Original Article
https://doi.org/10.3947/ic.2016.48.4.274
Infect Chemother 2016;48(4):274-284
ISSN 2093-2340 (Print) · ISSN 2092-6448 (Online)

Infection & Chemotherapy

Clinical and Therapeutic Implications of *Aeromonas* Bacteremia: 14 Years Nation-Wide Experiences in Korea

Ji Young Rhee[1], Dong Sik Jung[2], and Kyong Ran Peck[3]

[1]Division of Infectious Diseases, Department of Medicine, Dankook University Hospital, Cheonan; [2]Division of Infectious Diseases, Department of Medicine, Dong-A University Hospital, Busan; [3]Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: To elucidate the clinical presentation, antimicrobial susceptibility, and prognostic factors of monomicrobial *Aeromonas* bacteremia in order to determine the most effective optimal therapy.

Materials and Methods: We reviewed the medical records of *Aeromonas* bacteremia patients for the period January 2000 to December 2013 in a retrospective multi-center study.

Results: A total of 336 patient records were reviewed, with 242 having community-acquired bacteremia. The major clinical infections were of the hepatobiliary tract (50.6%) and peritonitis (18.5%), followed by primary bacteremia (17.9%). The infections usually occurred in patients with malignancy (42.3%), hepatic cirrhosis (39.3%), or diabetes mellitus (25.6%). High antimicrobial-resistance rates (15.5% for ceftriaxone, 15.5% for piperacillin/tazobactam) were noted. However, resistance to carbapenem and amikacin was only 9.8% and 3.0%, respectively. *Aeromonas hydrophila* (58.9%) was the most common pathogen, followed by *Aeromonas caviae* (30.4%). The severity of *A. caviae* bacteremia cases were less than that of *A. hydrophila* or *Aeromonas veronii* bacteremia (P <0.05). *A. hydrophila* showed higher antimicrobial resistance than did other *Aeromonas* species (P <0.05). Patients with hospital-acquired bacteremia were more likely to have severely abnormal laboratory findings and relatively high antimicrobial-resistance rates. Mortality was associated with metastatic cancer, shock, delayed use of appropriate antimicrobial agents, increased prothrombin time, and increased creatinine level (P <0.05).

Conclusions: *Aeromonas* species should be considered one of the causative agents of bacteremia in patients with intra-abdominal infections or malignancies. Although ceftriaxone-resistant *Aeromonas* bacteremia was not statistically related to mortality in this study, it was associated with severe clinical manifestations and laboratory abnormalities. Appropriate antibiotics, including carbapenem, should be administered early, especially in *Aeromonas* bacteremia patients with shock and impaired renal function.

Key Words: *Aeromonas*; Antimicrobial resistance; Bacteremia; Risk factors

Received: September 1, 2016 **Accepted:** November 21, 2016 **Publised online:** December 12, 2016

Corresponding Author : Kyong Ran Peck, MD, PhD
Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-0329, Fax: +82-2-3410-0041
E-mail: krpeck@skku.ac.kr

Introduction

Aeromonas species, belonging to the genus *Aeromonas*, are oxidase-producing Gram-negative rods that can grow on MacConkey agar and ferment carbohydrates [1]. These aquatic microorganisms have been associated with a variety of human diseases [1]. *Aeromonas* species are proliferative and omnipresent in both fresh water and soils [2], and are occasionally isolated from the feces of healthy people [3]. Among 14 known species identified in the genus *Aeromonas*, many, although not all, are considered to be pathogenic [4]. More than 85% of *Aeromonas*-implicated clinical diseases are caused by the *Aeromonas hydrophila, Aeromonas caviae*, and *Aeromonas veronii* biovar *sobria* [2]. These infections are acquired in both community and hospital settings, and both immunocompetent and immunocompromised patients are susceptible. *Aeromonas* species can cause invasive and fatal infections in immunocompromised hosts and have been recognized as a serious threat to human beings [4].

The *Aeromonas* infection-related disease spectrum in humans has expanded; it now includes acute gastroenteritis, bacteremia, pancreatitis, hepatobiliary-tract infections, soft-tissue infections, indwelling-device-related infections, brain abscesses, meningitis, endocarditis, pleuropulmonary infections, peritonitis, and hemolytic-uremic syndrome [1-8]. The most common underlying conditions known to be associated with *Aeromonas* bacteremia are malignancy and hepatobiliary diseases [5]. *Aeromonas* spp. tend to produce at least three ß-lactamases, namely a penicillinase, cephalosporinase, and carbapenemase, which are all chromosome-encoded [6]. Nevertheless, to date, antibiotic resistance has not been a major problem for strains isolated from the environment. In contrast, clinical studies of *Aeromonas* infections are relatively rare, and the relevant antibiotic susceptibility profile, accordingly, remains vague. Previous studies have attempted to identify risk factors; however, those studies considered only a few risk factors and resistance to a limited number of antimicrobials [2, 7, 8]. *Aeromonas* bacteremia in patients with cirrhosis or malignancy has been found to be associated with a higher mortality rate than bacteremia caused by other organisms [8]. The present study is the largest retrospective clinical investigation to analyze various data on monomicrobial *Aeromonas* bacteremia.

The objectives of this study were to elucidate the clinical characteristics of *Aeromonas* bacteremia and to scrutinize the antimicrobial susceptibility of *Aeromonas* to optimal therapy. We also aimed to identify risk factors for mortality in patients with *Aeromonas* bacteremia.

