal leukocytes</th>
<th>Therapeutic response*</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>F</td>
<td>Asthma, corticosteroids</td>
<td>12</td>
<td>Watery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>F</td>
<td>Colitis, corticosteroids</td>
<td>36</td>
<td>Watery</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Normalb</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>M</td>
<td>Hodgkin's, colon cancer</td>
<td>2</td>
<td>Watery</td>
<td>No</td>
<td>ND</td>
<td>NA*</td>
<td>Partial ND</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>M</td>
<td>HIV, cryptosporidium</td>
<td>32</td>
<td>Watery</td>
<td>No</td>
<td>ND</td>
<td>No</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>F</td>
<td>Diabetes, CRF&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1</td>
<td>Watery</td>
<td>No</td>
<td>No</td>
<td>NA*</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>M</td>
<td>HIV, colitis</td>
<td>28</td>
<td>Bloody</td>
<td>Yes</td>
<td>ND</td>
<td>No</td>
<td>Inflammation</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>M</td>
<td>Cirrhosis, vasculitis</td>
<td>2</td>
<td>Loose</td>
<td>No</td>
<td>ND</td>
<td>NA*</td>
<td>Inflammation</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>M</td>
<td>HIV, splenectomy</td>
<td>0</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Yes, well-defined clinical response to antimicrobial agents to which the strain was susceptible.
<sup>d</sup> Normal biopsy at the time of recovery of DF-3. Patient had inflammation on a previous biopsy.
<sup>b</sup> ND, not determined.
<sup>d</sup> CRF, chronic renal failure.
<sup>*</sup> NA, not applicable.

Recovery from stool specimens. The stool specimens were streaked onto blood agar plates containing cefoperazone-vancomycin-amphotericin (Remel Laboratories). All plates except one were incubated in 5% CO₂ at 35°C. One of the isolates was recovered after incubation at 42°C. After 24 h of incubation, colonies appear tiny and pinpoint in size, enlarging to gray and/or white, with entire colonies measuring 2 to 3 mm in diameter after 48 to 72 h of incubation. Presumptive identifications were made by recovery of typical colonies on the selective medium. The detection of a unique sweet, fruity odor and demonstration of negative catalase and cytochrome oxidase reactions by using standard techniques were helpful clues to the identification.

Biochemical identification. Definitive identifications were made by establishing the typical biochemical profile for the following characteristics by using media commercially available (Remel Laboratories), nitrate reduction (nitrate broth with Durham tube), indole production (indole broth), and esculin hydrolysis (esculin agar slant with ferric citrate) and the capability to produce acid from xylose, mannitol, lactose, sucrose, and maltose in fermentation broths with phenol red indicator.

Antimicrobial agent susceptibility testing. Antimicrobial agent susceptibility testing was performed by using the Bauer-Kirby disk diffusion method (8). Since specific zone diameter and equivalent MIC breakpoints have not been established for DF-3, the method and guidelines provided by the National Committee for Clinical Laboratory Standards (NCCLS) for the susceptibility testing of <i>Haemophilus</i> species was used as representative of the standards for fastidious organisms (8). The NCCLS recommended formula for supplemented Mueller-Hinton agar medium for the testing of <i>Haemophilus</i> species was used to test all of the DF-3 strains reported here. All plates were incubated at 35°C in an atmosphere with 5% CO₂ for 18 h. Zone diameters were measured following standard techniques and sensitive, intermediate, and resistant readings were made for each antimicrobial agent-organism combination by using NCCLS Table 2A, "Zone Diameter Interpretive Standards for Hemophilus" (8). For the antimicrobial agents not included in NCCLS Table 2A, namely, cefoxitin, cephalothin, clindamycin, erythromycin, gentamicin, mezlocillin, penicillin, and vancomycin, zone or no-zone readings were made. Zone sizes were measured for these antibiotics for comparative susceptibilities among the eight isolates.

Cell wall fatty acid analysis. Cell wall fatty acid analysis of all isolates was performed with a Hewlett-Packard 5970 series Mass Selective Detector and an HP 5890A gas chromatograph (Hewlett-Packard Co., Avondale, Pa.) by the methods of Miller (4a). The peak numbers and methyl ester eluates were determined by using the Supelco Bacterial Acid Methyl Esters CP Mix as the reference standard (Supelco, Inc., Bellefonte, Pa.).

