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Different Clinical Characteristics Among *Aeromonas hydrophila*, *Aeromonas veronii* biovar sobria and *Aeromonas caviae* Monomicrobial Bacteremia

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This study aimed to compare the clinical presentations of *Aeromonas hydrophila*, *A. veronii* biovar sobria and *A. caviae* monomicrobial bacteremia by a retrospective method at three hospitals in Taiwan during an 8-yr period. There were 87 patients with *A. hydrophila* bacteremia, 45 with *A. veronii* biovar sobria bacteremia and 22 with *A. caviae* bacteremia. Compared with *A. hydrophila* and *A. veronii* biovar sobria bacteremia, *A. caviae* bacteremia was more healthcare-associated (45 vs 30 and 16%; $P = 0.031$). The patients with *A. caviae* bacteremias were less likely to have liver cirrhosis (27 vs 62 and 64%; $P = 0.007$) and severe complications such as shock (9 vs 40 and 47%; $P = 0.009$) and thrombocytopenia (45 vs 67 and 87%; $P = 0.002$). The APACHE II score was the most important risk factor of Aeromonas bacteremia-associated mortalities. The APACHE II scores of *A. caviae* bacteremias were lower than *A. hydrophila* bacteremia and *A. veronii* biovar sobria bacteremia (7 vs 14 and 16 points; $P = 0.002$). In conclusion, the clinical presentation of *A. caviae* bacteremia was much different from *A. hydrophila* and *A. veronii* biovar sobria bacteremia. The severity and mortality of *A. caviae* bacteremia were lower than *A. hydrophila* or *A. veronii* biovar sobria bacteremia.

Key Words: *Aeromonas hydrophilia*; *Aeromonas veronii* biovar sobria; *Aeromonas caviae*; Bacteremia

INTRODUCTION

Aeromonas is a kind of oxidase-producing gram-negative rods and belongs to the family Aeromonadaceae. It is widely distributed globally in aquatic environments and associated with a variety of human infections, including gastroenteritis, soft tissue infection, septicemia, hepatobiliary tract infections, and occasionally pleuropulmonary infections, indwelling-device related infections, meningitis, peritonitis, and hemolytic uremic syndrome (1). Although this pathogen could infect healthy persons, most infections were found in immunocompromised hosts, especially those with liver cirrhosis and malignancies (1-4). The possible pathogenesis of *Aeromonas* infection is complex and multifactorial. The possible portals of entry for *Aeromonas* bacteremia were considered as gastrointestinal tracts and skin lesions (1-5). After the adhesion to the epithelial cells of the intestine, this pathogen produces many potential virulence factors to destroy epithelial barrier and impair immune cells, including exoenzymes, cytotoxic and cytotonic enterotoxins (6, 7).

Among 21 *Aeromonas* species differentiated on the basis of DNA-DNA hybridization, *Aeromonas caviae, Aeromonas veronii* biovar sobria and *Aeromonas hydrophila* are most associated with human infections and amount for > 85% of all clinical isolates (2-5). They have different biochemical properties (8, 9) and antimicrobial susceptibilities (10, 11). In addition, different *Aeromonas* species produce different virulence factors (12). However, it is unknown whether different *Aeromonas* species contribute different clinical presentations. Here, we conducted a retrospective study to compare clinical presentations of the bacteremias caused by different *Aeromonas* species.

MATERILAS AND METHODS

This is a retrospective study, in which the patients diagnosed with monomicrobial *Aeromonas* bacteremia were admitted at Buddhist Tzu Chi General Hospital, Buddhist Dalin Tzu Chi General Hospital and Buddhist Taipei Tzu Chi General Hospital (Taiwan) from January 2001 to November 2008. Buddhist Tzu Chi General Hospital is a 700-bed tertiary referral medical center locating in Eastern Taiwan with special units for bone marrow and organ transplantation, burn care and intensive care. Buddhist Dalin Tzu Chi General Hospital and Buddhist Taipei Tzu Chi General Hospital are 900-bed regional teaching hospitals locating in Southern Taiwan and Northern Taiwan. The demographic, clin-

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ical and laboratory information were retrieved from the medical charts of the included patients for analysis.

