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Authors

Whitehill, Gregory
Zhuo, Ran
Yang, Shangxin

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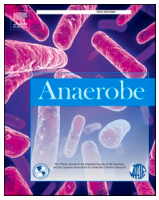

Clinical microbiology

Butyricimonas paravirosa bacteremia associated with acute terminal ileitis: Case report and literature review

Gregory Whitehill [a], Ran Zhuo [b], Shangxin Yang [b,*]

[a] Division of Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
[b] Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

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ABSTRACT

We present the first described case of bacteremia due to *Butyricimonas paravirosa*, a commensal gram-negative anaerobic bacterium identified by whole-genome sequencing in an elderly patient with acute terminal ileitis, who was successfully treated with ceftriaxone and metronidazole. We reviewed eleven previous cases of infection due to other *Butyricimonas* spp, which can cause a range of diseases but may be treated conservatively with a short antimicrobial course in the appropriate clinical setting. Additionally, while most *Butyricimonas* spp are susceptible to empiric anaerobic therapy, drug resistance has been reported in some cases.

1. Introduction

Endogenous gut anaerobes are symbionts which regulate immunity and homeostatic functions [1]. Disease states such as immunodeficiency, malignancy, or gut mucosal injury allow bacterial translocation into the bloodstream or other sterile body sites where these commensals act as pathogens [2]. Some anaerobic bacteria carry unique clinical significance due to increased rates of antimicrobial resistance, association with underlying disease such as malignancy, or tendency to cause severe invasive infection [3–5]. The genetic diversity of commensal microbiota greatly exceeds the breadth of cultured isolates [6]. As culture methods improve and techniques such as MALDI-TOF and genetic sequencing become more accessible, previously undescribed organisms can be identified at the species level and are increasingly emerging as 'new' pathogens [7]. Physicians will inevitably encounter the challenge of unfamiliar organisms with little or no published clinical experience to guide treatment.

Here we present the first described case of infection due to *Butyricimonas paravirosa*, a commensal gram-negative anaerobic bacterium first isolated from human feces in 2014 [8]. This cryptic organism could not be identified by MALDI-TOF, but was successfully identified by whole-genome sequencing. Eleven cases of infection due to other species within the *Butyricimonas* genus, namely *Butyricimonas virosa* and *Butyricimonas faecihominis*, have been described in infections of varying severity and outcomes [9–19]. We review these cases in the context of our own to hopefully demonstrate that *Butyricimonas* spp. are opportunistic gut pathogens which cause a range of disease but may be treated conservatively with a short antimicrobial course in the appropriate clinical setting. Additionally, while most *Butyricimonas* species are susceptible to empiric anaerobic therapy, resistance has been reported in some cases. Our in-house whole-genome sequencing approach was additionally able to identify the genetic mechanism of macrolide resistance, but not ampicillin resistance.

2. Case report

A 94-year-old woman presented to the emergency department with altered mental status and lethargy for two days duration. Medical history was notable for aortic stenosis, remote breast cancer treated with bilateral mastectomy, and dementia. She had no prior history of abdominal surgeries, and her last colonoscopy twelve years prior was normal without polyps or malignancy. On presentation, she was febrile to 38.1 °C; vital signs otherwise within normal limits. A comprehensive infectious workup was sent, including cross-sectional imaging as she was unable to provide a clear history. Her white blood cell count was 7810/μL (normal range 4160–9950). Liver and renal function tests were within normal limits. Urinalysis was negative for pyuria and urine culture was negative. A computed tomography (CT) scan of the head and chest showed no acute findings. CT of the abdomen and pelvis identified a twelve-centimeter area of focal wall thickening and enhancement in

* Corresponding author. UCLA Clinical Microbiology Laboratory, 11633 San Vicente Blvd, Los Angeles, CA, 90049, USA.
E-mail address: shangxinyang@mednet.ucla.edu (S. Yang).

