Helicobacter cinaedi Infections in Emergency Departments: A Descriptive Study

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Introduction

Helicobacter cinaedi, a gram-negative spiral bacterium, is a rare cause of hantavirus in humans. Unfortunately, little is known about H. cinaedi infections in emergency departments (EDs). We aimed to describe the clinical features of H. cinaedi infections in the ED.

Materials and Methods

Study design and settings

This descriptive study was conducted at the ED of Kobe City General Hospital (KCGH) from November 2011 to December 2020. KCGH is a tertiary care hospital with 760 beds and serves 1.5 million habitants in the city, including both urban and rural areas of approximately 554 km². As a referral critical care centre, the ED has an average of 55,000 patient visits and 10,000 ambulance calls per year. On average, half of the severely injured patients in the city are managed in this ED.

Emergency physicians attend to patients in the ED and determine the need for admission. Further, blood cultures are obtained when the blood cultures yield positive results. Unfortunately, little is known about H. cinaedi infections in ED settings. Although some patients developed complicated infections, the prognosis was not poor under appropriate treatment, most of them were successfully treated with antibiotics, primarily tetracycline.

Selection of participants

The target population comprised patients with culture-confirmed H. cinaedi infections who presented to the ED. First, we selected all patients with confirmed H. cinaedi infections from the electronic microbiology database that contains data of patients with culture specimens in the hospital. Then, we excluded patients who visited the general outpatient ward and those infected with H. cinaedi identified from culture specimens following hospitalization.

Data collection

We retrospectively obtained the following patient data from the electronic medical records: age, sex, comorbidities (diabetes mellitus, chronic kidney disease [serum creatinine concentration >2.0 mg/dL], any malignancy, diseases requiring immunotherapy [use of steroids or immunosuppressive drugs], malignancy, diseases requiring recent chemotherapy [within 50 days of the ED visit], infected sites, laboratory data (white blood cell counts and C-reactive protein levels) from the initial ED visit, incubation days of blood cultures, antibiotic susceptibility, method of antibiotic administration (intravenous and oral), durations of antibiotic therapy (days), in hospital days, complications or surgical interventions, and in hospital mortality.

Cultures for H. cinaedi

We collected the data of all patients with H. cinaedi infection from the database at the bacteriological laboratory, including the results of all cultures from any kind of specimen. Blood cultures were obtained for at least seven days and processed at the center's laboratory using the BACTEC FX system (Nippogen, Tokyo, Japan) and Company, Tokyo, Japan). Polymerase chain reaction (PCR) identification was performed in all cultures where gram-negative spiral were identified using Gram staining. The KAGyu Research PBC K (NIPPON Genetics Company), Tokyo, Japan) was used to perform the test. H. cinaedi was identified using gyrB-targeted PCR (95 bp forward primer, AGAATTGCAGAACTC, reverse primer, TCTCGCTCTCCTCAT).

Statistical analysis

Continuous data were expressed as the median (with interquartile range [IQR]). Categorical data were expressed as the number (with percentage). Statistical analysis was performed using the Mann-Whitney U test (continuous data) and the chi-squared test (categorical data). A p-value <0.05 was considered statistically significant.
expressed as counts and percentages/proportions. To describe patient characteristics and clinical course of H. cinaedi more informatively for emergency physicians, the patients were stratified into those who were admitted at initial presentation to the ED and those who were discharged from the ED. These features were compared between the groups, using the \( \chi^2 \) test for categorical variables and the Mann-Whitney U test for continuous variables.

Statement and ethical approval

This study was approved by the ethics committee of KCGH (zn21114). The current study was conducted in accordance with the guidelines of the Declaration of Helsinki for medical research involving human participants. Informed consent was disclosed through an opt-out consent process in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

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Results

Descriptive statistics and clinical covariates

During the 10-year study period, a total of 22 ED patients were diagnosed with H. cinaedi infections, and all isolates were detected in blood samples (Figure 1).

![FIGURE 1: Patient flow of the study](image)

ED, Emergency department; KCGH, Kobe City General Hospital.