Material and Methods

1. Patients

We retrospectively reviewed the medical records of patients who were diagnosed with *Aeromonas* bacteremia between January 2000 and December 2013 in multiple centers (Samsung Medical Center [Seoul], Dankook University Hospital [Cheonan], Dong-A University Hospital [Busan], and Jeju University Hospital [Jeju]). Patient records and information were anonymized and de-identified prior to analysis. Institutional review board approval was obtained for retrospective evaluation of the patients (DKUH 2015-01-014).

Aeromonas bacteremia was defined as the presence of an *Aeromonas*-positive blood culture, with concomitant signs and symptoms of infection. When the patient's blood culture yielded only one type of pathogen, monomicrobial bacteremia was diagnosed; when more than one type of pathogen was identified, the diagnosis of polymicrobial bacteremia was made. We included only patients with monomicrobial bacteremia in our analysis. Hospital-acquired infections were defined as bacteremic episodes detected at least 72 h after admission in patients who showed no clinical evidence of bacteremia on admission.

Information on age, sex, underlying disease, blood laboratory data, culture results, probable portals of entry, type of antimicrobial agents for treatment, type of medical procedure during treatment, and clinical outcome was collected for each of the patients. Illness severity and comorbidity at the patients' first presentation with bacteremia to the hospital were graded using the Pitt bacteremia score [5, 9] and Charlson's weighted comorbidity index [5], respectively. Patients with *Aeromonas* bacteremia were surveyed for concomitant infection foci; those lacking such foci were classified as having primary bacteremia.

2. Antimicrobial susceptibility test

Aeromonas isolates were obtained by processing of blood culture samples in a BACTEC Model 9240 (BD Diagnostic Instrument Systems, Sparks, MD, USA) or BacT/ALERT 3D (bioMerieux. Inc., Haselwood, MO, USA). *Aeromonas* was identified by means of a standard identification card. Antibiotic susceptibility testing of the isolates was carried out via an automated system at each hospital. Quality-control protocols and minimum inhibitory concentration breakpoints (MICs) were used in compliance with the standards established by the Clinical and Laboratory Standards Institute [10].

3. Statistical analysis

Statistical analyses were carried out in SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean and standard deviation (SD) or median (range) according to their homogeneity. The categorical variables were compared using the Chi-Square test or Fisher's exact test (when necessary). The quantitative variables were compared using the Student–Fisher *t* test or analysis of variance. The risk factors for infection-related mortality were evaluated by univariate and multivariate logistic regression analyses. Factors with a *P*-value of 0.2 in the univariate analysis, excepting those considered to be strongly associated with other variables, were entered into the multiple logistic regression analysis. A value of $P<0.05$ was considered statistically significant.

Results

1. Patient characteristics

Eight-hundred-and-twenty-four cases of *Aeromonas* bacteremia were enrolled, among which 488 cases of polymicrobial *Aeromonas* bacteremia were observed. The remaining 336 monomicrobial *Aeromonas* bacteremia cases were included in this study (Table 1). The major causes of bacteremia were hepatobiliary tract infections (50.6%), followed by peritonitis (18.5%) and primary bacteremia (17.9%). Community-acquired bacteremia was shown in 242 cases (72.0%). The infections usually occurred in patients with solid-organ malignancy (42.3%), hepatic cirrhosis (39.3%), diabetes mellitus (25.6%), or leukemia (7.1%). Concomitant anticancer chemotherapy had been administered in 74 patients (22.0%). The three leading clinical manifestations were fever (38.7%), septic shock (25.6%), and altered consciousness (17.9%). Initial usage of inappropriate antimicrobial agent was noticed in 140 cases. One-hundred-and-sixty-six cases showed antimicrobial-agent combination therapy. The median duration of treatment was 10 days. In 272 cases, antimicrobial-agent initiation within 6 h of symptom manifestations was observed. Fifty patients died of *Aeromonas* bacteremia.

2. Seasonal distribution of *Aeromonas* bacteremia

A trend toward more frequent occurrence during the warmer seasons (May to October; n = 232; 69.0%) was observed. Most of the community-acquired infections (176 of 242, 72.7%) occurred during these seasons (Fig. 1).

3. Differences in clinical characteristics and antimicrobial susceptibility between species

A. hydrophila was less frequently involved in primary bacteremia and was more frequent in skin and soft-tissue infections and peritonitis ($P<0.05$) than in infections with other species (Table 2). *A. caviae* was less prevalent in skin and soft-tissue infections ($P=0.009$) and more prevalent in primary bacteremia ($P=0.017$) than in infections with other species. Spontaneous bacterial peritonitis (SBP) was more common with *A. hydrophila* infections (50/62 SBP cases). Pneumonia was more common with *Aeromonas salmonicida* infection ($P<0.001$). Hospital-acquired infections were more common among patients with *A. caviae* and *A. salmonicida* infections ($P<0.001$).

Table 1. Characteristics of enrolled patients

Characteristics	Value (%)
Age (year, median)	57
Sex ratio (male/female)	2.36 (236/100)
Community-acquired: Hospital-acquired	242:94
Underlying diseases	
Solid organ malignancy	142 (42.3)
Hepatic cirrhosis	132 (39.3)
Diabetes mellitus	86 (25.6)
Leukemia	24 (7.1)
Concomitant chemotherapy	74 (22.0)
Clinical manifestations	
Fever (>38°C)	130 (38.7)
Hypothermia	34 (10.1)
Shock	86 (25.6)
Altered consciousness	60 (17.9)
Abdominal pain	52 (15.5)
Dyspnea	48 (14.3)
Site of infection	
Hepatobiliary infections	170 (50.6)
Peritonitis	62 (18.5)
Primary bacteremia	60 (17.9)
Pneumonia	20 (5.9)
Skin and soft-tissue infection	14 (4.2)
Catheter related infection	10 (3.0)
Usage of Antimicrobial agent	
Initial Appropriate : Inappropriate	196:140
Combination therapy	166 (49.4)
Duration of treatment (days, median)	10
Number of patients in which antimicrobial agents were initiated within 6 h of symptom manifestation	272 (81.0)

