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MAJOR ARTICLE

Bacteremia and Skin Infections in Four Patients Caused by *Helicobacter*-Like Organisms

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Background. Enterohepatic *Helicobacter*-like organisms (HLO) have been recognized as causes of human infection since 1984, primarily as a cause of bacteremia and cellulitis in immunocompromised individuals, but the spectrum of illness due to HLO has expanded based on numerous reports from Japan.

Methods. We report 4 epidemiologically unrelated immunocompetent patients with HLO bacteremia diagnosed within a 2-year period. Three patients had cellulitis and 1 patient had unexplained fever. 16S ribosomal deoxyribonucleic acid (rDNA) sequence analysis of 2 isolates suggested that they were *Helicobacter cinaedi*, and whole-genome sequencing showed that they differed only slightly from reference strains.

Conclusions. We believe that this syndrome is more common than reported, but it is easily overlooked because the skin lesions resemble streptococcal cellulitis and respond very rapidly to β-lactam antibiotics, and the organism is difficult to isolate from the blood. All HLO in our series were isolated from blood using the ESP system and were not detected in 2 other widely used commercial blood culture systems.

Keywords. bacteremia; *Helicobacter*-like organisms; pyrosequencing; 16S rRNA.

Helicobacter spp are fastidious, microaerophilic, spiral, Gram-negative bacteria with sheathed polar flagella. In old cultures, they have the tendency to become coccoid. At present, the genus *Helicobacter* comprises 48 species, which can be divided into gastric strains (most importantly *Helicobacter pylori*) and enterohepatic strains. Several species in the enterohepatic group have been isolated from the gastrointestinal (GI) tract of many different species of animals and birds, and some have been isolated from humans [1–3]. The most commonly isolated enterohepatic species is *Helicobacter cinaedi*, but even this organism has rarely been reported to cause infections in the United States, and they have primarily been in immunocompromised hosts [4]. *Helicobacter*-like organisms (HLO) are difficult to speciate, because they are fairly inert biochemically and biochemical characteristics are unstable [5]. Identification has been attempted using biochemical and growth characteristics, electron microscopy (EM), 16S ribosomal deoxyribonucleic acid (rDNA) sequencing, whole-genome sequencing, DNA-DNA hybridization, and cellular fatty acid (CFA) composition analysis [6]. More recently, mass spectroscopy (matrix-assisted laser desorption ionization time-of-flight [MALDI-TOF]) has been used successfully [7]. Even with sequence analysis, distinguishing between different species of enterohepatic *Helicobacter* has been difficult. Some of these isolates were originally classified as *Flexispira*, but that is no longer accepted as a valid genus name [8].

The first report of isolation of HLO from people was in 1984, but they were misidentified as *Campylobacter*, because they were microaerophilic and had spiral morphology [9]. They were isolated from rectal cultures from 25 of 158 men who have sex with men who were diagnosed with either proctitis or proctocolitis. Even at that time, the authors believed that there was more than 1 species responsible for this syndrome, based on DNA hybridization [10]. In recent studies, there has been a spate of reports of *H cinaedi* infections from Japan, occurring in both normal and immunosuppressed individuals, including apparent nosocomial infections after orthopedic surgery [11]. One medical center in Kamogawa, Japan reported 28 cases of *H cinaedi* bacteremia between 2009 and 2014; half were nosocomial infections [12].

In this study, we report 4 cases of community-acquired *H cinaedi*-like bacteremia in immunocompetent men. The identification was originally based on morphology, CFA analysis, 16S ribosomal ribonucleic acid (rRNA) gene sequences, and biochemical testing. We subsequently did pyrosequencing of the whole genome and MALDI-TOF analysis that confirmed their identification as *H cinaedi*, although the 2 sequenced isolates had several open reading frames that were not found in the type strains.