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the terminal ileum with upstream dilation, normal caliber appendix with adjacent fat stranding, and moderate stool burden in the colon, suggesting acute terminal ileitis.

Two sets of blood cultures were collected and empiric antimicrobial therapy with piperacillin-tazobactam followed by ceftriaxone and metronidazole was initiated. She responded rapidly to antibiotic therapy, tolerating oral diet without recurrence of fever. At 72 hours after collection, admission blood cultures grew gram-negative rods in the anaerobic vials from both sets. Repeat blood cultures were collected which resulted negative. No surgical intervention was required, and the patient made a full recovery. After completing a seven-day total course of empiric therapy with ceftriaxone and metronidazole, she was discharged home.

Anaerobic culture was performed in house as previously described [20]. Identification of the blood culture isolate was unsuccessful by VITEK MS MALDI-TOF (BioMérieux, Salt Lake City, USA), library version 3.2. The MALDI-TOF workflow does not include on-plate formic acid extraction. An in-house whole-genome sequencing, described previously [21], was performed which identified the isolate to the species level as *Butyrycimonas paravirosa,* with >99 % pairwise identity in the *rpoB* gene. Definite species identification was confirmed by Kmer phylogenetic analysis of whole genome sequences of *Butyricimonas* spp. UCLA-1761 is most closely related to *Butyricimonas paravirosa* DSM 105722^T (CP043839) in the *Odoribacteraceae* family (Fig. 1). Other strains included in the analysis were *Butyricimonas virosa* strain DSM 23226^T, *Butyricimonas faecihominis* strain DSM 105721^T, *Butyricimonas faecalis* strain H184^T and *Odoribacter splanchnicus* DSM 20712^T (CP102269, CP043836, CP032819, CP002544). *Porphyromonas macacae* strain NCTC 11632 (UGTF01000002.1) was used as an out group.

Antimicrobial susceptibility testing by Etest showed resistance to ampicillin and clindamycin, and susceptibility to meropenem and metronidazole according to breakpoints suggested by the Clinical and Laboratory Standards Institute (CLSI) M100 34 edition. Whole genome sequencing analysis identified *erm(F)* which confers resistance to macrolide and clindamycin, and *tet(Q)* which confers resistance to tetracycline. We did not identify a beta-lactamase in this isolate using BD BBL Cefinase disc (BD, Franklin Lakes, NJ, USA), therefore, the resistance mechanism for ampicillin is unclear. No further treatment was pursued after definitive organism identification, and at follow-up one month after completing treatment she had not suffered further complications.

3. Literature review and discussion

To our knowledge, this case is the first published report of infection due to *Butyricimonas paravirosa* and twelfth description of human disease caused by *Butyricimonas* spp (Table 1), [9–19]. Etiologic species in other cases included *Butyricimonas virosa* in eight of eleven cases, *Butyricimonas faecihominis* in two of eleven cases, and unspecified *Butyricimonas* sp. in one case.

Most anaerobic bloodstream infections originate from the gastrointestinal tract [22]. *Butyricimonas* spp. are gut commensals isolated from the feces of humans and other animals [8,23]. Gastrointestinal pathology or underlying malignancy have accordingly been identified in most *Butyricimonas* infections. In our patient, bacteremia occurred in the setting of acute ileitis without other evident pathology or infectious source. These findings suggest bacterial translocation secondary to gut inflammation. Eight previously described bloodstream infections occurred in the settings of intestinal perforation [12–14,17], diverticulitis [10], perianal abscess [19], and recent major surgery in patients with underlying gastrointestinal adenocarcinoma [16,18]. De Donder et al. described *Butyricimonas virosa* and *Finegoldia magna* surgical wound infection mimicking necrotizing fasciitis following pelvic lymph node removal in a patient with underlying colon adenocarcinoma and prostate cancer [9]. Lau et al. described a case of lymphocytic-predominant peritoneal dialysis-associated peritonitis in a patient later discovered to have extensive rectosigmoid ulcerations [15]. The only case without evident gastrointestinal pathology was a polymicrobial (*Butyricimonas* sp., *Bacteroides vulgatus*, and *Clostridium tertium*) bone abscess at the site of a prior fasciotomy wound described by Ferry et al. [11]. Thus, *Butyricimonas* spp. are most often associated with gastrointestinal disease but can cause a range of infections.

