

Clinical Characteristics of Seven Patients with *Aeromonas* Septicemia in a Japanese Hospital

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The genus *Aeromonas* comprises flagellated gram-negative rods widely distributed in freshwater, estuarine and marine environments. *Aeromonas* species may cause a variety of illnesses in humans, such as enterocolitis and septicemia, especially in warmer tropical or subtropical environments. To recognize the characteristics of *Aeromonas* septicemia in Japan, we reviewed laboratory data and medical records in our hospital. During 11 years (from 2000 to 2010), *Aeromonas* septicemia was observed in seven patients involving six female subjects. Six patients were observed in summer or fall. The incidence of *Aeromonas* septicemia was about 0.07 per 1000 admissions, and two out of the seven patients died. All patients had underlying diseases such as malignancy (six patients) and choledocholithiasis (one patient). Two patients developed septicemia within two days after ingesting raw seafood. Five patients developed *Aeromonas* septicemia > 48 h after admission. Fever was present in all patients, and four out of the seven patients developed septic shock. All patients developed monomicrobial septicemia. *A. hydrophila* was isolated from five patients, and *A. caviae* and *A. veronii* biovar *sobria* were isolated from one patient each. Most antimicrobial agents had high activity against the isolated strains. However, a carbapenem-resistant strain appeared in one patient during treatment and led to death. *Aeromonas* septicemia is uncommon in temperate areas but can occur particularly in warm seasons. Immunocompromised conditions and recent ingestion of raw fish or shellfish are important characteristics of developing *Aeromonas* septicemia.

Keywords: *Aeromonas caviae*; *Aeromonas hydrophila*; *Aeromonas veronii* biovar *sobria*; *Aeromonas* septicemia; seafood

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The genus *Aeromonas* comprises flagellated gram-negative rods widely distributed in freshwater, estuarine and marine environments. Although *Aeromonas* species can grow at a range of temperatures, they are isolated more frequently in warmer tropical or subtropical environments. They have the potential to infect or colonize humans and are associated with a variety of illnesses, such as enterocolitis (Holmberg and Farmer 1984), septicemia (Janda et al. 1994), skin and soft tissue infections (Furusu et al. 1997), and peritonitis (Huang et al. 2006).

Severe infections sometimes occur in clinically ill patients and septicemia is an important invasive disease associated with *Aeromonas* infections. *Aeromonas* infections can develop into septicemia not only in immunocom-

promised patients but in trauma patients as well as healthy persons. However, immunocompromised patients with hepatobiliary diseases or hematologic malignancy are considered to be at the greatest risk for *Aeromonas* septicemia (Tsai et al. 2006).

Some studies with large numbers of patients with *Aeromonas* infections have been reported from countries located in tropical or subtropical climates (Ko et al. 2000; Lau et al. 2000). However, epidemiological differences in *Aeromonas* infections have been noted to be based on geographic locales or populations (Janda and Abbott 2010). Although increasing antibiotic resistance in clinical isolates has been reported in Taiwan (Ko et al. 1996), the patterns of susceptibility to drugs may also vary due to geographic

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locations or selection pressures.

Because Japan lies in a temperate zone and has four distinct seasons, the characteristics of *Aeromonas* infections in Japan are different from those in tropical or subtropical countries, and *Aeromonas* septicemia is relatively uncommon in Japan. To understand the characteristics of patients with *Aeromonas* septicemia in Japan, we retrospectively reviewed patients at our hospital.

Materials and Methods

Nagasaki University Hospital is a facility with about 850 beds. Hospital microbiology laboratory databases were reviewed for all species of *Aeromonas* isolated between the years 2000 to 2010. Positive blood culture for *Aeromonas* was considered to represent evidence of septicemia. Primary septicemia was defined in patients with fever or hypotension without an apparent focus or portal of entry. Data on clinical characteristics were obtained retrospectively by reviewing patient medical records. The laboratory parameters were extracted from same- or next-day blood sampling data. Patients were identified as either community-acquired or healthcare-associated. Healthcare-associated patients were defined as having occurred > 48 h after hospital admission, with signs and symptoms of infection that were absent at the time of admission. *Aeromonas* species were isolated on blood agar and identified to the species level by using the Vitek2 system (bioMerieux, Hazelwood, MO, USA) or Phoenix 100 instrument (BD, Franklin Lakes, NJ, USA). Antimicrobial susceptibility testing of *Aeromonas* isolates was performed by the hospital microbiology laboratory by broth microdilution assay according to the Clinical and Laboratory Standards Institute (The Clinical and Laboratory Standards Institute 2010).