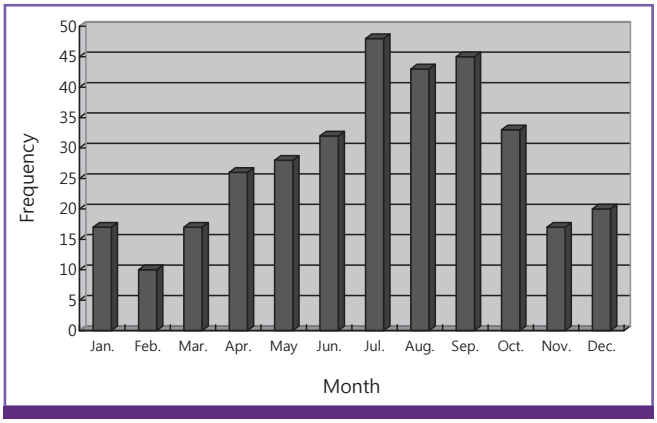

Figure 1. Monthly distribution of *Aeromonas* bacteremia.

Underlying diseases differed according to species: *A. veronii* and *A. sorbia* infections were more frequent in liver cirrhosis; *A. caviae* and *A. sorbia* infections were more frequent in patients with solid-organ cancers; *A. salmonicida* infections were more common in those with leukemia. Moreover, *A. caviae* infections occurred more frequently during concurrent chemotherapy ($P = 0.004$), and *A. hydrophila* tended to be present in cases of shock ($P < 0.001$). Liver function test results were worse in cases with *A. hydrophila* infection than in cases with infections involving other species ($P = 0.001$).

A. hydrophila accounted for 58.9% of cases; there were 102 cases of *A. caviae* (30.4%), 20 cases of *A. sobria* (6.0%), 10 cases of *A. veronii* (3.0%), and six cases of *A. salmonicida* (1.7%) infections (Table 2).

All 336 isolates were included in the analysis of antimicrobial susceptibility. More than 90% of cases were susceptible only to ceftazidime, ciprofloxacin, imipenem, gentamicin, and amikacin. Among the five distinct *Aeromonas* complexes identified, *A. hydrophila* was more often resistant to antimicrobial agents. The exceptions were the *Aeromonas* isolates from Jeju University Hospital: these 20 (100%) cases were susceptible to piperacillin, piperacillin/tazobactam, ceftriaxone, ceftazidime, imipenem, ciprofloxacin, tobramycin, gentamicin, and amikacin.

4. Comparison of community-acquired and hospital-acquired *Aeromonas* bacteremia

No clustered cases of hospital-acquired *Aeromonas* bacteremia were noted. Individual cases developed within 4–42 days (median: 10 days) after admission. Community-acquired *Aeromonas* bacteremia differed from hospital-acquired bacteremia in several aspects (Table 3).

A total of 242 patients had been diagnosed with community-acquired *Aeromonas* bacteremia. Univariate analysis revealed statistically significant differences in age, ICU admission, hospital stay, site of infection, underlying diseases (liver cirrhosis, leukemia), concurrent chemotherapy, presence of a central line catheter, blood laboratory results (hemoglobin, prothrombin time [PT], activated partial thromboplastin time [aPTT], aspartate transaminase [AST], bilirubin, and glucose), presence of cardiopulmonary resuscitation, species differences, proportion of initial discordant antimicrobial agent use, initiation of appropriate antimicrobial agent after 6 h, and antimicrobial resistance between community- and hospital-acquired *Aeromonas* bacteremia. Hepatobiliary infections ($P = 0.003$) and spontaneous bacterial peritonitis ($P = 0.038$) were more common in community-acquired bacteremia; primary bacteremia ($P = 0.003$), pneumonia ($P = 0.002$), and catheter-related infection ($P = 0.000$) were more common in hospital-acquired bacteremia. Liver cirrhosis was the common underlying condition in community-acquired bacteremia ($P = 0.023$), whereas leukemia ($P = 0.001$) and concurrent chemotherapy ($P = 0.002$) were the common underlying conditions in hospital-acquired bacteremia. The laboratory findings were more abnormal in cases of hospital-acquired bacteremia ($P = 0.009$ to 0.045).

5. Antimicrobial therapy

Empirical therapy. Twelve patients died of septic shock with multi-organ failure before appropriate antimicrobial agent treatment could be started. A total of 140 cases were started with inappropriate antibiotics; half of the patients (166) were administered combination therapy, while 56 were placed on aminoglycoside combination therapy. The most common initially administered antimicrobial agents were ceftriaxone and metronidazole (100 cases). Ceftriaxone was the single most common agent in the empirical therapy for *Aeromonas* bacteremia (61.1%).

Definitive therapy. The therapeutic efficacy of the definitive therapy was evaluated in 310 patients. There were no statistically significant differences in mortality between monotherapy and combination therapy ($P > 0.050$).

Time to the start of antimicrobial agents. There was a statistically significant difference in mortality between the 6 h prior to and after the initiation of appropriate antimicrobial agents ($P = 0.049$).