Aeromonas bacteremia was defined as growth of an *Aeromonas* sp. from a blood culture of a patient with sepsis. Bacteremia was considered healthcare-associated if an *Aeromonas* isolate was obtained from blood sampled after more than 72 hr of hospitalization in a patient who had been asymptomatic for infection upon admission, or from a patient who had received antineoplastic chemotherapy in the preceding 2 weeks after drawing blood for culture, regardless of symptomatology at admission. *Aeromonas*-involved polymicrobial bacteremia defined as simultaneous growth of an *Aeromonas* sp. and other microbe(s) from a blood culture of a patient with sepsis were excluded from this study. Death was considered to be attributable to *Aeromonas* bacteremia if, during the same hospital stay, death occurred within 7 days after a positive blood culture for *Aeromonas* bacteremia without other cause for death, death occurred in the presence of clinical evidence of persistent sepsis, or the cause of death as recorded on the death certificate was *Aeromonas* bacteremia. Survivor from *Aeromonas* bacteremia was defined as if the patient was discharged alive or an improvement of bacteremia-associated symptoms occurred in the absence of recurrence within 30 days during the same hospital stay.

According to the Sepsis-related Organ Failure Score criteria, the diagnosis of respiratory failure is based on the ratio of arterial oxygen tension (PaO_2) to fractional inspired oxygen (FiO_2) < 200 mmHg. Disease severity was assessed by Acute Physiology and Chronic Health Evaluation II (APACHE II) score within 72 hr after the occurrence of symptoms associated with *Aeromonas* bacteremia. Acid-suppressant therapy was defined as use of proton pump inhibitors or histamine H_2 blockers for more than 7 days within 4 weeks before onset of the symptoms associated with *Aeromonas* bacteremia.

Species identification and antimicrobial susceptibility

Blood samples were tested daily for microbial growth by the BACTEC 9240 (BD, Diagnostic Instrument Systems, Spark, MD, USA). Gram-negative bacilli from blood culture bottles were identified as *Aeromonas* species by positive oxidase reaction, no growth on thiosulfate-citrate-bile-sucrose agar, growth on MacConkey agar, and resistance to the vibriostatic compound O/129. Biochemical profiles with the Vitek II system (bioMérieux, Lyon, France), BD-Phoenix system (BD Diagnostic Instrument Systems) or API-20NE system (bioMérieux) were utilized for identification of *Aeromonas* species. Additional tests for API-20NE system included hydrolysis of esculin and gas production from glucose fermentation. Additional tests for Vitek II system or BD-Phoenix system included hydrolysis of esculin, Voges-Proskauer reaction, acid production from sucrose fermentation, ornithine decarboxylase, acid from arabinose fermentation, and arginine dihydrolase production.

In vitro antimicrobial susceptibilities of *Aeromonas* isolates were tested using the Kirby-Bauer disk-diffusion method, or automated methods (Vitek II system or the BD-Phoenix system). Antibiotics selected for testing included ampicillin, amikacin, cefazolin, gentamicin, cefmetazole, ceftriaxone, cefuroxime, ciprofloxacin, imipenem, flomoxef, cefpirome, ceftazidime, sulfamethoxazole/trimethoprim, aztreonam, ticarcillin/clavulanic acid, and piperacillin/tazobactam. The breakpoint concentrations for interpretation were in accordance with Clinical and Laboratory Standards Institute (13).

Statistical analyses

SPSS v. 11.5 for MS Windows software (SPSS, Chicago, IL, USA) software was used for statistical analyses. Pearson's chi-square test was used to examine nominal data, and one-way ANOVA was used for continuous data. All tests were two-sided and a P value of ≤ 0.05 was considered significant.

Ethics statement

This study was approved by the institutional review board of Buddhist Dalin Tzu Chi General Hospital (IRB No. B09801017). Informed consent was exempted by the board.