Results

From the years 2000 to 2010, *Aeromonas* species were isolated from 101 patients at Nagasaki University Hospital. *Aeromonas* species were isolated from the blood samples of seven patients (6.9%) (Table 1). The incidence of *Aeromonas* septicemia in our hospital was about 0.07 per 1,000 admissions. The patient subjects included one male and six females, ranging in age from 15 to 89 years (median age, 76 years). *A. hydrophila* was isolated from five patients, and *A. caviae* and *A. veronii* biovar *sobria* were isolated from one patient each. Malignant diseases were observed in six patients (85.7%). Four patients had hematological malignancies, one had colon cancer, and one had pancreatic cancer. None of the patients had liver cirrhosis as an underlying condition. Two patients presented secondary septicemia followed by cholangitis associated with stenosis due to choledocholithiasis or pancreatic cancer. The other patients presented primary septicemia. In two patients primary septicemia developed during nadir of neutropenia due to chemotherapy.

One hundred percent of the patients had fevers and four patients (57.1%) developed septic shock. Five (71.4%) of the seven patients were healthcare-associated. As episodes, two patients (patients 1 and 2) had ingested raw seafood within 2 days prior to developing symptoms. Patient 1 consumed raw sea bream and manila clam at home. Patient

Table 1. Clinical summary of seven patients with *Aeromonas* septicemia.

| Patient no. | Age | Sex | Onset month | Isolates | Comorbidities | Clinical presentation | Day of septicemia onset after hospitalization | Body temperature (°C) | Abdominal pain | Shock | WBC (μL) | Drugs | Outcome |
|-------------|-----|-----|-------------|--|----------------------------|--------------------------|---|-----------------------|----------------|-------|----------|-----------------------|---------|
| 1 | 74 | F | Jul | <i>A. hydrophila</i> | Choledocholithiasis | Cholangitis + septicemia | (community-acquired) | 39.8 | + | - | 12,400 | Meropenem | Cured |
| 2 | 35 | F | Jul | <i>A. hydrophila</i> | Colon cancer | Primary septicemia | 17 | 39.9 | - | - | 5,900 | Biapenem | Cured |
| 3 | 79 | F | Jul | <i>A. hydrophila</i> | Multiple myeloma, Diabetes | Primary septicemia | 169 | 38.3 | + | - | 2,300 | None | Died |
| 4 | 76 | F | Sep | <i>A. hydrophila</i> | MDS/ALL | Primary septicemia | (community-acquired) | 39.2 | - | + | 13,400 | Cefepime + Isepamicin | Cured |
| 5 | 78 | M | Feb | <i>A. caviae</i> | AML | Primary septicemia | 26 | 39.5 | - | + | 100 | Meropenem | Cured |
| 6 | 89 | F | Oct | <i>A. hydrophila</i> | Pancreatic cancer | Cholangitis + septicemia | 9 | 40.1 | - | + | 9,100 | Imipenem | Cured |
| 7 | 15 | F | Jul | <i>A. veronii</i> biovar <i>sobria</i> | ALL, Down syndrome | Primary septicemia | 371 | 40.4 | - | + | 100 | Meropenem | Died |

WBC, white blood cell; MDS, myelodysplastic syndromes; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia.

2 had a history of eating unspecified raw fish that were brought by family during hospitalization. In addition, the stool of patient 2 was cultured, but *Aeromonas* species were not isolated.

With antimicrobial therapy, five out of six patients received a carbapenem as a first-line therapy. Patient 1 required endoscopic sphincterotomy to remove a common bile duct stone. Ceftazidime, cefepime, aztreonam, meropenem, gentamicin, and ciprofloxacin showed good antimicrobial activity against *Aeromonas* species isolated in the study, although ampicillin/sulbactam did not.

Two patients (28.6%) died due to *Aeromonas* septicemia. For patient 3, aggressive treatment with antibiotics was not selected because the patient was in a terminal state of multiple myeloma. For patient 7, meropenem was started for the treatment of neutropenic fever. However, the effect of treatment with meropenem alone was insufficient. Combination treatment with meropenem, vancomycin, and ciprofloxacin was then selected. The minimum inhibitory concentration (MIC) of meropenem against the strain isolated at onset was $\leq 0.5 \mu\text{g/mL}$, but $\geq 32 \mu\text{g/mL}$ on the seventh day after septicemia onset. The MIC of ciprofloxacin remained at $\leq 0.5 \mu\text{g/mL}$ in each isolate. However, the patient's condition did not respond to the treatment, resulting in death on the tenth day after onset.

Discussion

Aeromonas species are universally isolated from a variety of environmental sources, including water, seafood, meats and vegetables (Palumbo et al. 1985). Their growth is encouraged in thermal gradients ranging from 25°C to 35°C (Hazen et al. 1978) and *Aeromonas* infections can be relatively frequent in warm tropical or subtropical climates. Therefore, many reports concerning *Aeromonas* infections have been published from these areas (Chan et al. 2000; Ko et al. 2000; Tsai et al. 2006). Indeed, the number of patients with *Aeromonas* septicemia in our hospital during the past 11 years was small compared to reports from Taiwan (Ko et al. 2000; Lau et al. 2000). Characteristics of the Japanese climate may affect bacterial growth, especially in winter. Japanese people may also have fewer opportunities to be exposed contaminated water or foods containing high concentrations of bacteria compared to people in subtropical countries. In fact, six out of seven of patients were observed between July and September, the period when the sea temperature is relatively warm.