6. Ceftriaxone resistance

Among 336 cases of *Aeromonas* monomicrobial bacteremia, 284 (84.5%) had been caused by ceftriaxone-susceptible (CS) *Aeromonas* bacteremia and 52 (15.5%) by ceftriaxone-resis-

Table 2. Clinical presentation, laboratory findings, and antimicrobial susceptibility in *Aeromonas hydrophila, Aeromonas caviae, Aeromonas sobria, Aeromonas veronii,* and *Aeromonas salmonicida* bacteremia

Variables	*Aeromonas hydrophila* (n = 198)	*Aeromonas caviae* (n = 102)	*Aeromonas sobria* (n = 20)	*Aeromonas veronii* (n = 10)	*Aeromonas salmonicida* (n = 6)	*P*-value
Age (mean)	56.5	53.8	54.25	53.3	69.3	0.605
Sex (Male:Female)	126:72	82:20	16:4	8:2	4:2	0.032
Pitt bacteremia score (mean)	1.98	1.12	0.80	2.60	4.67	< 0.001
Charlson weighted comorbidity index (mean)	4.39	4.02	6.40	5.00	2.00	< 0.001
Hospital stay (day, mean)	35.90	19.45	8.60	12.20	39.67	0.004
Hospital-acquired bacteremia	44 (22.2%)	42 (41.2%)	2 (10.0%)	2 (20.0%)	4 (66.7%)	< 0.001
Mortality	34 (17.2%)	12 (11.8%)	0 (0%)	2 (20.0%)	2 (33.3%)	0.140
Source of infection						< 0.001
Hepatobiliary infections	90 (45.5%)	62 (60.8%)	10 (50.0%)	6 (60.0%)	2 (33.3%)	0.116
Peritonitis	50 (25.3%)	8 (7.8%)	2 (10.0%)	2 (20.0%)	0 (0%)	0.003
Primary bacteremia	30 (15.2%)	22 (21.6%)	8 (40.0%)	0 (0%)	0 (0%)	0.017
Pneumonia	12 (6.1%)	4 (3.9%)	0 (0%)	0 (0%)	4 (66.7%)	< 0.001
Skin and soft-tissue infections	12 (6.1%)	0 (0%)	0 (0%)	2 (20.0%)	0 (0%)	0.009
Underlying diseases						
Diabetes mellitus	42 (21.2%)	30 (29.4%)	8 (40.0%)	4 (40.0%)	2 (33.3%)	0.182
Hepatic cirrhosis	78 (39.4%)	32 (31.4%)	14 (70.0%)	8 (80.0%)	0 (0%)	< 0.001
Solid organ malignancy	68 (34.3%)	52 (51.0%)	18 (90.0%)	4 (40.0%)	0 (0%)	< 0.001
Cerebrovascular attack	4 (2.0%)	2 (1.96%)	0 (0%)	2 (20.0%)	2 (33.3%)	< 0.001
Concurrent chemotherapy	34 (17.2%)	28 (27.5%)	10 (50.0%)	2 (20.0%)	0 (0%)	0.004
Central venous catheterization	56 (28.3%)	20 (19.6%)	0 (0%)	0 (0%)	4 (66.7%)	0.001
Urinary catheterization	62 (31.3%)	16 (15.7%)	0 (0%)	0 (0%)	4 (66.7%)	< 0.001
Ventilator-assisted state	14 (7.1%)	0 (0%)	0 (0%)	0 (0%)	4 (66.7%)	< 0.001
Shock	66 (33.3%)	14 (13.7%)	0 (0%)	4 (40.0%)	2 (33.3%)	< 0.001
Use combination of antimicrobial agents	107 (54.0%)	50 (49.0%)	0 (0%)	3 (30.0%)	6 (100.0%)	< 0.001
Inappropriate antimicrobial agent use	72 (36.4%)	60 (58.8%)	8 (40.0%)	0 (0%)	0 (0%)	0.065
Duration of antimicrobial agent use (day, mean)	11.23	12.69	9.40	8.40	18.00	< 0.001

Table 2. Continued.

Variables	*Aeromonas hydrophila* (n = 198)	*Aeromonas caviae* (n = 102)	*Aeromonas sobria* (n = 20)	*Aeromonas veronii* (n = 10)	*Aeromonas salmonicida* (n = 6)	*P*-value
Laboratory findings						
White blood cell count (number/ mm^3)	12.45	16.66	4.83	10.02	17.02	< 0.001
Platelet ($\times 10^3/mm^3$)	118.35	136.53	59.10.	72.40	226.33	< 0.001
Glucose (mg/dL)	164.76	162.18	132.70	165.00	292.00	< 0.001
Alkaline phosphatase (ALP) (IU/L, mean)	380.95	217.63	159.00	153.00	499.33	< 0.001
Aspartate transaminase (AST) (U/L, mean)	209.30	286.27	56.50	596.00	140.67	< 0.001
Alanine transaminase (ALT) (U/L, mean)	140.33	184.31	42.90	344.00	72.00	< 0.001
Bilirubin (mg/dL)	6.62	6.20	2.78	7.71	0.60	< 0.001
Prothrombin time (PT) (INR, mean)	2.01	1.98	1.60	1.73	1.18	< 0.001
activated partial thromboplastin time (aPTT) (sec)	55.29	47.97	45.76	47.14	29.03	< 0.001
Creatinine (mg/dL)	1.27	1.20	0.93	1.12	1.03	< 0.001
Antimicrobial agent (susceptibility within all isolates, n [%])	Susceptibility within species, n (%)					
Ampicillin (28 [8.3%])	8 (4.0%)	16 (15.7%)	4 (20%)	0 (0%)	0 (0%)	<0.001
Ampicillin/Sulbactam (92 [28.9%])	50 (25.3%)	32 (31.4%)	10 (50%)	0 (0%)	0 (0%)	0.014
Piperacillin (268 [79.8%])	154 (77.8%)	82 (80.4%)	20 (100%)	10 (100%)	2 (33.3%)	0.003
Piperacillin/Tazobactam (284 [84.5%])	160 (80.8%)	92 (90.2%)	20 (100%)	10 (100%)	2 (33.3%)	<0.001
Ceftriaxone (284 [84.5%])	170 (85.9%)	84 (82.4%)	20 (100%)	8 (80%)	2 (33.3%)	0.002
Ceftazidime (312 [92.9%])	182 (91.9%)	98 (96.1%)	20 (100%)	10 (100%)	2 (33.3%)	<0.001
Ciprofloxacin (302 [89.9%])	176 (89.9%)	90 (88.2%)	20 (100%)	10 (100%)	6 (100%)	0.334
Imipenem (303 [90.2%])	165 (83.3%)	102 (100%)	20 (100%)	10 (100%)	6 (100%)	0.021
Tobramycin (288 [85.7%])	160 (80.8%)	100 (98.0%)	14 (70%)	8 (80%)	6 (100%)	<0.001
Gentamicin (312 [92.9%])	178 (89.9%)	100 (98.0%)	20 (100%)	8 (80%)	6 (100%)	0.024
Amikacin (326 [97.0%])	188 (94.9%)	102 (100%)	20 (100%)	10 (100%)	6 (100%)	0.127
Trimethoprim/Sulfamethoxazole (294 [87.8%])	167 (84.3%)	97 (95.1%)	20 (100%)	8 (80%)	2 (33.3%)	<0.001