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CASE REPORTS

Patient 1 was a 44-year-old male with past medical history significant for a left calcaneus fracture with a surgical repair that was complicated by a *Staphylococcus aureus* infection of the implanted hardware. The hardware was removed, and he was successfully treated with cefazolin and rifampin for 6 weeks. He also had a past medical history of gastric bypass surgery for morbid obesity, acoustic neuroma, and obstructive sleep apnea. One year after the hardware was removed, he presented with complaints of redness and swelling around left ankle and anterior shin and was admitted and treated with cefazolin. The cellulitis improved and he was discharged home on cephalexin. Admission blood cultures grew an HLO 3 days later, after he was discharged. The antibiotic was changed to amoxicillin/clavulanic acid. He was treated with that drug for 14 days without a recurrence (Figure 1).

Patient 2 was a 30-year-old male with bipolar disorder who presented to urgent care with complaints of erythema and pain on the anterior and medial aspect of his left ankle. He was treated for cellulitis with dicloxacillin then cephalexin with minimal improvement. He was then admitted to the hospital and received intravenous cefazolin; within 24 hours, improvement was noted. The patient was discharged on cephalexin to complete 10 days of treatment. Three days later, an HLO (Figure 1) (later identified as *H cinaedi*) was isolated from an admission blood culture, and the antibiotic was changed to amoxicillin/clavulanic acid. Antibiotic sensitivities eventually showed the organism to be sensitive to aminoglycosides, imipenem, piperacillin, amoxicillin/clavulanic acid, and ceftazidime. Two days later, the patient reported that his leg was still swollen, red, and painful, and erythromycin was added, with some improvement. Three days after stopping antibiotics, the symptoms recurred. He was seen in clinic with localized erythema and then re-admitted because the erythema and swelling had progressed from approximately 1-cm diameter at his ankle to involve his lower leg from his ankle to his knee in less than 4 hours. Repeat blood cultures were again positive for an HLO. He again improved rapidly on intravenous cefazolin, and after 3 days he was discharged on amoxicillin/clavulanic acid for 14 days. Cellulitis resolved and subsequent blood cultures were without growth.

Patient 3 was a 41-year-old male with a past medical history significant for reactive airway disease and *S aureus* mitral

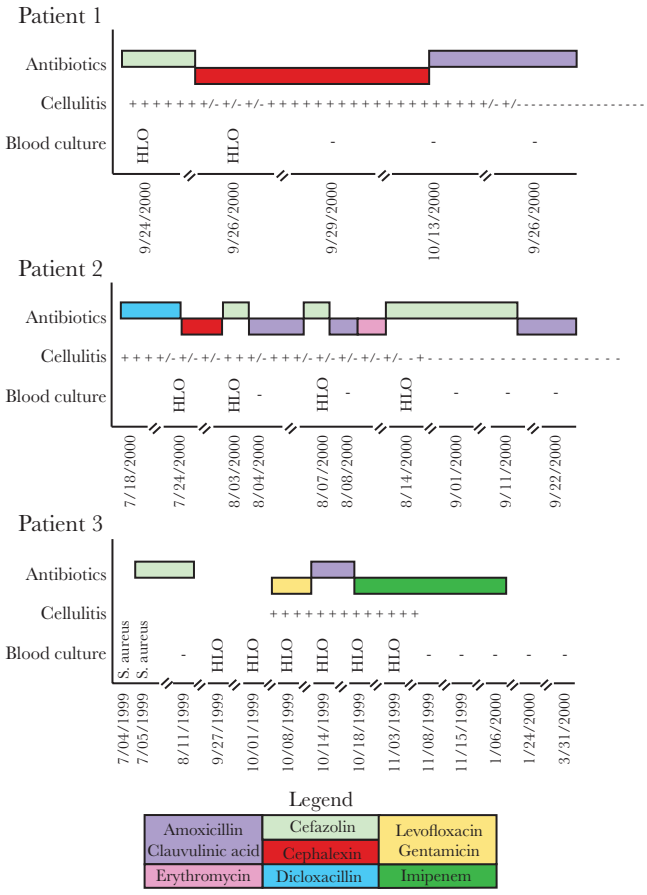

Figure 1. Summary of clinical histories of patients with cellulitis. The time course of infection and treatment is illustrated for patients 1–3. *Helicobacter*-like organisms (HLO) indicates the dates that blood cultures grew Helicobacter *cinaedi*, and dashes on that line indicate dates of negative blood cultures. The + symbols indicate when lower extremity cellulitis was apparent, and ± indicates resolving cellulitis.

