**Young-infant Sepsis Combined with Urinary Tract Infection Due to *Hafnia alvei***

Chia-Hung Liu,1,2 Wei-Jen Lin,1 Chih-Chien Wang,1 K-Long Lee,3 Ming-Chih Tsai1*

*Hafnia alvei* infections are uncommon and occur mainly in adult patients featuring underlying illnesses. Its isolation in pediatric cases is even more unusual. We report a rare case of sepsis combined with urinary tract infection caused by *H. alvei* in a 39-day-old infant who did not appear to feature any underlying disease. The infant was successfully treated with ceftriaxone over a 14-day period. In this case, we want to remind clinicians that the possibility of an extraintestinal invasive infection such as bacteremia or urinary tract infection caused by *H. alvei* should be taken into account in young infants who feature no apparent underlying disease. [J Formos Med Assoc 2007;106(3 Suppl):S39–S43]

**Key Words:** *Hafnia alvei*, sepsis, urinary tract infection

*Hafnia alvei* is a Gram-negative bacillus belonging to the family *Enterobacteriaceae*, and it is believed to be an opportunistic pathogen responsible for causing invasive disease in debilitated patients.1,2 This bacillus is rarely associated with invasive disease in pediatric patients, especially in the young-infant period.3–8

We report the case of a 39-day-old infant with urinary tract infection combined with sepsis due to *H. alvei* infection. We also review the relevant literature for previously reported cases of extraintestinal invasive disease suspected to have been caused by *H. alvei* and occurring in pediatric patients.

**Case Report**

A 39-day-old infant presented to the emergency department at a local hospital for evaluation of a fever of approximately 48 hours’ duration. The infant’s initial physical examination was notable for a body temperature of 38.6°C and demonstrated irritability, although there appeared to be no obvious foci of infection. The contact history for the infant was traced back for the preceding several days during which time the patient had had a diaper change alongside another infant who was suffering from acute gastroenteritis at that time. Our patient’s past history revealed that he was delivered by an uncomplicated vaginal delivery following a gestation period of 37 weeks, and that there appeared to have been no history of a prolonged rupture of the membrane. The infant’s birth weight was 3070 g and there appeared to have been no prenatal, peripartum or postpartum complications reported for either the patient or his mother.

At the local hospital, the complete blood cell count revealed a white blood cell (WBC) count of $14.7 \times 10^3/\mu L$, featuring 40.9% neutrophils, 56.1% lymphocytes, and 2.0% monocytes. The C-reactive...
protein (CRP) level appeared to be elevated to 16.1 mg/dL. Urine analysis revealed abundant leukocytes (WBC count > 100/high powered field), and positive leukocyte esterase reaction (3+). Infant blood and urine (via bladder catheterization) samples were cultured, and antibiotic treatment with ampicillin and gentamicin commenced at the local hospital under the suspicion of a condition of sepsis. The infant was transferred to our hospital the following day due to persistent fever, and the blood culture yielded certain Gram-negative bacilli. At our hospital, the infant appeared acutely ill and displayed a rather poor activity level. Initially, he had a body temperature of 38.7°C, a respiration rate of 41 breaths/minute, a blood pressure of 96/68 mmHg, and a heart rate of 145 beats/minute. The complete blood cell count revealed a WBC count of 29.5 \times 10^3/μL, featuring 30.0% neutrophils, 45.0% lymphocytes, and 12.0% monocytes. The CRP level was 14.27 mg/dL. A lumbar puncture was performed and revealed clear cerebrospinal fluid (CSF) with zero WBC/mL, normal glucose (41 mg/dL) and protein (41 mg/dL) levels, and no evident organisms upon Gram-staining. Latex agglutination antigen studies of CSF revealed negative results for group-B *Streptococcus*, *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, and *Neisseria meningitides*. The CSF culture was negative for any specific micro-organisms. However, the initial cultures of blood and urine obtained at the referring hospital all showed that *H. alvei* grew in a pure isolate (> 10^5 colonies) and all featured the same antibiotic susceptibility. *H. alvei* was identified by the computer-assisted Vitek 2 System GN card (BioMerieux Vitek Inc., Hazelwood, MO, USA) plus conventional biochemical test for further identification. Biochemical reactions for which *H. alvei* were positive included lysine decarboxylase, ornithine decarboxylase, and mannitol fermentation, whereas it was negative for fermentation of sorbitol, inositol, sucrose, and melibiose; these negative reactions differentiated *H. alvei* from *Enterobacter aerogenes*. For those cultures, antimicrobial susceptibility was performed by the disc-diffusion method, which revealed that *H. alvei* was resistant to ampicillin, cefazolin, piperacillin, chloramphenicol, and trimethoprim-sulfamethoxazole, and was susceptible to amoxicillin/clavulanate, cefaclor, cefotaxime, ceftriaxone, gentamicin, amikacin, ciprofloxacin, and meropenem. The patient was treated with a 14-day course of ceftriaxone at our institution and recovered completely.