Endoscopic biopsies. Endoscopic biopsies were performed on four of the patients by using standard endoscopic techniques.

RESULTS

Over an 8-month period, we were able to isolate DF-3 from the stool specimens from eight patients (Table 1). Three isolates were recovered from 129 different specimens from 78 (2.3%) patients with HIV at the Denver Department of Veterans Affairs Medical Center. Of the 129 specimens from the HIV-infected patients, fifty-three were unformed or liquid and contained two of three DF-3 isolates. Two isolates (1.1%) were recovered from 178 stool samples submitted for <i>C. difficile</i> assays at the Department of Veterans Affairs Medical Center. The remaining three isolates were recovered from routine stool specimens collected as part of a diagnostic work up of diarrhea; two were from the National Jewish Center and one was from the Presbyterian Hospital.

Biochemical profiles. The biochemical profiles for the DF-3 isolates were virtually identical. All strains had the distinctive fruity odor and produced acid fermentatively from xylose, lactose, sucrose, and maltose, except for case 8, which was a slow lactose fermenter, and the strain from case 6, which was lactose negative. All strains were catalase and oxidase negative, none reduced nitrate to nitrite, and none produced acid from mannitol. Six of eight isolates hydrolyzed esculin, and neither of two isolates tested produced indole from tryptophan broth.

Antimicrobial agent susceptibility patterns. Except for minor variations, the antimicrobial agent susceptibility profiles were similar for all seven strains (Table 2). Most strains were susceptible to chloramphenicol, except cases 1 and 2, which were intermediate. Clindamycin showed large zones of inhibition to all strains except number 1. Imipenem, trimethoprim-sulfamethoxazole, and erythromycin had smaller but consistent zones. Most strains were susceptible to tetracycline, with two (strains from patients 2 and 5) showing intermediate sensitivity and 1 (strain from patient 8) showing...
resistance. Near universal resistance was noted to ampicillin, ampicillin-sulbactam, ceftazidime, cephalothin, ciprofloxacin, and gentamicin. Small zones of inhibition were noted for penicillin and vancomycin.

Cell wall fatty acids. Cell wall fatty acid analysis results showed that all strains possessed 12-methyltetradecanoate and all but three of the strains also possessed tetradecanoate and hexadecanoate. There was no correlation between the cell wall fatty acid profiles and clinical symptoms, biochemical characteristics, or antimicrobial agent susceptibility testing.

Endoscopic biopsies. The findings on endoscopic biopsies varied in the four patients examined. Patients 1 and 2 had normal colonic mucosa without inflammation; both patients were receiving corticosteroids at the time of biopsy. A mild chronic inflammatory infiltrate was observed in the lamina propria of patient 7. Biopsy on patient 6 revealed heavily inflamed granulation tissue without normal colonic mucosa being present, which is consistent with underlying chronic ulcerative colitis.

| DISCUSSION |

The recovery of DF-3 from eight immunocompromised patients (HIV infected, immunosuppressed, or chronic underlying disease) within an 8-month period from patients at three institutions indicates that this organism may be more prevalent than previously suspected. The prevalence in normal hosts is presently unknown. However, we anticipate that DF-3 will be isolated with increasing incidence from immunocompromised patients when selective media are used. The term dysgonic fermenter (indicating poor growth) has been used by the Centers for Disease Control to describe a group of fastidious gram-negative bacilli. Originally named DF-1, this group of organisms was later transferred to the genus Capnocytophaga by Ledbetter et al. (6). These organisms are typically catalase and oxidase negative and demonstrate a peculiar gliding motility when grown on the surface of blood agar. They have been associated with dental plaque and periodontal infections.

More recently, a second group of dysgonic fermenters, referred to as DF-2, have been found as a cause of septice-

miae, cellulitis, and endocarditis in patients who had been bitten by or had close contacts with dogs (5, 15). These organisms have also been placed in the genus Capnocytophaga (C. canimorsus and C. cynodegi), even though they produce catalase and cytochrome oxidase. The species name for DF-3 has not yet been designated; however, the biochemical profile is similar to that of the DF-1 organisms.