valve endocarditis that was treated with 6 weeks of cefazolin from July 5, 1999 until August 11, 1999. Follow-up blood cultures were done in August and were negative; however, in September 1999 when he was asymptomatic, his erythrocyte sedimentation rate remained elevated and they grew HLO (Figure 1) (later identified as *H cinaedi*). He was re-admitted because of the positive blood culture and concern for possible endocarditis. His initial examination was unremarkable except for a systolic murmur, but on the second day of hospitalization he developed left leg cellulitis. Levofloxacin and gentamicin were given as treatment to the patient for 1 day, and then he was discharged on amoxicillin/clavulanic acid. Blood cultures taken on admission were again positive for HLO, but the results did not return before his discharge. He remained asymptomatic, but when additional blood cultures were all positive, he was re-admitted. This isolate was resistant to doxycycline, erythromycin, levofloxacin, and co-trimoxazole. It was sensitive to imipenem, ceftriaxone, cefepime, and gentamicin. In all, 13 of 13 blood cultures were positive over 22 days. All other laboratory results were unremarkable except for microscopic hematuria. An EM picture of the isolate from a blood culture bottle organism is shown in Figure 2. A transthoracic echocardiogram did not show a vegetation, but he was treated for 6 weeks with imipenem for presumptive endocarditis based on a history of endocarditis, microscopic hematuria, and persistent bacteremia over a 1-month period. All subsequent blood cultures were negative and the hematuria resolved.

Patient 4 was a 51-year-old homeless man with a long history of alcoholism and was admitted for complaints of "liver pain". He reported one and a half weeks of increasing abdominal girth associated with increased shortness of breath and abdominal tenderness. He had a past medical history of hepatitis C, alcoholic hepatitis, hypertension, and polysubstance abuse that included crystal methamphetamine and alcohol. He was jaundiced, had ascites, but was afebrile. His *alanine aminotransferase* and *aspartate aminotransferase* were >3 times normal, his bilirubin was 15 mg/dL, and his white blood cell (WBC) count was 14.9 K/μL. Abdominal computed tomography scan showed an enlarged fatty liver, splenomegaly, and gastric varices. His fever rose to 103°F on the second hospital day, and 1 of 2 blood cultures eventually grew an HLO later identified as *H cinaedii*. An abdominal paracentesis yielded clear ascitic fluid that had low albumin and low cell counts and was sterile. Because of the fever, he was empirically started on cefotaxime for 7 days. He gradually became afebrile although his WBC and liver enzymes remained elevated. He was discharged to a nursing home. One week later, he was readmitted and his repeat blood cultures were negative, but he died of a GI hemorrhage during that admission.

All 4 patients had negative human immunodeficiency virus (HIV) serologies during their work-up, and patients 1–3 had no prior history of immunodeficiency. Patient 4 was immunocompromised by liver failure. Social and clinical information from the 4 patients is summarized in Table 1.

Figure 2. Scanning electron microscopy (EM) image of *Helicobacter cinaedi* isolated from patient 3. Magnification, ×55 000. Note the polar flagella. The organisms appear to be dividing.

MATERIALS AND METHODS

Antibiotic susceptibility testing was performed by disk diffusion and with Etest (bioMérieux) on chocolate agar in a microaerobic atmosphere. Electron microscopy was performed on bacteria that were washed off chocolate agar plates with Karnovsky's fixative, and the organisms were stained with uranyl acetate. Fatty acid analysis was performed by David Lindquist in the special pathogens unit of the Microbial Diseases Laboratory of the California Department of Health and at the Centers for Disease Control and Prevention. Matrix-assisted laser desorption ionization-TOF mass spectrometry was done using the Bruker MALDI biotyper according to the manufacturer's instructions.