RESULTS

There were 154 patients with monomicrobial *Aeromonas* bacteremia. The mean age was 58 yr (range, 24 to 92 yr) and the overall duration of hospitalization was 15 days (range, 1-82). There were 112 (73%) male patients and 43 (28%) patients with healthcare-associated bacteremias. There were 63 (41%) patients receiving acid-suppressant therapy. Liver cirrhosis was most common underlying disease (58%), followed by diabetes mellitus (28%) and solid cancer (26%). There were 126 (82%) patients with fever, 107 (69%) patients with thrombocytopenia, and only 40 (26%) patients with leukocytosis. Of the 87 (56%) patients with *A. hydrophila* bacteremia, one presented with acute cholangitis, one with spontaneous bacterial peritonitis, two with traumatic wound infections, two with urosepsis, four with necrotizing fasciitis, and the others with primary bacteremia. Of the 45 (29%) patients with *A. veronii* biovar sobria bacteremia, one presented with urosepsis, one with spontaneous bacterial peritonitis, one with necrotizing fasciitis, one with meningitis and the others with primary bacteremia. Of the 22 (14%) patients with *A. caviae* bacteremia, one patient presented with acute cholecystitis, one with traumatic wound infection, one with lung abscess and the others with primary bacteremia. There were 55 patients who died during hospitalization. Three patients with *A. hydrophila* bacteremia and one patient with *A. caviae* bacteremia survived more than 30 days after onset of *Aeromonas* bacteremia. Their deaths were considered not to be associated with *Aeromonas* bacteremia. One died due to hepatoma rupture, another due

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to esophageal veins bleeding, and the others due to septic shock caused by other pathogens. The remaining 51 patients' deaths were attributed to *Aeromonas* bacteremia.

Table 1 summarizes clinical presentations of the monomicrobial bacteremias caused by *A. hydrophila*, *A. veroni* biovar sobria, and *A. caviae*. *A. caviae* was more associated with healthcare-associated bacteremia than *A. hydrophlia* and *A. veronii* biovar sobria. However, *A. veronii* biovar sobria and *A. hydrophila* were more associated with the cirrhotic patients than *A. caviae*. Thrombocytopenia and shock were more common in *A. veronii* biovar sobria bacteremia and *A. hydrophila* bacteremia than *A. caviae* bacteremia. The APACHE II scores and mortality of *A. hydrophila* and *A. veronii* biovar sobria bacteremia were higher than *A. caviae* bacteremia.

Of the 87 *A. hydrophila* isolates, 61 were identified mainly by API-20NE system, 17 by Vitek II system, and 9 by BD-Phoenix system. Of the 45 *A. veronii* biovar sobria isolates, 34 were identified mainly by API-20NE system, 5 by Vitek II system, and 6 by BD-Phoenix system. Of the 22 *A. caviae* isolates, 16 were identified mainly by API-20NE system, 3 by Vitek II system, and 3 by BD-Phoenix system. In vitro antimicrobial susceptibilities of different *Aeromonas* species were listed in Table 2. More *A. veronii* biovar sobria isolates were susceptible to cefazolin and flomoxef than the other *Aeromonas* species. Less *A. caviae* isolates were susceptible to sulfamethoxazole/trimethoprim than the other *Aeromonas* species.

Univariate analyses for risk factors of bacteremia-associated mortalities were listed in Table 3. In *A. hydrophila* bacteremia, thrombocytopenia, diarrhea, APACHE II score > 20 points, and adequate empirical antibiotics were risk factors for bacteremia-associated mortality. The four factors were included for multivariate logistic regression analysis. Only APACHE II score was the independent factor for survival (odds ratio: 22.501; $P < 0.001$). In *A. veronii* biovar sobria bacteremia, APACHE II score was significant risk factor for bacteremia-associated mortality. Only one 77-yr-old woman with community-acquired *A. caviae* bacteremia died. She had liver cirrhosis, diabetes mellitus, and chronic usage of acid-suppressant therapy. She presented with fever, dyspnea, septic shock, and thrombocytopenia with 31 points of APACHE II score at admission. She was treated with levofloxacin, which was considered as an adequate empirical antibiotics according in vitro antimicrobial susceptibility. However, she still died after 24-day hospitalization. Fig. 1 showed box plots of the distributions of APACHE II scores for monomicrobial *Aeromonas* bacteremia stratified by different *Aeromonas* species and survival.

Table 1. Different clinical presentations among *A. hydrophila*, *A. caviae* and *A. veronii* biovar sobria bacteremia