The key biochemical characteristics of DF-3 include absence of growth on MacConkey and similar enteric isolation media; acid production in the butt of Kliger's and triple sugar iron slants; negative reactions for catalase, oxidase, indole, and nitrate reduction; and a positive reaction for esculin hydrolysis. Fermentation patterns are acid production from glucose, maltose, xylose, lactose, and sucrose but no acid from mannitol. The detection of a distinctly fruity odor produced by colonies growing on agar culture media is also a helpful clue.

Cell wall fatty acid analysis of our eight isolates showed a consistent peak of 12-methyltetradecanoate and lesser amounts of tetradecanoate and hexadecanoate. This is consistent with the findings of Wallace et al. (13) that DF-3 has a characteristic fatty acid profile which is distinct from those of other biochemically similar fastidious organisms and is useful in distinguishing DF-3 strains from other dysgonic fermenters such as Capnocytophaga species. The minor differences in fatty acids among our isolates did not correlate with a particular clinical syndrome.

The antimicrobial agent susceptibility test results for the eight isolates recovered in this series demonstrated a consistent pattern. Both tetracycline and clindamycin were effective for eradicating DF-3 from the stools of our patients, including case 1, which had a relatively small zone of inhibition. Tetracycline failed in one case, which is consistent with demonstrated in vitro intermediate sensitivity. In vitro resistance to clindamycin has been reported (4) and seemed to correlate with lack of clinical response. Thus, awareness should be made of susceptibilities on future isolates, should therapy be considered.

Isolation of an organism from stool in association with diarrhea does not establish its pathogenicity. This has been seen with organisms such as B. hominis (7). The casual relationship becomes even less clear in immunocompro-
mised hosts in which organisms not usually considered pathogens may cause diarrhea. As our understanding of the intestinal ecology increases, novel organisms may be identifiable as true pathogens.

The spectrum of presentations associated with DF-3 in our series of patients ranged from an asymptomatic carrier from whom the organism was spontaneously eliminated to a chronic diarrheal illness showing clinical response to antimicrobial agent treatment. Treated patients had negative follow-up stool cultures for DF-3; however, symptoms did not always clear after elimination of the organism. Four patients with diarrhea had other possible etiologies for their symptoms (B. hominis, Cryptosporidium species, and inflammatory bowel disease).

The group of hosts with altered immunity is rapidly expanding as a result of chemotherapy, transplantation, and more recently as a result of infection with HIV. With appropriate antimicrobial agent therapy DF-3 was relatively easy to eliminate from the patients coinfected with HIV. This contrasts to experience with other organisms such as Campylobacter jejuni which have been difficult to eradicate from stool in the setting of HIV infection in spite of appropriate antimicrobial agent therapy (9).

Most gastrointestinal pathogens such as the genera Salmonella, Shigella, and Campylobacter require an environmental acquisition in a susceptible host. Other pathogens such as C. difficile can be acquired nosocomially or may require alteration in normal enteric flora only. Still other pathogens such as Cytomegalovirus and Mycobacterium avium complex are associated with impairment of host immunity. Risk factors for acquisition of DF-3 in our patients may have included impairment of immunity due to malignancy, corticosteroid therapy, or coinfection with HIV. In addition, many of our patients also had recently received antimicrobial agents, suppressing the colonization resistance of normal enteric flora. The antimicrobial agents used in these patients, while being broad spectrum, such as ciprofloxacin, metronidazole, and amoxicillin, are agents to which DF-3 shows in vitro resistance. Further reports of asymptomatic carriers of DF-3 will support the possibility that DF-3 is part of normal enteric flora and hence an opportunistic pathogen.

Our experience suggests that by using selective media such as ceftoperazone-vancomycin-ampicillin, DF-3 can be recovered in stool from immunocompromised patients. Enteric DF-3 is associated with a wide range of clinical manifestations. Therapy which successfully eliminates the organism from stool cultures is not always associated with resolution of symptoms. Further prospective studies are needed to better define the association of DF-3 with human gastrointestinal disease.

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