Pyrosequencing and Genomic Assembly

Deoxyribonucleic acid was extracted from 2 isolates using the QIAamp Blood DNA mini kit per manufacturer protocol. Deoxyribonucleic acid was concentrated by ethanol precipitation using 1 μL glycogen, 1:10 3M sodium acetate, and 2× of 100% ethanol storing samples overnight at −20°C. Samples were spun at 4°C for 15 minutes, washed with 70% ethanol, and spun at 4°C for 10 minutes twice and eluted in 100 μL TE buffer. Library preparation for pyrosequencing was performed using 500 ng of DNA from isolates from patients 2 and 3. We used the standard protocol for shotgun sequencing except that we fragmented the DNA (400-base pair [bp] mean length) using the Covaris M220 Focused Ultrasonicator (Woodburn, MA). Pyrosequencing was performed using the Roche 454 GS Junior at the Center for AIDS Research Translational Virology Core at University of California, San Diego. Filtering and assembly were performed using Newbler (Roche). Contiguous sequences with a read length greater than or equal to 500 bp were kept and annotated and used to assemble the

Table 1. Patient Characteristics

Patient	1	2	3	4
Sex/race/age	Male/white/44	Male/white/30	Male/white/41	Male/white/51
Social history	Smokes 2 packs of cigarettes a day	Sex with men	Frequent travel to Mexico	Homeless, living in a truck
Animal exposure	Pet dog, tropical fish	Pet dog	Pet cat	Unknown
Past medical history	*Staphylococcus aureus* prosthetic joint infection, gastric bypass, acoustic neuroma surgery	Bipolar disorder, migraines	*S aureus* endocarditis 4 months prior, asthma	Laennec's cirrhosis with ascites
Output medications	Over-the-counter antacids	None	Albuterol inhaler	Lactulose
Onset of painful cellulitis	9/24/2000	7/18/2000	10/18/1999	N/A
First^{+} HLO blood culture	9/28/2000	8/3/2000	9/29/1999	1/15/98
Admission temperature	99.6°F	99.2°F	99.0°F	99.0°F
WBC K/μL	7.4 (63% segs)	6.5 (68% segs)	6.6 (53% segs, few bands on second admission)	14.2
ESR mm/hr	17	16	35	ND
HIV ELISA	Negative	Negative	Negative	Negative
Skin biopsy	ND	Minimal inflammation and neovascularization of the papillary dermis. Gram-stain negative.	ND	ND
Response to antibiotic[a]	Cefazolin	Cefazolin	Imipenem	Cefotaxime and metronidazole

Abbreviations: ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; HLO, *Helicobacter*-like organisms; N/A, not applicable; ND, not done; segs, segmented cells; WBC, white blood cell.

[a]Treatment in hospital that resolved fever and/or cellulitis.

genome, utilizing the rapid annotation using subsystem technology (RAST) [13]. Sequences for *H cinaedi* strains (PAGU611 and CCUG188) were obtained from HelicoBase [14] and uploaded to RAST for sequence-based comparisons with our 2 clinical isolates. The sequence of *Helicobacter hepaticus* American Type Culture Collection (ATCC) 51449 strain was obtained from the SEED viewer [13]. Histograms comparing our 2 isolates with the 2 reference strains were made from the resulting data, using the percentage identity of only protein-encoding genes found on both reference genomes. Unmapped proteins and hypothetical and unique proteins with known or predicted functions were removed for the analysis.

16S Ribosomal Ribonucleic Acid Gene Sequence Analysis

All sequence analyses were performed using Geneious [15]. We obtained the full-length 16S rRNA gene from the whole-genome assembly of both isolates, and we used the Linnaeus Search tool provided by Geneious to obtain 16S rRNA gene from related bacteria. For comparison, we chose 1 representative *Helicobacter* sequence for each species and constructed a neighbor-joining tree using the TN93 substitution model with bootstrap. We repeated the analysis using only the *H cinaedi* sequences.

RESULTS

Microbiology

Growth was detected in ESP (VersaTrek) media between 72 and 90 hours after incubation. As shown in Supplementary Figure 1, the instrument signaled because of a fall in pressure within the bottle, indicating net consumption of gas during growth. The initial Gram stains were read as negative, and subcultures to blood agar in a 5% CO_2 atmosphere did not grow. However, a wet mount revealed rapidly motile bacteria with cork-screw motility similar to *Campylobacter*. The isolates from each patient grew slowly under microaerobic conditions at 35°C, poorly at 42°C, but not at all at 25°C on both 5% sheep blood agar in Columbia base and chocolate agar, forming small, flat, translucent colonies that spread along the streak marks. We attempted to subculture the isolates in other blood culture systems by inoculating 5 cc from a positive blood culture into aerobic and anaerobic bottles of the BACTEC (BD) and BacT-alert (bioMérieux) systems, but they did not indicate growth after 7 days of incubation, whereas the subculture into a fresh VersaTrek blood culture bottle was successful within 48 hours.