tant (CR) *Aeromonas* bacteremia (Table 3). The CS and CR *Aeromonas* bacteremia groups had similar demographic characteristics. There was a higher rate of mortality in the CR *Aeromonas* bacteremia group, but this difference was not statistically significant (P = 0.088; Table 3). The CR *Aeromonas* bacteremia group showed a tendency to disease acquired in a hospital setting (P = 0.002).

7. Outcome analysis for non-survivors

The overall mortality among the 336 patients was 15.0% (50 cases). Death occurred at a median of 10 days post-admission. Twelve patients died within 72 h of their arrival at the hospital. All of the non-survivors had experienced shock. Furthermore, according to univariate analysis, these cases manifested a higher rate of resistance to antimicrobial agents. A number of risk factors for *Aeromonas* bacteremia-related mortality were found in the multivariate analysis: metastatic cancer, shock, high Pitt bacteremia score, high Charlson's weighted comorbidity index, high prothrombin time, high serum creatinine level, and initiation of appropriate antimicrobial agents 6 h after manifestation of symptoms (P <0.05 for all variables; Table 4). The predicted *Aeromonas* monomicrobial bacteremia mortality rate was found to be closely related to the known Pitt bacteremia score.

Predicted mortality rate (%) = (Pitt bacteremia score × 0.084 + 0.005) × 100

Discussion

Our study included a large number of cases of monomicrobial *Aeromonas* bacteremia, with full laboratory and medical records; these were amenable to analysis and could provide useful information for better clinical practice.

The three major clinical categories of *Aeromonas* infection are hepatobiliary tract infection, peritonitis, and primary bacteremia. These have been identified in more than 80% of reported *Aeromonas* infections. An earlier study found that the most common underlying conditions associated with *Aeromonas* septicemia were malignancy (21–50%) and hepatobiliary diseases (15–54%) [2, 4, 7, 11-14], although healthy patients were also shown to be susceptible to *Aeromonas* infection. Likewise, underlying illness with malignancy, hepatobiliary diseases, and diabetes mellitus were frequently encountered in *Aeromonas* bacteremia in this study. As many as 25.6% of patients in the present study had diabetes mellitus, which was a significantly higher rate than that previously reported 11% [5]. Our data suggested that individuals presenting with *Aeromonas* bacteremia should be evaluated for the possibility of underlying malignancy, hepatobiliary diseases, or diabetes mellitus.

Previous reports have shown that patients with *Aeromonas* bacteremia could be treated with one of the broad-spectrum β-lactam agents, such as third-generation cephalosporins, aztreonam, and imipenem, or with fluoroquinolone alone [2, 5, 7]. However, antimicrobial resistance to extended-spectrum cephalosporins (such as cefotaxime) in clinical *Aeromonas* isolates has been noted [1, 2, 4-7, 11, 12, 14-17]. Indeed, fluoroquinolone resistance is increasing, as evidenced by the ciprofloxacin-resistance rate of 14% that was previously reported [2]. In the current study, the rates of resistance to ceftriaxone, ciprofloxacin, and imipenem were 15.5, 10.1, and 9.8%, respectively. It has been shown that, for carbapenemase-producing *Aeromonas* strains, the MICs of imipenem were above 8 mg/L [6]. However, the clinical effect of the inducible carbapenemases in clinical *Aeromonas* species has not been clearly delineated as yet [2, 6]. One case study reported an imipenem-resistant *A. veronii* clinical isolate, recovered from a patient with cholangitis; this case also did not show any clinically significant carbapenem-resistance in *Aeromonas* species [18, 19]. A history of carbapenem use was associated with mortality in the present univariate analysis. This suggests that previous carbapenem use can induce resistance and thereby lead to a poor clinical outcome.