Of the 22 patients, 18 (81.8%) were male (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Total (n=22)</th>
<th>Admitted at initial visit (n=11)</th>
<th>Discharged at initial visit (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>65.5 (49.3–63.3)</td>
<td>66 (53.0–78.0)</td>
<td>64 (49.5–67.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (81.8)</td>
<td>10 (90.9)</td>
<td>8 (72.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (31.8)</td>
<td>2 (18.2)</td>
<td>5 (45.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>With complications, n (%)</td>
<td>2 (9.1)</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
<td>-</td>
</tr>
<tr>
<td>Haematological malignancies or solid tumours, n (%)</td>
<td>5 (22.7)</td>
<td>4 (36.4)</td>
<td>1 (8.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Recent chemotherapy, n (%)</td>
<td>4 (18.2)</td>
<td>4 (36.4)</td>
<td>0 (0)</td>
<td>0.027</td>
</tr>
<tr>
<td>Chronic renal disease, n (%)</td>
<td>4 (18.2)</td>
<td>3 (27.3)</td>
<td>1 (8.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Immunosuppressant use, n (%)</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (8.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>None, n (%)</td>
<td>13 (59.1)</td>
<td>1 (9.1)</td>
<td>12 (10.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Focus of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis, n (%)</td>
<td>3 (13.6)</td>
<td>2 (18.2)</td>
<td>1 (8.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Vertebral osteomyelitis, n (%)</td>
<td>3 (13.6)</td>
<td>2 (18.2)</td>
<td>1 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Infected aortic aneurysm, n (%)</td>
<td>2 (9.1)</td>
<td>2 (18.2)</td>
<td>0 (0.0)</td>
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<tr>
<td>Colitis, n (%)</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
<td>2 (18.2)</td>
<td></td>
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<tr>
<td>Infected cyst, n (%)</td>
<td>2 (9.1)</td>
<td>2 (18.2)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Lymphadenitis, n (%)</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>9 (40.9)</td>
<td>3 (27.3)</td>
<td>6 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White blood cell count (10^3/µL), median (IQR)</td>
<td>9.4 (7.8–15.7)</td>
<td>8.6 (7.8–15.0)</td>
<td>11.8 (8.3–17.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>C-reactive protein (mg/L), median (IQR)</td>
<td>3.41 (1.49–10.8)</td>
<td>10.7 (7.1–19.1)</td>
<td>2.00 (1.02–4.39)</td>
<td>0.071</td>
</tr>
<tr>
<td>In-hospital days, median (IQR)</td>
<td>25 (7.5–30.5)</td>
<td>20 (9.0–35.0)</td>
<td>10 (7.5–17.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Complications or surgical interventions, n (%)</td>
<td>4 (18.2)</td>
<td>1 (9.1)</td>
<td>3 (27.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

**TABLE 1: Characteristics and outcomes of patients with H. cinaedi bacteraemia who were admitted and discharged at their initial emergency department visits**

IQR: Interquartile range

[Admitted at the follow-up visit to the ED (n=4)]
TABLE 2: Characteristics of patients with *H. cinaedi* bacteraemia in the emergency department

The youngest patient was 52 years old, while the oldest was 95 years old (median: 65.5 [IQR: 45.5-65.5] years). The most common chief complaints and findings in the ED were fever (18/22, 81.8%), chills (10/22, 45.5%), and localized pain or tenderness at the site of infection (9/22, 40.9%). Additionally, patients often presented with a history of recent digestive symptoms, such as diarrhoea, nausea/vomiting, or abdominal pain (6/22, 27.3%). Diabetes mellitus was reported in seven of 22 (31.8%) patients, while haematological malignancies or solid tumours were reported in five of 22 (22.7%) patients. In addition, four of 22 (18.2%) patients presented with chronic kidney disease (3/22, 13.6%) patients had no comorbidities. Patients with recent chemotherapy were more likely to be admitted at initial presentation to the ED compared with those who were discharged (4/11 [18.2%] versus 0/11 [0%]). Furthermore, the C-reactive protein levels were higher in the admitted patients (median: 10.7 [IQR: 1.59-12.9] versus 3.41 [IQR: 1.49-3.6] mg/L).