Parameters	*A. hydrophila* (n = 87)	*A. veronii* biovar sobria (n = 45)	*A. caviae* (n = 22)	*P* value
Age, mean years ± SD	58.8 ± 14.3	56.3 ± 16.0	59.4 ± 16.4	0.600
Gender (male), No. (%)	65 (75)	33 (73)	14 (64)	0.578
Healthcare-associated infection, No. (%)	26 (30)	7 (16)	10 (45)	0.031*
Underlying disease				
Post-surgery, No. (%)	12 (14)	6 (13)	6 (27)	0.263
Solid cancer, No. (%)	19 (22)	13 (29)	8 (36)	0.332
Diabetes mellitus, No. (%)	27 (31)	9 (20)	7 (32)	0.370
Cirrhosis, No. (%)	54 (62)	29 (64)	6 (27)	0.007*
Neutropenia, No. (%)	3 (3)	5 (11)	1 (5)	0.198
Acid-suppressant therapy	39 (45)	20 (44)	4 (18)	0.064
Symptoms and signs				
Leukocytosis, No. (%)	23 (26)	14 (31)	3 (14)	0.306
Thrombocytopenia, No. (%)	58 (67)	39 (87)	10 (45)	0.002*
Fever, No. (%)	69 (79)	38 (84)	19 (86)	0.643
Shock, No. (%)	35 (40)	21 (47)	2 (9)	0.009*
Diarrhea, No. (%)	7 (8)	5 (11)	3 (14)	0.684
Abdominal pain, No. (%)	65 (75)	16 (36)	5 (23)	0.578
Acute renal failure, No. (%)	22 (25)	10 (22)	2 (9)	0.262
Acute respiratory failure, No. (%)	12 (14)	8 (18)	0 (0)	0.120
APACHE II score, median points (IQR)	14 (16)	16 (16)	7 (5)	0.002*
Prognosis				
Death attributable to *Aeromonas* bacteremia, No. (%)	31 (36)	19 (42)	1 (5)	0.007*

APACHE, Acute Physiology and Chronic Health Evaluation; SD, standard deviation; IQR, interquartile range. *$P < 0.05$.

DISCUSSION

Commercial phenotyping systems used routinely in clinical mi-

Table 2. In vitro antimicrobial susceptibilities of different *Aeromonas* species

Antimicrobial agents	*A. hydrophila* (n = 87) Susceptible/ tested isolates (%)	*A. veronii* biovar sobria (n = 45) Susceptible/ tested isolates (%)	*A. caviae* (n = 22) Susceptible/ tested isolates (%)	*P* value
Gentamicin	83/87 (95)	45/45 (100)	21/22 (95)	0.344
Amikacin	86/87 (99)	44/44 (100)	22/22 (100)	0.679
Cefazolin	7/87 (8)	17/45 (38)	0/22 (0)	< 0.001*
Cefuroxime	55/72 (76)	31/39 (79)	15/20 (75)	0.906
Cefmetazole	32/57 (56)	22/29 (76)	7/14 (50)	0.137
Flomoxef	34/59 (58)	24/28 (86)	7/14 (50)	0.018†
Ceftriaxone	81/87 (93)	45/45 (100)	20/22 (91)	0.161
Ceftazidime	47/50 (94)	35/35 (100)	18/19 (95)	0.137
Cefpirome	54/57 (95)	29/29 (100)	14/14 (100)	0.311
Aztreonam	53/54 (98)	38/38 (100)	19/19 (100)	0.345
Ticarcillin/ clavulanic acid	26/31 (84)	23/30 (77)	10/17 (59)	0.152
Piperacillin/tazobactam	46/48 (96)	35/35 (100)	19/21 (90)	0.198
Imipenem	85/86 (99)	44/45 (98)	22/22 (100)	0.742
Ciprofloxacin	74/79 (94)	40/40 (100)	21/22 (95)	0.270
Sulfamethoxazole/ Trimethoprim	29/35 (83)	30/32 (94)	9/19 (47)	< 0.001‡
Ampicillin	1/87 (1)	0/45 (0)	0/22 (0)	0.679

*More isolates of *A. veronii* biovar sobria were susceptible to cefazolin than *A. hydrophila* and *A. caviae*; †More isolates of *A. veronii* biovar sobria were susceptible to flomoxef than *A. hydrophila* and *A. caviae*; ‡Less isolates of *A. caviae* were susceptible to sulfamethoxazole/trimethoprim than *A. hydrophila* and *A. veronii* biovar sobria.