Based on the resistance rates found in our data, amikacin, gentamicin, ceftazidime, imipenem, and ciprofloxacin are reasonable antimicrobial therapy choices for treatment of *Aeromonas* infections. Ceftriaxone is the usual empirical treatment of choice for patients with hepatobiliary infections. Ceftriaxone was started as the initial treatment in most cases of suspected gastrointestinal or hepatobiliary infection identified in the present study. The high resistance patterns led to 41.7% of patients being treated with inappropriate empirical antimicrobial therapy. Additionally, ceftriaxone-resistant *Aeromonas* bacteremia groups showed severe clinical manifestations and laboratory findings. The only exceptions were the *Aeromonas* isolates from Jeju University Hospital, all of which (n = 20) were susceptible to piperacillin, piperacillin/tazobactam, ceftriaxone, ceftazidime, imipenem, ciprofloxacin, tobramycin, gentamicin, and amikacin. Thus, geographic differences may affect resistance patterns. Recommendations for combination therapy in *Aeromonas* bacteremia have come from studies of a small number of cases with both polymicrobial and monomicrobial bacteremia [20, 21]. In contrast, in

Table 3. Comparison of community-acquired vs. nosocomial *Aeromonas* bacteremia and ceftriaxone-resistant vs. ceftriaxone-susceptible *Aeromonas* bacteremia

	Community-acquired (n = 242)	Nosocomial (n = 94)	*P*-value	Ceftriaxone-susceptible (n = 284)	Ceftriaxone-resistant (n = 52)	*P*-value
Age, years	58.48	52.00	0.013	59.12	56.22	0.578
Male, n (%)	174 (71.9%)	62 (65.6%)	0.846	204	32	0.338
Pitt bacteremia score	1.85	1.36	0.333	1.54	2.69	0.008
Mortality	32 (13.2%)	18 (19.1%)	0.171	38 (13.4%)	12 (23.1%)	0.088
Site of infection, n (%)						
Hepatobiliary infection	140 (57.9%)	30 (31.9%)	0.003	136 (47.9%)	34 (65.4%)	0.003
Spontaneous bacterial peritonitis	54 (22.3%)	8 (8.5%)	0.003	62 (21.8%)	0 (0%)	< 0.001
Pneumonia	6 (2.5%)	14 (14.9%)	0.002	12 (42.3%)	8 (15.4%)	0.006
Underlying diseases, n (%)						
Hepatic cirrhosis	108 (44.6%)	24 (25.5%)	0.001	122 (43.0%)	10 (19.2%)	0.001
Solid organ malignancy	105 (43.4%)	37 (39.4%)	0.056	119 (41.9%)	23 (44.2%)	0.008
Devices, n (%)						
Central line insertion	42 (17.4%)	38 (40.4%)	< 0.001	58 (20.4%)	22 (42.3%)	0.001
Urinary catheter insertion	50 (20.7%)	32 (34.0%)	0.010	58 (20.4%)	24 (46.2%)	< 0.001
Laboratory data (mean)						
Hemoglobin (g/dL)	10.58	9.42	< 0.001	10.25	10.33	0.506
Prothrombin time (INR)	2.06	2.96	0.004	1.88	1.97	0.021
Alanine transaminase (ALT) (U/L)	99.6	111.1	0.088	133.6	257.4	< 0.001
Bilirubin (mg/dL)	7.96	10.67	0.008	5.97	6.74	0.093
Glucose (mg/dL)	166.8	230.4	0.001	160.98	182.69	0.207
Clinical manifestations, n (%)						
Shock	64 (26.4%)	22 (23.4%)	0.566	68 (23.9%)	18 (34.6%)	0.120
Cardiopulmonary resuscitation	12 (5.0%)	2 (2.1%)	0.244	6 (2.1%)	8 (15.4%)	< 0.001
Mental change	45(18.6%)	15(16.0%)	0.045	48 (16.9%)	12 (23.1%)	0.445
Aeromonas isolates	0.003					0.004
Usage of Antimicrobial agent						
Initial inappropriate antimicrobial agent	72 (29.8%)	68 (72.3%)	0.004	44 (15.5%)	26 (50.0%)	< 0.001
Initiation of antimicrobial agent within 6 h of symptom manifestation	68 (28.1%)	60 (63.8%)	<0.001	34 (12.0%)	30 (57.7%)	< 0.001
Antimicrobial resistance						
Ampicillin/Sulbactam	162 (66.9%)	82 (87.2%)	0.018	202 (71.1%)	42 (80.7%)	0.351
Piperacillin	46 (19.0%)	42 (44.7%)	< 0.001	56 (19.7%)	32 (61.5%)	< 0.001
Piperacillin/Tazobactam	28 (11.6%)	24 (25.5%)	0.001	24 (8.5%)	28 (53.8%)	< 0.001
Ceftriaxone	28 (11.6%)	24 (25.5%)	0.001	0 (0%)	52 (100%)	
Ceftazidime	6 (2.5%)	18 (19.1%)	<0.001	2 (0.7%)	22 (42.3%)	< 0.001
Imipenem	21 (5.8%)	12 (12.8%)	0.009	26 (9.2%)	7 (13.5%)	0.377
Gentamycin	10 (5.6%)	14 (14.9%)	0.001	18 (6.3%)	6 (11.5%)	0.401
Ciprofloxacin	24 (9.9%)	10 (10.6%)	0.844	18 (6.3%)	16 (30.8%)	0.001