The isolates gave positive catalase (weakly), cytochrome C oxidase, and nitrate reactions and were negative for urease. These biochemical characteristics are consistent with *H cinaedi*. We examined 3 isolates with EM, and the bacteria each had single or double sheathed flagella at both poles as shown in Figure 2.

16S Ribosomal Ribonucleic Acid Gene and Whole-Genome Sequence Analysis

Sequence analyses of the 16S rRNA gene revealed that both isolates are closely related to *H cinaedi* (Figure 3A). Once it

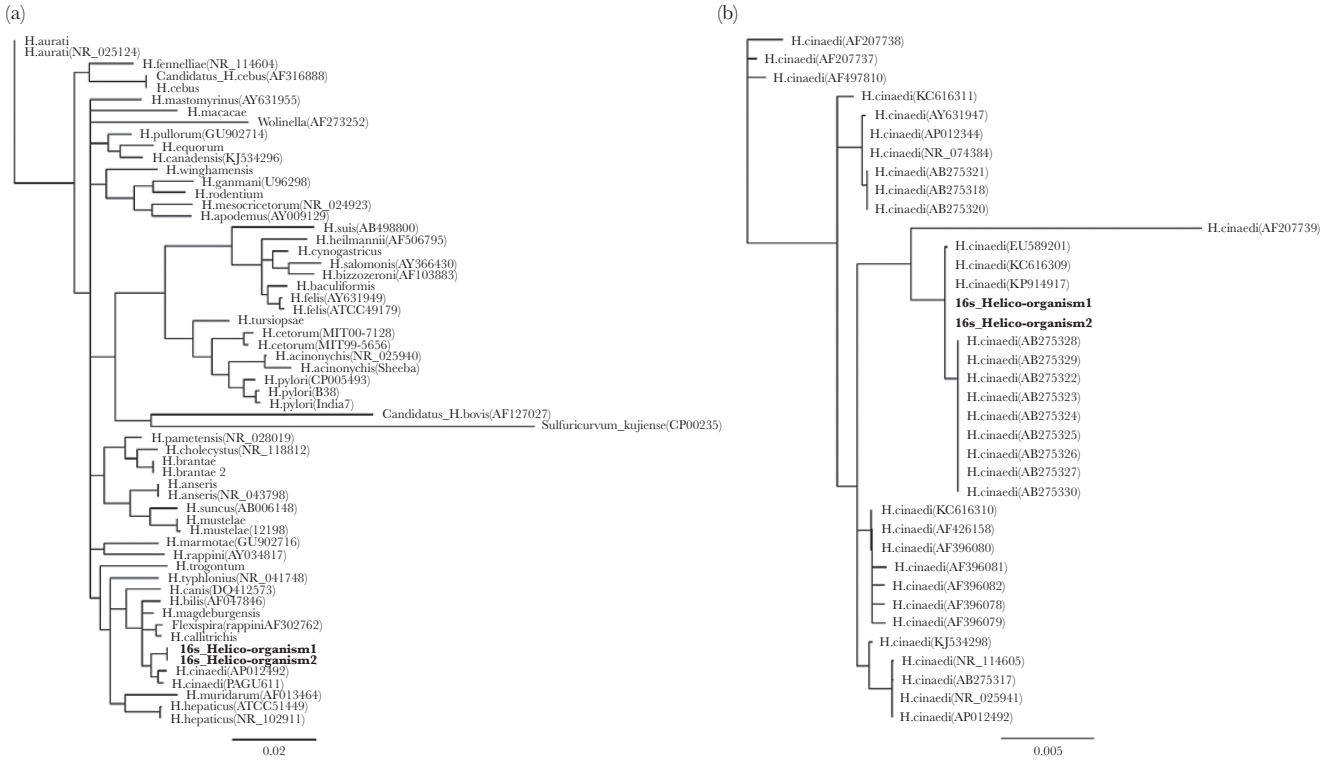

Figure 3. Sequence analyses of the 16S ribosomal ribonucleic acid (rRNA) genes from 2 *Helicobacter cinaedi* isolates. (A) Neighbor-joining trees with bootstrap revealed of closely related *Helicobacter* species using 16S rRNA gene sequences identified that both isolates were closely related to *H cinaedi*. (B) Further comparison to a set of *H cinaedi* strains revealed that both isolates were most closely related to *H cinaedi* strains: EU589201, KC616309, and KP914917.