In addition, he also underwent a 2,3-dimercaptosuccinic acid (DMSA) renal scan and sonography of the kidneys. The DMSA renal scan demonstrated no evidence of pyelonephritis, while kidney sonography revealed bilateral mild hydronephrosis. Otherwise, all results from the patient’s immunologic evaluation (including serum IgA, IgM, IgE, IgG, and IgD levels, lymphocyte profile, and C3, C4, and CH50) lay within the normal ranges. Furthermore, an HIV enzyme-linked immunosorbent assay antibody test was negative.

**Discussion**

*H. alvei* is a motile, facultatively anaerobic, Gram-negative bacillus, formerly referred to as *Enterobacter hafnia*. This organism typically constitutes a component of the normal human gastrointestinal flora and is typically found in environmental habitats such as surface water and certain foods. These bacteria are rarely isolated from human specimens and are thought to be rarely pathogenic. In 1991, Albert et al identified this organism as an enteric pathogen, noting that several cases of diarrhea caused by *H. alvei* had previously been reported in the literature, such cases arising mainly in children. Subsequent to the findings of Albert et al, several cases of extraintestinal infections, including septicemia, endocarditis, meningitis, pneumonia, abscess, and surgical-wound infection, have been reported. *H. alvei* is a rare but significant etiologic agent of nosocomial and community-acquired infections. It is primarily isolated from patients featuring underlying illness, apart from cases when it exists as an enteric pathogen. Some iatrogenic factors have been associated with *H. alvei* bacteremia, including abdominal surgery, the
presence of central venous catheters, endotracheal tubes and urethral catheters, and/or previous administration of antibiotics.9,11

The pathogenesis of the invasive disease remains somewhat unclear, but the gastrointestinal tract has been implicated as a frequent source of the infection.11 To our knowledge, the first reported case of purulent meningitis ascribable to *H. alvei* was in 1978, when it was assumed that the gastrointestinal tract was the port of entry for the bacteria and that meningitis arose secondarily to bacteremia.7 In our case, the patient did feature a urinary tract infection and also bacteremia, and had a contact history with another infant who suffered from acute gastroenteritis at the time of contact. Such a medical scenario may suggest that *H. alvei* was retrograded to the urinary tract from where it then induced bacteremia.

*H. alvei* would appear to be an infrequently reported pathogen among children, and its isolation from a neonate or a young infant is even more unusual.1,2 This organism is rarely associated with invasive disease, but it may be a pathogen among neonates.1,2 In 1988, Ginsberg and Goldsmith2 suggested that attempts should be made to identify this bacillus (if present), such that additional information may be elucidated if *H. alvei* was isolated from blood or stool samples taken from neonates. In 2004, the first case of late-onset neonatal sepsis caused by *H. alvei* in an infant who featured no underlying disease was reported.1 Here, we have summarized previously (English) literature-reported cases of extraintestinal invasive infections in pediatric patients caused by *H. alvei*, including our own case (Table). Of the eight literature-reported pediatric cases of extraintestinal invasive infections caused by *H. alvei*, six occurred in males, two occurred in neonates, and one occurred in a young infant. Four cases cited underlying conditions, including acute nonlymphocytic leukemia after allogeneic bone marrow transplantation, preterm infant with necrotizing enterocolitis, human immunodeficiency virus infection, and liver transplantation.