Table 4. Risk factors for fatality of *Aeromonas* bacteremia

	Odd ratio (95% confidence interval)	*P*-value
Univariate analysis		
Underlying disease		
Chronic renal failure	14.737	< 0.001
Metastatic cancer	7.154	0.007
Diabetes mellitus	5.603	0.018
Cerebrovascular attack	4.367	0.037
Quadriparesis	4.367	0.037
Myocardial infarct	4.367	0.037
Pitt bacteremia score	50.871	< 0.001
Charlson weighted comorbidity index	5.473	0.019
Primary site of infections		
Hepatobiliary origin	8.064	0.005
Skin and soft-tissue infection	4.739	0.034
Clinical manifestations		
Shock	35.861	< 0.001
Altered mental status	56.179	< 0.001
Hypothermia	24.029	< 0.001
Cardiopulmonary resuscitation	25.005	< 0.001
Acute renal failure	23.520	< 0.001
Devices		
Central line	17.546	< 0.001
Urinary catheterization	29.127	< 0.001
Ventilator	4.850	0.028
Laboratory data		
Hemoglobin (g/dL)	-3.177	0.003
Prothrombin time (INR)	16.159	0.000
activated partial thromboplastin time (aPTT)	4.395	0.036
Albumin (g/dL)	-2.699	0.011
Bilirubin (mg/dL)	11.266	0.001
Aspartate transaminase (AST) (U/L)	3.382	0.001
Alanine transaminase (ALT) (U/L)	3.641	< 0.001
Blood urea nitrogen (mg/dL)	3.329	0.011
Creatinine (mg/dL)	30.617	< 0.001
Glucose (mg/dL)	6.024	0.014
Potassium (mmol/L)	6.121	0.013
Antimicrobial resistance		
Resistance to Tobramycin	4.840	0.028
Resistance to Gentamicin	3.969	0.046
Resistance to Amikacin	4.367	0.037
History of Previous carbapenem use	4.786	0.029
Initiation of antimicrobial agent within 6 h after symptom manifestation	0.445	0.049
Initial inappropriate antimicrobial agent	13.064	0.001
Duration of antimicrobial agents	18.292	< 0.001
Others		
Previous hepatobiliary operation	7.147	0.028
Aeromonas hydrophila	8.064	0.005
Multivariate analysis		
Metastatic cancer	7.166 (5.354–9.004)	0.003
Shock	3.909 (3.214–5.417)	0.048
Pitt bacteremia score	6.486 (1.980–21.249)	0.002
Charlson weighted comorbidity index	1.536 (1.0222.309)	0.039
Prothrombin time (INR)	2.446 (1.270–4.709)	0.007
Creatinine (mg/dL)	4.093 (1.165–14.376)	0.028
Initiation of antimicrobial agent within 6 h after manifesting symptoms	0.527 (0.112-0.912)	0.043

the current study, there was no significant difference in the clinical outcomes of patients definitively treated with either monotherapy or combination therapy. However, we cannot recommend either monotherapy or combination therapy for treatment of *Aeromonas* bacteremia at this point, because the proportion of inappropriate initial therapy was high in our experience. Given the lack of available therapeutic options for *Aeromonas* bacteremia, well-controlled clinical trials of combinations of existing antibiotics are urgently needed.

A. caviae is the most frequent pathogen causing *Aeromonas* bacteremia in Japan [19, 22], whereas *A. hydrophila*, followed by *A. veronii* biovar *sobria*, is the most common *Aeromonas* species causing bacteremia in Taiwan [23]. In our study, *A. hydrophila* was the most common *Aeromonas* species caus-

ing bacteremia, followed by *A. caviae*, which is interesting, as Korea is geographically located between China and Japan. Therefore, additional epidemiological studies are required in order to establish the bacteriology of different types of *Aeromonas* infections in different regions. Isolates need to be collected, and the links between genetic factors and geographic areas should be analyzed. This is relevant, as in this study, *A. hydrophila* showed higher antimicrobial resistance and resulted in greater clinical severity than did the other *Aeromonas* spp. (P <0.05).

The mortality rates among patients with *Aeromonas* bacteremia range from 28 to 63% in the literature [1, 2, 4, 7, 18, 24, 25]. However, our study showed a significantly lower mortality rate (14.9%). In our cases, patients with skin and soft-tissue infection had worse clinical outcomes than did those with other secondary bacteremia; this finding was statistically significant only in univariate analysis. Bacterial peritonitis has been associated with an approximate 15% mortality rate, and necrotizing fasciitis with a higher mortality rate of 50% (one death in two patients). In our study, the number of patients with necrotizing fasciitis was 14. We postulated that the lower mortality rate in our study was associated with a low prevalence of soft-tissue infection as well as a relatively low rate of liver cirrhosis [7]. Inappropriate therapy has been regarded as a prognostic factor in patient outcomes [26], and was correlated with mortality in this study.

The main limitation of this study was its retrospective design. As such, specific information on the antibiotic types (cefepime and aztreonam) used was missing from the medical records. Furthermore, our study was conducted at four tertiary hospitals and examined data spanning 14 years. During that time, medical and microbiological environments changed, and thus our results cannot be generalized to all other hospitals.

In conclusion, patients with *Aeromonas* bacteraemia can be treated with carbapenem, ceftazidime, or fluoroquinolone. Although *Aeromonas* species showed a higher resistance rate to ceftriaxone, *Aeromonas* bacteremia was correlated with a relatively low mortality rate compared with previous studies. All of the non-survivors experienced shock. Ceftriaxone-based metronidazole combination treatment might not be recommendable as an initial empirical therapy, in particular due to the high antimicrobial resistance rates to various agents in septic-shock patients. In patients with septic shock, carbapenem-based aminoglycoside combination treatment may also not be considered as an initial empirical therapy, due to the high antimicrobial-resistance rates to various agents present in septic shock. Considering the risk factors for mortality, adequate antibiotics should be given early, especially to patients with shock and impaired renal function. In order to make recommendations for definitive therapy based on available susceptibility results, further studies with larger numbers of cases and supportive experiment, such as DNA sequencing, are warranted.

Conflicts of Interest

No conflicts of interest.