Cellulitis and sepsis were the most common sources of *H. cinaedi* bacteraemia, followed by an infected aortic aneurysm, colitis, and infected cysts (renal cyst and pancreatic cyst with concomitant empyema) (2/22, 9.1%, for all). Meanwhile, the sources of infections were not identified in nine (40.9%) patients. Patients with recent digestive symptoms were more likely to be discharged (4/11 [36.4%] versus 0/11 [0%]). Two patients had missing data on the incubation time.

*H. cinaedi* isolates were susceptible to carbapenems (meropenem and imipenem), amikacin, gentamicin, and minocycline. Fewer *H. cinaedi* isolates were susceptible to cefotaxim (5/18, 27.8%), ceftriaxone (4/10, 40.0%), ciprofloxacin (6/10, 60.0%), and levofloxacin (5/17, 29.4%); (Table 1).
Antibiotics Susceptibility of H. cinaedi (%)

Penicillin
- Ampicillin 16/18 (88.9)

Cephalosporins
- Cefazolin (first generation) 15/17 (88.2)
- Cefotiam (second generation) 5/18 (27.8)
- Ceftriaxone (third generation) 4/10 (40.0)
- Cefepime (fourth generation) 17/17 (100)

Tetracyclines
- Minocycline 17/17 (100)

Carbapenems
- Meropenem 10/10 (100)

Fluoroquinolones
- Levofloxacin 3/17 (17.6)
- Ciprofloxacin 0/10 (0.0)

Aminoglycosides
- Gentamicin 17/17 (100)
- Amikacin 17/17 (100)

Sulfonamides
- Trimethoprim-sulfamethoxazole 9/10 (90.0)

**TABLE 3: Antimicrobial susceptibility of H. cinaedi isolates obtained from patients presenting to the emergency department**

We demonstrated antibiotics and a number of H. cinaedi samples susceptible/total number of tested samples (%).

**Management of H. cinaedi bacteraemia**

Patients with H. cinaedi bacteraemia were treated with antibiotics administered through different routes (Table 4).

<table>
<thead>
<tr>
<th>Intravenous antibiotics chosen as definitive therapy (n=15 patients)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Minocycline, n (%)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Cefazolin (first-generation cephalosporins)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Sulbactam/ampicillin</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Ticarcillin/piperacillin</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Cefotiam (second-generation cephalosporins)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Cefepime (fourth-generation cephalosporins)</td>
<td>1 (6.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral antibiotics chosen as definitive therapy (n=20 patients)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline, n (%)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Cefaclor (first-generation cephalosporin)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Cefditoren pivoxil (third-generation cephalosporin)</td>
<td>1 (5.0)</td>
</tr>
</tbody>
</table>

**TABLE 4: Intravenous and oral antibiotics for patients with H. cinaedi bacteraemia**

Of them, one patient (1/21, 4.8%) was treated with intravenous antibiotics alone, 14 (14/21, 66.7%) patients were treated with intravenous antibiotics and subsequently oral antibiotics, and six patients (4/21, 28.6%) were treated with oral antibiotics alone. The median total duration of antimicrobial treatment was 20.5 days (IQR: 14.0-29.3). The duration of antibiotic treatment exceeded 40 days in six patients with complex infections: vertebral osteomyelitis (three), infected aortic aneurysms (two), and cyst infection (one).

The most frequently administered intravenous antibiotics were minocycline (5/15, 33.3%), cefazolin (3/15, 20.0%), and sulbactam/ampicillin (3/15, 20.0%). Minocycline was the most common oral antibiotic (3/21, 14.3%), followed by levofloxacin and doxycycline (3/21, 14.3% for both). Of note, one patient recovered from the infection without receiving antibiotic treatment. The patient was hospitalized and treated for hypokalaemia and discharged with potassium correction alone.

**Discussion**

In this descriptive study conducted at a single ED in Japan, we reported the patient characteristics and common clinical practices for H. cinaedi infections. The patients with H. cinaedi infections presented to the ED with vague clinical features, making it difficult to obtain an accurate diagnosis, and complicated infections were often the cases, including vertebral osteomyelitis and infected aortic aneurysms, unlike the previously reported cases in the primary care settings. Of note, H. cinaedi was detected only in blood cultures, and the duration of blood cultures exceeded five days in 45% of the patients.