A. hydrophila, *A. caviae*, and *A. veronii* biovar *sobria* are major *Aeromonas* species that cause septicemia (Janda et al. 1994). These species were also observed in our study. In several reports of *Aeromonas* septicemia, the male-female ratio ranged from 1.6 to 4.0 and community-acquired patients comprised 71 to 79% of all patients (Ko et al. 2000; Lau et al. 2000; Llopis et al. 2004). In contrast, our study involved a lower percentage of men and a lower percentage of community-acquired patients. The difference in our male-female ratio may be due to the few patients in

our study. In regards to the lower percentage of community-acquired patients, fewer opportunities of contact with *Aeromonas* species may decrease the potential of septicemia. In contrast, *Aeromonas* septicemia was observed mainly in hospitalized patients. The fact that *Aeromonas* strains colonize in multiple ways and the host develops a serious immunosuppressive condition requiring hospitalization may increase the potential of bacteremia. However, we should also pay attention to food-borne patients from the ingestion of raw fish or shellfish, as in patients 1 and 2. The seafood can carry a lot of *Aeromonas* strains even in Japanese climate, especially in the warm seasons. These results suggest that consumption of *Aeromonas*-contaminated foods such as raw seafood as well as immunocompromised conditions can be risk factors for *Aeromonas* septicemia in temperate areas. Considering that most of the patients presented in this study developed *Aeromonas* septicemia in summer or fall, the patients who had uncertain episodes might also consume some *Aeromonas*-contaminated foods.

Aeromonas septicemia can be categorized into four groups according to the patient's condition: immunocompromised patients, trauma patients, healthy persons, and post-reconstructive surgery patients. *Aeromonas* septicemia are seen mainly in immunocompromised patients (Janda and Abbott 2010). Several studies with a large number of patients reported that predisposing conditions for *Aeromonas* septicemia were chronic liver disease, malignancy, and biliary tract disease (Ko et al. 2000; Lau et al. 2000; Llopis et al. 2004). In individuals with hematologic malignancies, anti-neoplastic medications may cause disintegration of the gastrointestinal mucosa and allow transmigration of colonized *Aeromonas* species from the bowel into the circulatory system. Among hematological malignant diseases, acute myeloblastic leukemia, acute lymphoblastic leukemia, and non-Hodgkin's lymphoma were three leading risk conditions for *Aeromonas* septicemia (Tsai et al. 2006). As reported in these studies, the comorbidities of our patients were similar, except we had no patients with chronic liver disease. Patients whose onset was during nadir of neutropenia or a terminal state had risks of developing bacteremic translocation.

In reports with a large number of patients, the most common symptoms associated with *Aeromonas* septicemia were fever (74 to 89%), jaundice (57%), abdominal pain (16 to 45%) and septic shock (40 to 45%) (Lau et al. 2000; Tsai et al. 2006). Similarly, these symptoms were observed in our patients except for jaundice. Because these symptoms are nonspecific, it is difficult to distinguish *Aeromonas* septicemia from those caused by other gram-negative septicemia by clinical features. The percentage of monomicrobial septicemia (100%) in our study was higher than that in previous reports (64 to 75.6%) (Lau et al. 2000; Llopis et al. 2004; Tsai et al. 2006). Our results may have been influenced by the presence of a few patients with hepatobiliary diseases. When polymicrobial septicemia occurs, *Escheri-*

chia coli, *Klebsiella pneumoniae* and *Staphylococcus aureus* can be identified with *Aeromonas* species (Lau et al. 2000; Tsai et al. 2006). The mortality rate in this study was similar to the result of some previous reports, (Ko et al. 2000; Tsai et al. 2006). However, only in hospitalized patients, the mortality rate in our study was 40%, whereas Ko et al. (2000) reported 15%. The patients who required long-term hospitalization because of their poor conditions seemed to elevate the mortality rate, suggesting that *Aeromonas* septicemia can be fatal in immunocompromised patients.

In conclusion, we reported seven patients of *Aeromonas* septicemia in a university hospital in Japan. Immunocompromised conditions, such as hematological malignancy or cholangitis, and recent ingestion of raw fish or shellfish were important characteristics of developing *Aeromonas* septicemia. All patients were monomicrobial. Most of the isolates were susceptible to antimicrobial agents. However, the appearance of a drug-resistant isolate during the treatment indicates the need for caution in the selection of drugs.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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