Table 3. Univariate analyses of risk factors of bacteremia-associated mortalities in patients with monomicrobial bacteremia caused by different *Aeromonas* species

Variables	*A. hydrophila* (n = 87)			*A. veroni* bioar sobria (n = 45)		
	Survival (n = 56)	Death (n = 31)	*P* value	Survival (n = 26)	Death (n = 19)	*P* value
Age ≥ 65 yr, No. (%)	23 (41)	10 (32)	0.561	7 (27)	7 (37)	0.701
Gender (male), No. (%)	42 (75)	23 (74)	1.000	17 (65)	16 (84)	0.191
Healthcare-associated infection, No. (%)	18 (32)	8 (26)	0.629	3 (12)	4 (21)	0.433
Post-surgery, No. (%)	6 (11)	6 (19)	0.334	4 (15)	2 (11)	1.000
Solid cancer, No. (%)	13 (23)	6 (19)	0.884	10 (38)	3 (16)	0.185
Diabetes mellitus, No. (%)	14 (25)	13 (42)	0.164	7 (27)	2 (11)	0.264
Cirrhosis, No. (%)	32 (57)	22 (71)	0.252	17 (65)	12 (63)	1.000
Neutropenia, No. (%)	1 (2)	2 (6)	0.288	2 (8)	3 (16)	0.636
Acid-suppressant therapy, No. (%)	27 (48)	12 (39)	0.530	12 (46)	8 (42)	1.000
Thrombocytopenia, No. (%)	31 (55)	27 (87)	0.006*	22 (85)	17 (89)	1.000
Diarrhea, No. (%)	7 (13)	0 (0)	0.047*	3 (12)	2 (11)	1.000
Abdominal pain, No. (%)	17 (30)	5 (16)	0.228	12 (46)	4 (21)	0.155
APACHE II score ≥ 20 points, No. (%)	5 (9)	23 (74)	< 0.001*	2 (8)	17 (89)	< 0.001*
Adequate empirical antibiotics, No. (%)	56 (100)	23 (74)	< 0.001*	25 (96)	14 (74)	0.720

APACHE, Acute Physiology and Chronic Health Evaluation. *$P < 0.05$.

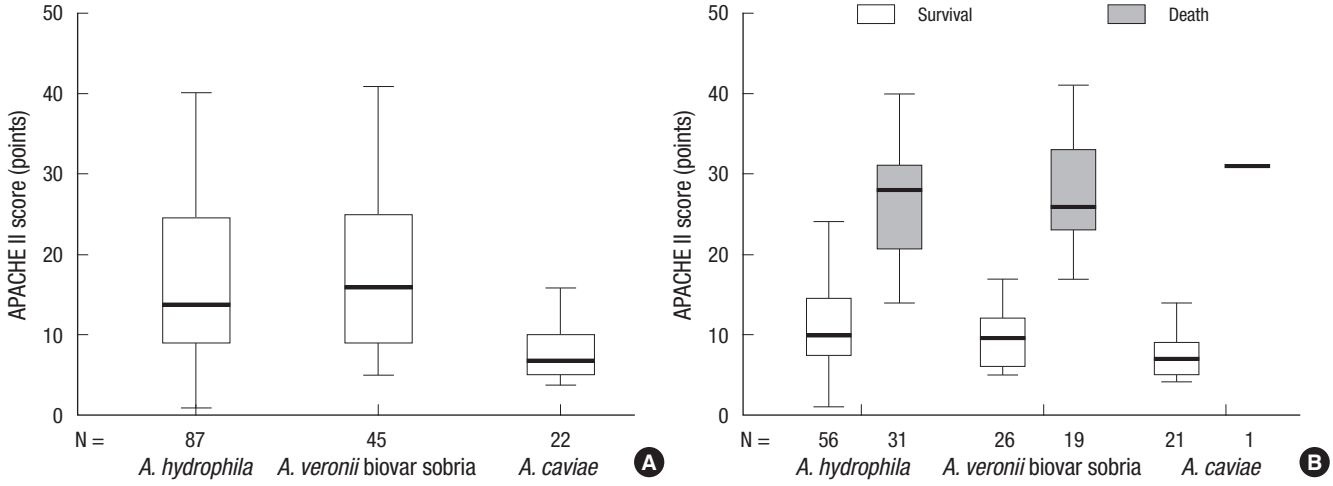

Fig. 1. Box plots of Acute Physiology and Chronic Health Evaluation II (APACHE II) scores distributions for *A. hydrophila*, *A. veronii* biovar sobria, and *A. caviae* bacteremia (**A**) and box plots of APACHE II scores distributions for survivals and deaths in different *Aeromonas* groups (**B**).