Our study adds to the existing literature by providing a more detailed picture of H. cinaedi infections in emergency settings. The clinical features, especially symptoms, and signs are unclear; therefore, the clinical features of H. cinaedi infections were described as vague and non-specific, reflecting various patterns in the different sites of infection. The present study also demonstrated that patients with complicated cases such as vertebral osteomyelitis, infected aortic aneurysms, and infected cysts were more commonly reported in.
the emergency settings; these cases were primarily documented in case reports conducted in primary care settings [14, 15]. These complicated cases required antibiotic therapy for over 40 days; however, the prognosis were not poor with appropriate treatments, with only one patient requiring surgical intervention. Meanwhile, stable patients with H. cinaedi bacteremia can be safely managed in outpatient settings close follow-ups, provided that they do not have any complicated concomitant source of infections and are not immunocompromised. Indeed, the clinical courses and outcomes, such as complications and need for surgical treatments, in hospital days, and mortality, were not aggravated in the present study. On the contrary, immunocompromised patients, especially those with recent chemotherapy, were likely admitted at the first visit to the ED in the present study, and previous studies also pointed out that these patients are at risk for recurrence [9, 19, 22, 27].

The diagnosis of H. cinaedi was only made when the general observation period for blood cultures was employed, as the time to positive blood culture was longer than five days. Our bacteriological laboratory employed a minimum observation period of seven days for blood cultures, which potentially facilitated the detection of H. cinaedi bacteremia in a greater number of patients. Furthermore, H. cinaedi was detected only in blood cultures and not in other specimens such as tissue and wound tissues. These findings highlight the importance of blood cultures for detecting H. cinaedi infections in emergency departments.

As regards the antibiotic of choice, intravenous or oral tetracycline is the primary treatment for H. cinaedi infection. All H. cinaedi isolates were susceptible to tetracycline. Furthermore, the treatment of complex infections often necessitates a prolonged course of antimicrobial therapy to achieve a complete cure. Indeed, the present study demonstrated that approximately 70% of the patients underwent antimicrobial therapy for more than 40 days and were diagnosed with complex infections; these patients had ventilator-associated pneumonia, two had infected aortic aneurysms, and one had a cyst infection. We also recommend a 14- day antibiotic course for most patients, with a longer duration considered for immunocompromised patients to prevent recurrence. The optimum duration of treatment might vary depending on the specific source of infection in each patient.

This study had several limitations. First, it was descriptive in nature, and no control groups were established for comparison; hence, we could not draw conclusive clinical recommendations. Further studies are warranted to evaluate the optimal choice and route of antibiotic treatment for H. cinaedi infections. Second, the present study was performed at a single ED, which may have introduced a selection bias. The patients included in the present study might have more severe cases, as the study setting was a tertiary-care center. Third, it is difficult to generalise the findings of the present study to other communities, where medical systems and resources differ. For example, admission criteria may vary in other countries, as well as the antibiotic preference and availability. Further studies of diverse patient populations are warranted.

Conclusions

The diagnosis of H. cinaedi infections may be challenging owing to its rarity and unfamiliarity; performing blood cultures appropriately is the key to prompt and accurate diagnosis. In emergency settings, complicated cases of H. cinaedi bacteremia were more frequently observed. However, the prognosis of H. cinaedi bacteremia was good when it was managed with appropriate antibiotics, primarily tetracycline. Further studies are required to develop an individualised approach based on the patient’s infection and immunological status.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. The ethics committee of Kobe City Medical Center General Hospital issued approval 22-0184. The current study was conducted in accordance with the Declaration of Helsinki guidelines for medical research involving human subjects. Informed consent was disclosed as an opt-out consent process in accordance with Ethical Guidelines for Kobe City Medical Center General Hospital issued approval zn21114. The current study was conducted in human subjects: additional information.

Animal subjects: All authors have declared that they have no financial relationships at present or of any kind.

Payment/services info: All authors have declared that they have no financial relationships at present or of any kind.

References