Blood culture identified the majority of *Butyricimonas* infections,

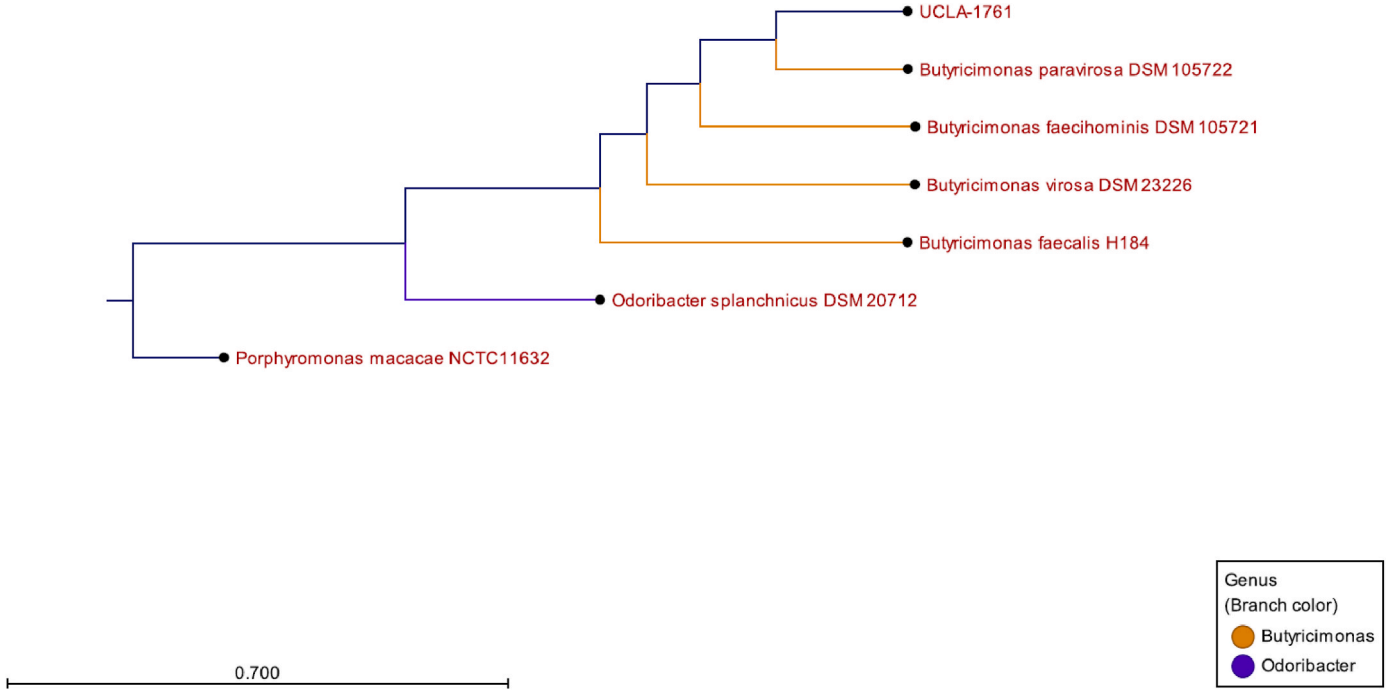

Fig. 1. UCLA-1761 is most closely related to *Butyricimonas paravirosa* DSM 105722 in the *Buryticimonas* genus of the *Odoribacteraceae*. Genetic relatedness was assessed by constructing a Kmer phylogenetic tree with representative species in the *Butyricimonas* genus and a member of the *Odribacteraceae*. *Porphyromonas macacae* was used as an out group.