was determined that *H cinaedi* was the most closely related organism to our isolates, the comparison between the given set of *H cinaedi* strains revealed that both isolates are most closely related to the following *H cinaedi* strains: EU589201, KC616309, and KP914917 (Figure 3B). Annotation of the assembled contiguous sequences showed that the 2 sequenced organisms were 99.9% similar. We compared the protein-coding genes that were conserved in our 2 sequenced isolates and in all 3 *H cinaedi* reference strains (PAGU6, CCUG188, and APO12492), and the 2 isolates had an average protein similarity of 98.8% to the reference strains. We also compared both isolates to *H hepaticus* ATCC 51449, and there was only 74.1% average protein similarity. However, the isolate from patient 2 had 240 protein-encoding genes that were not present in the reference *H cinaedi* PAGU6 strain genome and 126 that did not map to *H cinaedi* PAGU611. Of the former, 190 were hypothetical proteins and 50 proteins had either predicted or known functions (Supplementary Table 1). We also compared patient 2's isolate with the *H cinaedi* CCUG188 genome and found 126 unique proteins; 103 were hypothetical proteins and 23 had known or predicted functions (Supplementary Table 2). The isolate from patient 3 had 256 proteins that did not map to the *H cinaedi* PAGU611 genome; 200 were hypothetical proteins and 56 had either predicted functions or known functions (Supplemental Table 3). The comparison with CCUG188 revealed 138 unmapped proteins; 113 were hypothetical proteins and 25 were proteins with predicted or known functions (Supplementary Table 4).

DISCUSSION

Helicobacter-like organism intestinal infections were originally thought (1) to occur only in men who have sex with men [10] and then (2) to be an invasive opportunistic pathogen in patients with HIV infection and other immunosuppressive illnesses [4, 16, 17]. However, this case series together with other reports [8, 11, 12, 18, 19] demonstrates that HLO can cause bacteremia in immunocompetent heterosexual people, presenting most commonly as fever and cellulitis. Our cases also demonstrate that bacteremia can be prolonged in the absence of an apparent localized infection, suggesting an intravascular site of infection.

Our 4 cases were diagnosed in 1999–2000 when we were using the ESP blood culture system. One of our isolates did not grow in aerobic Bactec or BacT/Alert (bioMérieux) bottles. However, others have shown that at least some HLO grow in those blood culture systems, although they may grow slowly. In a report from 2 Tokyo hospitals that used the Bactec system for blood cultures, 2% of all their positive blood cultures were identified as *H cinaedi*, but approximately 50% of those blood cultures took 6–12 days to become positive [19]. Miyake et al

[20] reported that they only started isolating *H cinaedi* after they switched from the BacT/Alert system to the Bactec system. When they inoculated both Bactec and BacT/Alert 3D bottles with an HLO, only the Bactec bottles signaled growth even though the bacteria grew in both systems, indicating the BacT/Alert problem was in detecting not supporting growth [20]. Kawamura et al [18] reviewed *H cinaedi* infections and they found that the ESP system is superior for the detection of *H cinaedi*, generally turning positive after only 3 days of incubation. This fits with our experience.

Helicobacter cinaedi are part of the intestinal flora, so it has been assumed that the skin is infected hematogenously. Patient 3 illustrates that, because he was bacteremic for several days before he developed cellulitis. The cellulitis can progress rapidly as illustrated by patient 2. There are not many reports of the pathology of the skin lesions, but at least some of them show a mixed inflammatory infiltrate in the dermis [21]. Another feature that we and others [11] have noted is that the bacteremia and skin lesions have a tendency to recur, suggesting that the organism can evade the immune response, as is true of other extracellular spiral pathogens such as *Borrelia* and *Treponema*.