ORCID

Ji-Young Rhee http://orcid.org/0000-0003-4664-7048
Kyong Ran Peck http://orcid.org/0000-0002-7464-9780

References

1. Tsai MS, Kuo CY, Wang MC, Wu HC, Chien CC, Liu JW. Clinical features and risk factors for mortality in Aeromonas bacteremic adults with hematologic malignancies. J Microbiol Immunol Infect 2006;39:150-4.
2. Wu CJ, Wu JJ, Yan JJ, Lee HC, Lee NY, Chang CM, Shih HI, Wu HM, Wang LR, Ko WC. Clinical significance and distribution of putative virulence markers of 116 consecutive clinical Aeromonas isolates in southern Taiwan. J Infect 2007;54:151-8.
3. Lee WS, Puthucheary SD. Retrospective study of Aeromonas infection in a Malaysian urban area: a 10-year experience. Singapore Med J 2001;42:57-60.
4. Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bettett's Principles and practice of infectious diseases. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005.
5. Llopis F, Grau I, Tubau F, Cisnal M, Pallares R. Epidemiological and clinical characteristics of bacteraemia caused by Aeromonas spp. as compared with Escherichia coli and Pseudomonas aeruginosa. Scand J Infect Dis 2004;36:335-41.
6. Ko WC, Wu HM, Chang TC, Yan JJ, Wu JJ. Inducible beta-lactam resistance in Aeromonas hydrophila: therapeutic challenge for antimicrobial therapy. J Clin Microbiol 1998;36:3188-92.
7. Ko WC, Lee HC, Chuang YC, Liu CC, Wu JJ. Clinical features and therapeutic implications of 104 episodes of monomicrobial Aeromonas bacteraemia. J Infect 2000;40:267-73.

8. Choi JP, Lee SO, Kwon HH, Kwak YG, Choi SH, Lim SK, Kim MN, Jeong JY, Choi SH, Woo JH, Kim YS. Clinical significance of spontaneous Aeromonas bacterial peritonitis in cirrhotic patients: a matched case-control study. Clin Infect Dis 2008;47:66-72.
9. Rhee JY, Kwon KT, Ki HK, Shin SY, Jung DS, Chung DR, Ha BC, Peck KR, Song JH. Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: a comparison of the Pitt bacteremia score and the acute physiology and chronic health evaluation II scoring systems. Shock 2009; 31:146-50.
10. Clinical and Laboratory StandardsInstitute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: Fifteenth informational supplement. Wayne, PA: CLSI; 2005;M100-S11
11. Campo C, Navarro V, Pérez C, Gutiérrez I, Alonso R. Aeromonas spp bacteremia: study of 12 cases and review of the literature. Enferm Infecc Microbiol Clin 2001;19:161-4.
12. Ko WC, Chuang YC. Aeromonas bacteremia: review of 59 episodes. Clin Infect Dis 1995;20:1298-304.
13. Lai CC, Shiao CC, Lu GD, Ding LW. Aeromonas hydrophila and Aeromonas sobria bacteremia: rare pathogens of infection in a burn patient. Burns 2007;33:255-7.
14. Lau SM, Peng MY, Chang FY. Outcomes of Aeromonas bacteremia in patients with different types of underlying disease. J Microbiol Immunol Infect 2000;33:241-7.
15. Doudier B, Imbert G, Vitton V, Kahn M, La Scola B. Aeromonas septicaemia: an uncommon complication following placement of transhepatic biliary drainage devices in Europe. J Hosp Infect 2006;62:115-6.
16. Huang LJ, Chen HP, Chen TL, Siu LK, Fung CP, Lee FY, Liu CY. Secondary Aeromonas peritonitis is associated with polymicrobial ascites culture and absence of liver cirrhosis compared to primary Aeromonas peritonitis. APMIS 2006;114:772-8.
17. Sebo P, Sakbani K, Rohner P, Gavazzi G. Aeromonas bacteremia in an elderly immunocompetent patient. Aging Clin Exp Res 2006;18:344-6.
18. Sánchez-Céspedes J, Figueras MJ, Aspiroz C, Aldea MJ, Toledo M, Alperí A, Marco F, Vila J. Development of imipenem resistance in an Aeromonas veronii biovar sobria clinical isolate recovered from a patient with cholangitis. J Med Microbiol 2009;58:451-5
19. García-Irure JJ, Navascués A, Vivanco M, Rodrígo A. Spontaneous bacterial peritonitis and bacteraemia due to Aeromonas hydrophila. An Sist Sanit Navar 2003;26:429-31.
20. Funada H, Matsuda T. Aeromonas bacteremia in patients with hematologic diseases. Intern Med 1997;36:171-4.
21. Harris RL, Fainstein V, Elting L, Hopfer RL, Bodey GP. Bacteremia caused by Aeromonas species in hospitalized cancer patients. Rev Infect Dis 1985;7:314-21.
22. Kimura M, Araoka H, Yoneyama A. Aeromoans caviae is the most frequent pathogen among cases of Aeromonas bacteremia in Japan. Scand J Infect Dis 2013;45:304-9.
23. Kao HT, Huang YC, Lin TY. Fatal bacteremic pneumonia caused by Aeromonas hydrophila in a previously healthy child. J Microbiol Immunol Infect 2003;36:209-11.
24. Tang HJ, Lai CC, Lin HL, Chao CM. Clinical manifestations of bacteremia caused by Aeromonas species in southern Taiwan. PLoS One 2014;9:e91642
25. Tena D, González-Praetorius A, Gimeno C, Pérez-Pomata MT, Bisquert J. Extraintestinal infection due to Aeromonas spp.: review of 38 cases. Enferm Infecc Microbiol Clin 2007;25:235-41.
26. Kim J, Lee Y, Park Y, Kim M, Choi JY, Yong D, Jeong SH, Lee K. Anaerobic bacteremia: impact of inappropriate therapy on mortality. Infect Chemother 2016;48:91-8.