Table 1
Demographics, clinical characteristics and treatment data of published cases of *Butyricimonas* infections.

Reference	Organism	Age/ Sex	Sample Source	Drug Resistance	Clinical Context	Treatment	Treatment Duration	Outcome
Toprak [18]	*B. virosa*	72M	blood	n/a	fever 24 days after aortic aneurysm repair, history of colon adenocarcinoma	MPM, COL	n/a	expired in hospital
Ferry [11]	*B.* spp[a]	30M	bone abscess	n/a	bone abscess after open wrist fracture/ compartment syndrome	ETP, MET, CD	3 months	recovered
Mehta [16]	*B. virosa*	81M	blood	n/a	fever 18 days after Whipple for duodenal adenocarcinoma	No Treatment	n/a	recovered
Enemchukwu [10]	*B. virosa*	69M	blood	PCN, CTX	diverticulitis	MET, CIP	14 days	recovered
Ogawa [17]	*B. virosa*[a]	68M	blood	n/a	intestinal perforation due to adhesions	DP	21 days	recovered
Garcia-Agudo [12]	*B. virosa*	90M	blood	PCN	perforated appendicitis	TZP	n/a	recovered
De Donder [9]	*B. virosa*[a]	78M	wound	n/a	surgical wound infection, history of colon and prostate cancer	TZP	12 days	recovered
Gasos [13]	*B. virosa*	72M	blood	PCN	colocutaneous fistula due to invasive adenocarcinoma	MPM	n/a	expired in hospital
Kamel [14]	*B. faecihominis*[a]	38F	blood	AMP, CD	perforated appendicitis	AMC	n/a	recovered
Lau [15]	*B. virosa*	65M	peritoneal fluid	AMP, CD, MET	peritoneal dialysis associated peritonitis	IPM, AMK	21 days	recovered
Wessendorf [19]	*B. faecihominis*	50M	blood	PCN, TZP	perianal abscess	MPM	n/a	recovered
This study	*B. paravirosa*	94F	Blood	AMP, CD	terminal ileitis	CTX, MET	7 days	recovered

F: female sex; M: male sex; PCN: penicillin; AMP: ampicillin; AMC: amoxicillin-clavulanate; CD: clindamycin; MET: metronidazole; MPM: meropenem; CTX: ceftriaxone; TZP: piperacillin-tazobactam; DP: doripenem; COL: colistin; IPM: imipenem; AMK: amikacin; CIP: ciprofloxacin; ETP: ertapenem.
[a] Indicates polymicrobial infection.

including our case. Bacteremia is a serious but heterogenous clinical syndrome. Isolation of bacteria from the bloodstream indicates that pathogen burden at the site of infection has reached sufficient magnitude to allow dissemination and potentially seeding of new foci in distant tissues. Conversely, asymptomatic transient bacteremia by commensal microbes in the absence of infection likely occurs frequently from daily activities such as brushing teeth and is mostly inconsequential [24]. While gram-positive skin microbiota members are common blood culture contaminants, isolation of gram-negative anaerobes from blood cultures almost always indicates true infection [25]. Treatment of bloodstream infection is informed by host status, clinical syndrome, and inherent likelihood of the etiologic organism to seed distant or intravascular foci of infection. Uncomplicated gram-negative bacteremia due to *Enterobacterales* can be effectively treated with a short antimicrobial course [26], while highly virulent bloodstream pathogens such as *Staphylococcus aureus* require more rigorous clinical evaluation and longer treatment duration [27]. Anaerobic bacteremia is less well understood; large-scale trials to guide treatment approach or duration do not exist. Therefore, it is useful to review the likelihood of *Butyricimonas* spp. to establish distal sites of infection to inform whether the short (one week) antibiotic course we describe is a reasonable approach for future cases.