Much remains to be learned about the pathogenesis of this infection. Experimentally oral infection of macaques causes diarrhea and transient bacteremia as long as 1 week after infection, so the organism can invade the circulation from the GI tract [22]. The only known potential virulence factor is cytolethal distending toxin (CDT), which was shown to be necessary for production of typhlitis in IL-$10^{-/-}$ mice that are orally infected [23]. However, we did not find CDT in the genomes of our 2 isolates, suggesting that it is not necessary for causing bacteremia in people.

We propose that HLO cellulitis is often misdiagnosed in immunocompetent patients because it is easily mistaken for streptococcal cellulitis, except for the lack of predisposing factors such as trauma or pre-existing edema, and both infections respond to many β-lactam antibiotics. Even if blood cultures are taken, HLO may not be isolated due to the slow growth of the organism in blood culture media in the more commonly used automated blood culture systems [20], or perhaps to the systems not being able to detect growth because they rely on pH changes. The bacteria are difficult to see with Gram stain with safranin counter stain, but they may be more visible with fuchsin counterstain. They are easily detected in a wet mount or with acridine orange staining. Unless the blood is subcultured on rich media in a microaerophilic atmosphere at 37°C they will not grow, and even then it can take up to 3 days to see colonies. Identification of isolates may be difficult because HLO-specific molecular diagnostic methods (eg, 16S rRNA gene sequencing) are not established in most clinical laboratories. Even 16S sequencing may not be sufficient to identify *H cinaedi* because the 16S sequences of *H cinaedi* isolates vary considerably [5]. In a more recent study [7], 16S sequencing and MALDI-TOF mass spectrometry were used for the identification of species of *H cinaedi*. However, the use of MALDI-TOF mass spectrometry for identification of *Helicobacter* spp has not been extensively investigated. Because there is so much variability in biochemical characteristics, in 16S rRNA sequences, and perhaps the ability to grow in different blood culture media, it remains to be seen whether there are multiple related species of *Helicobacter* that are now all classified as *H cinaedi*.

CONCLUSIONS

It is difficult to tell from reported experience what the optimal treatment is for these infections. They apparently respond to different β-lactams, but relapse of infection is common. Furthermore, some infections may resolve spontaneously, making apparent response to treatment difficult to interpret. There have been no controlled studies of the treatment of *H cinaedi* cellulitis, but first- and third-generation cephalosporins and carbapenems have been effective for treating *H cinaedi*. *Helicobacter*-like organisms are resistant to vancomycin [4], and almost all isolates are resistant to macrolides and fluoroquinolones [18] but are susceptible to minocycline [24]. Fluoroquinolone resistance seems to be more common in Japan than in other countries. However, there are no established standards for interpreting susceptibility test results or for doing susceptibility testing. One of our patients was not cured with oral amoxicillin/clavulanic acid, perhaps because the minimum inhibitory concentration (MIC_{50}) for amoxicillin is 4–8 mg/dL [25].

It is unlikely that we know the full extent of the pathogenic potential of *H cinaedi*, because case reports of osteomyelitis [26] septic arthritis [27], endocarditis [28], meningitis [29], and abdominal mycotic aneurysms [30] have recently been published. Most of these cases were diagnosed by positive blood cultures. One of our cases was a cirrhotic patient who had spontaneous bacteremia, which has been reported before [3]. As molecular diagnostic methods improve, a broader range of HLO infection manifestations will likely become apparent [30]. Because diagnosis depends entirely on microbiologic identification, clinicians should be aware of this pathogen and request prolonged incubation of blood cultures in suspected cases.

In this case series, we used a variety of methods to speciate HLO. Unfortunately, we were able to perform all tests on only 2 isolates because of sample availability. Whole-genome sequencing was performed more than 10 years after the organism was isolated because new technology made it feasible. We also demonstrate by 16S rRNA phylogenetic analysis and whole-genome comparison that both of the pathogens are likely to be *H cinaedi*, but they contain significant amounts of additional DNA, likely phage-associated genes.

Supplementary Data

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

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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