**Table.** Clinical features of pediatric cases featuring extraintestinal invasive infections caused by *Hafnia alvei*

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Gender</th>
<th>Specimen source</th>
<th>Underlying disease</th>
<th>Antibiotic therapy</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 yr</td>
<td>F</td>
<td>Blood</td>
<td>No</td>
<td>CAR + GEN, → stop GEN</td>
<td>Recovered</td>
<td>Grajwer et al6</td>
</tr>
<tr>
<td>2</td>
<td>1 yr</td>
<td>F</td>
<td>CSF</td>
<td>No</td>
<td>GEN → add CLI + TET</td>
<td>Died</td>
<td>Mojtabaei &amp; Siadati7</td>
</tr>
<tr>
<td>3</td>
<td>6 yr</td>
<td>M</td>
<td>Blood</td>
<td>ANLL after allogeneic BMT</td>
<td>AMI + C + TIC × 14d</td>
<td>Recovered</td>
<td>Yeager et al8</td>
</tr>
<tr>
<td>4</td>
<td>20 d</td>
<td>M</td>
<td>Blood, stool</td>
<td>Preterm 31 wk with NEC perforation</td>
<td>MET + GEN → add TIC, stop GEN × 14d</td>
<td>Recovered</td>
<td>Ginsberg &amp; Goldsmith2</td>
</tr>
<tr>
<td>5</td>
<td>8 yr</td>
<td>M</td>
<td>Blood</td>
<td>HIV infection</td>
<td>TMP-SMX → add CTRX</td>
<td>Recovered</td>
<td>Conte et al6</td>
</tr>
<tr>
<td>6</td>
<td>2 yr</td>
<td>M</td>
<td>Blood, abscess</td>
<td>Liver transplantation</td>
<td>TMP-SMX + AMP + GEN × 11 d</td>
<td>Recovered</td>
<td>Barry et al4</td>
</tr>
<tr>
<td>7</td>
<td>8 d</td>
<td>M</td>
<td>Blood</td>
<td>No</td>
<td>CTRX × 10 d</td>
<td>Recovered</td>
<td>Casanova-Roman et al1</td>
</tr>
<tr>
<td>8</td>
<td>39 d</td>
<td>M</td>
<td>Blood, urine</td>
<td>No</td>
<td>CTRX × 14 d</td>
<td>Recovered</td>
<td>Present case</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; ANLL = acute nonlymphocytic leukemia; BMT = bone marrow transplantation; NEC = necrotizing enterocolitis; HIV = human immunodeficiency virus; CAR = carbenicillin; GEN = gentamicin; CLI = clindamycin; TET = tetracycline; AMI = amikacin; C = chloramphenicol; TIC = ticarcillin; MET = methicillin; TMP-SMX = trimethoprim-sulfamethoxazole; CTRX = ceftriaxone; CTX = ceftaxime.
Subsequent to adequate antibiotic treatment, seven cases exhibited a full recovery. For the remaining one case, that of a 1-year-old female infant with *H. alvei* meningitis, the patient showed only a slight improvement subsequent to antibiotic treatment and, unfortunately, died of *Pseudomonas aeruginosa* sepsis. For the seven cases that recovered, 10–14 days of antimicrobial therapy proved to be entirely effective for full patient recovery.

*H. alvei* is usually resistant to ampicillin and first-generation cephalosporins because it features inducible and constitutive beta-lactamases, and under certain circumstances, can develop resistance to second- and third-generation cephalosporins. For severe cases, treatment with imipenem or a third-generation cephalosporin in combination with an aminoglycoside is recommended by many clinicians. In general, piperacillin and gentamicin have been previously shown to be active against *H. alvei*. According to our review in children, four cases (cases 5, 6, 7, 8; Table) underwent antibiotic-susceptibility testing prior to treatment. Three of them who underwent antibiotic-susceptibility testing for ampicillin were resistant (75% resistant). Two cases underwent antibiotic-susceptibility testing for piperacillin and revealed 100% resistance; four cases underwent susceptibility testing for gentamicin and the resistance rate was 25%. Apart from the abovementioned antibiotics, we noted that amikacin, imipenem and/or meropenem, and third-generation cephalosporins were the most effective antimicrobials for the four cases (zero resistance). In our case, ceftriaxone was used for 14 days, with a successful outcome.

Cases of urinary tract infections due to *H. alvei* among adults have been reported previously. The largest case study report, which included 80 isolates of *H. alvei* recovered from 61 patients, reported that there were 12 such isolates detected from the urogenital tracts of seven patients. Further, Ramos and Damaso described three adult cases of hospital-acquired urinary tract infection, of which two patients had undergone previous urethral catheterization. This finding emphasizes the potential role of urethral catheters in the acquisition of nosocomial urinary tract infections. Here, we have reported a rare case of young-infant sepsis combined with urinary tract infection caused by *H. alvei*. This is the first literature-reported case of urinary tract infection combined with sepsis caused by *H. alvei* in a young infant who featured no other underlying disease.

In conclusion, our case reminds diagnosing physicians that the possibility of an extraintestinal invasive infection such as bacteremia or urinary tract infection being caused by *H. alvei* should be taken into account in young infants who feature no apparent underlying disease. For cases of *H. alvei* infection featuring extraintestinal infection, effective treatment should be carefully selected based on the results of preliminary antimicrobial-susceptibility testing. Cases usually recover uneventfully after adequate antibiotic treatment for 10–14 days, except for the case of central nervous system infection. Although there would appear to be an absence of any large pediatric case studies relating to this topic reported in the literature, increased awareness and evaluation of the susceptibility pattern of the organism would allow appropriate antibiotic therapy in the future.

References