No cases of *Butyricimonas* bacteremia identified hematogenous spread of infection to distal tissues outside of the abdomen. Furthermore, bacteremia with *Butyricimonas* spp did not recur in any case of bloodstream infection after treatment. Duration of treatment varied greatly between cases (zero to twenty-one days). Mehta et al. described a patient with *Butyricimonas virosa* bacteremia identified during a post-operative febrile episode who did not receive antibiotic treatment but still recovered without complication [16]. Enemchukwu et al. reported a patient found to be bacteremic with *Butyricimonas virosa* in the setting of otherwise mild diverticulitis [10]. After presentation to the emergency department, they were initially discharged home without antimicrobial therapy. When gram-negative bacilli were isolated from blood cultures five days later, the patient's symptoms had resolved. The patient was still treated with a fourteen-day antimicrobial course [10]. Our patient's fevers ceased within 24 h of antibiotic administration and her symptoms improved rapidly. These cases support shorter treatment duration in patients who have mild clinical disease, improve rapidly with treatment, and in whom adequate control of infectious source is achieved.

Gastrointestinal pathology can carry significant morbidity independently of bacteremia. This is demonstrated by two cases of *Butyricimonas virosa* infection in which the patient did not survive hospitalization. Ulger Toprak et al. reported a patient who suffered a *Butyricimonas* bacteremia twenty-four days after an aortic aneurysm repair and received appropriate treatment with meropenem, but later perished due to *Acinetobacter* infection [18]. Gasos et al. reported a patient who presented with *Butyricimonas virosa* bacteremia and sepsis in the setting of a large colonic neoplasm fistulizing to the abdominal wall. Despite appropriate antimicrobial treatment with meropenem, the patient required multiple extensive surgeries and suffered esophageal ischemia, ultimately passing three weeks after presentation [13]. More complex and dynamic clinical scenarios may necessitate longer treatment courses. Ogawa et al. reported a patient who suffered polymicrobial bacteremia (*Butyricimonas virosa, Bacteroides vulgatus, Brachyspira pilosicoli*) secondary to intestinal perforation, later complicated by post-operative suture rupture. Antimicrobial therapy with doripenem was extended for a twenty-one-day course and the patient recovered [17]. While short duration of therapy is appropriate in some cases of *Butyricimonas* bacteremia, response to therapy and clinical course must be apprised before stopping treatment.

Antimicrobial resistance for anaerobic species can be unpredictable due to heterogenous populations, slow growth in culture, and limitations of correlating standardized antimicrobial susceptibility testing methods with clinical impact [28]. Appropriate antimicrobial therapy is critical to treatment of bloodstream infections and significantly reduces mortality in anaerobic bacteremia [29,30]. Empiric therapy for gram-negative anaerobic infections often includes beta-lactam-beta-lactamase inhibitor, metronidazole, or carbapenems. The *Butyricimonas paravirosa* isolate in our case was susceptible to metronidazole and meropenem, but resistant to ampicillin and clindamycin. We identified *erm(F)* and *tet(Q)*, both are commonly found in gram-negative anaerobes (e.g. *Bacteroides* spp). Erm(F) is a 23S rRNA methyltransferase which confers resistance to macrolide, lincosamide and streptogramin B (collectively referred to as the MLS class) by post-transcriptional modification of the drug target [31], which explains the resistance to clindamycin. Tet (Q) protects the ribosomes from the inhibitory effects of tetracycline by ribosome modification [32]. Consistent with our findings, previous studies showed *Butyrycimonas* can be resistant to ampicillin and clindamycin, although the molecular

mechanism was not elucidated [15]. This susceptibility profile allowed for adequate coverage by the empiric regimen of ceftriaxone and metronidazole.

Five prior cases reported *Butyricimonas virosa* isolates with broad susceptibility. Ulger Toprak et al.'s isolate was susceptible to ampicillin, amoxicillin-clavulanic acid, piperacillin-tazobactam, imipenem, meropenem, clindamycin, and metronidazole [18]. Enemchukwu et al.'s isolate was resistant to penicillin and ceftriaxone but susceptible to piperacillin-tazobactam and metronidazole [10]. Gasos et al.'s isolate was resistant to penicillin but susceptible to amoxicillin-clavulanic acid, piperacillin-tazobactam, meropenem, clindamycin, and metronidazole [13]. Kamel et al.'s isolate was resistant to ampicillin and clindamycin, but susceptible to amoxicillin-clavulanic acid, imipenem, meropenem, and metronidazole [14]. Garcia-Agudo et al.'s isolate was resistant to penicillin but susceptible to clindamycin, piperacillin-tazobactam, metronidazole and meropenem [12]. Susceptibility was determined using Etest in all five cases. Case two utilized the CLSI breakpoints available in 2016; case three to five utilized breakpoints from EUCAST v8 or prior; the source of breakpoints used in case one was unclear.

Two prior cases encountered resistance that affected treatment. The peritoneal *Butyricimonas virosa* isolate in the case described by Lau et al. was susceptible to imipenem but resistant to both clindamycin and metronidazole. Their patient was initially treated with imipenem, but suffered unacceptable neurotoxicity necessitating discontinuation and transition of therapy to piperacillin-tazobactam (Etest, CLSI M100 33 ed) [15]. Wessendorf et al. described *Butyricimonas faecihominis* bloodstream infection secondary to perianal abscess. The patient presented with septic shock and was empirically treated with piperacillin-tazobactam but remained critically ill. Susceptibility testing showed resistance to penicillin and piperacillin-tazobactam, but susceptibility to meropenem, clindamycin, and metronidazole (Etest, EUCAST 2024). Transition of therapy from piperacillin-tazobactam to meropenem in response to these results resolved shock within 24 h [19]. While the majority of *Butyricimonas virosa* species causing invasive infections did not demonstrate clinically significant antimicrobial resistance, one isolate was resistant to metronidazole, a common empiric therapy for anaerobic infection. Of two *Butyricimonas faecihominis* cases, one was resistant to piperacillin-tazobactam requiring adjustment of therapy to achieve recovery. Whether susceptibility patterns vary between species within the *Butyricimonas* genus may be revealed with further reporting of susceptibility testing and treatment outcomes.

In summary, *Butyricimonas* spp. cause a broad range of clinical diseases mostly but not always associated with the gastrointestinal tract. Antimicrobial resistance varies widely between isolates. While *Butyricimonas virosa* is the most robustly described in the literature, *Butyricimonas faecihominis* has been implicated as a pathogen as well. Here we identify *Butyricimonas paravirosa* as a pathogen in a case of uncomplicated bacteremia secondary to acute ileitis treated with a short antimicrobial course. The outcome in our case was excellent, but in prior cases with more severe underlying disease, treatment proved more complex. Further reporting of future cases may reveal disparities in the pathogenicity and antimicrobial resistance between distinct *Butyricimonas* species. We also showed the value of whole-genome sequencing, which not only provided the accurate identification of rare anaerobic bacterial pathogens that otherwise may not be correctly identified. *Butyricimonas paravirosa* is not included in the VITEK MS v3.2 or Bruker MALDI Biotyper CA libraries. Whole genome sequencing analysis also revealed resistance mechanism for clindamycin with the detection of *erm(F)* gene in this case. Further study is needed to understand the beta-lactam resistance mechanism in this genus. Our research contributes to the expanding knowledge base on opportunistic infections caused by endogenous anaerobes originating from the human gut.

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UCLA Department of Pathology and Laboratory Medicine.

CRediT authorship contribution statement

Gregory Whitehill: Writing – original draft, Project administration, Investigation, Data curation, Conceptualization. **Ran Zhuo:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Shangxin Yang:** Writing – review & editing, Validation, Supervision, Software, Resources, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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