crobiology laboratories are not exactly correct for identification of aeromonads (14, 15). Lamy and his coworkers compared 6 commercial systems for identifying clinical *Aeromonas* isolates (16). The accuracy of API-20NE system was good for *A. hydrophila* and *A. veronii* but not for *A. caviae*. The accuracy of Vitek II system for *A. hydrophila* and *A. caviae* was good but not for *A. veronii*. The accuracy of BD-Phoenix system for *A. caviae* and *A. veronii* was good but not for *A. hydrophila*. Additional tests, like esculin hydrolysis, gas production from glucose, Voges-Proskauer reaction, ornithine decarboxylase, and arginine dihydrolase production are necessary for confirmation of *Aeromonas* species identified by the commercial systems. However, their accuracy of identification is still not compatible with the molecular method. In the present study, large sample size alleviated this bias and complementary effect of these three commercial systems can decrease the extreme deviation caused by single commercial system.

The case mortality among patients with *Aeromonas* bacteremia in the literature ranges from 24%-63% (2-5, 17-22). Clinical presentations among different *Aeromonas* species were rarely discussed due to limited cases. In a study including 104 episodes, *Aeromonas* species was divided into *hydrophila* and non-*hydrophila* and the resulting fatalities were 35.5% (22/62) and 23.8% (10/42) respectively (2). In another report including 59 episodes, the mortalities caused by *A. hydrophila*, *A. veronii* biovar sobria, and *A. caviae* are 33% (13/40), 56% (5/9), and 17% (1/6) respectively (22). However, this tendency could not be noted in another report, in which *Aeromonas*-associated polymicrobial bacteremia was not excluded (4). The present study only included monomicrobial *Aeromonas* bacteremia and proved that the mortality of *A. caviae* bacteremia was lower than *A. hydrophila* bacteremia or *A. veronii* biovar sobria bacteremia.

Different *Aeromonas* species showed different virulence factors in immunocompromised mouse models (23). Majority of

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A. hydrophila and *A. veronii* biovar sobria isolates were capable of persistent colonization but *A. caviae* isolates was not. In vitro study showed that *A. caviae* isolates, unlike other *Aeromonas* isolates were less toxic to HEp-2 cell. However, most of *Aeromonas* isolates used for these studies were from the natural environment and the virulence factors of *Aeromonas* species from infected hosts and natural environments were different (24). Only a study showed the virulence factors from the bacteremia-associated *Aeromonas* isolates (12). The genes for cytotoxic enterotoxin were more common in the *A. veronii* biovar sobria (13/13) and *A. hydrophila* (15/20) isolates than the *A. caviae* isolates (3/14). Cytotoxic enterotoxin could activate mitogen-activated protein kinases and induce classical caspase-associated apoptosis in murine macrophages (25). Poor macrophage function caused by cytotoxic enterotoxin may contribute to severe sepsis. Therefore, poor abilities of *A. caviae* to produce cytotoxic enterotoxin may be the reason for better prognosis of *A. caviae* bacteremia. However, this opinion should be proved in a further study.

The patients diagnosed with healthcare-associated *Aeromonas* bacteremia had been considered to have colonization of *Aeromonas* species in their gastrointestinal tracts before admission (2). In the previous study, liver cirrhosis was associated with community-acquired *Aeromonas* bacteremia and malignancy with healthcare-associated *Aeromonas* bacteremia (2-4). In the present study, we found that *A. caviae* was more associated with healthcare-associated infection and less associated with cirrhosis than the other species. This phenomenon may be also due to poor abilities of *A. caviae* to produce cytotoxic enterotoxin. Cirrhotic patients have impaired intestinal permeability due to intestinal congestion, edema, and local hypoxia due to portal hypertension, which creates a good environment for bacterial translocation (26-29). However, additional factors for destroying mucosal barrier are necessary to help bacterial translocation. Cytotoxic enterotoxin produced by *Aeromonas* species can induce apoptosis of human intestinal epithelial cells and may play an important role for bacterial translocation (25). Due to poor production of enterotoxin, *A. caviae* has lower chance to cause bacterial translocation in cirrhotic patients than the other *Aeromonas* species. Compared with the cirrhotic patients, the cancer patients had more chances to receive surgeries or cytotoxic agents during hospitalization, which caused extensive intestinal mucosal damage. That may be the reason why *A. caviae* was more associated with healthcare-associated bacteremia.

In our study, the susceptibility of these microorganisms to trimethoprim-sulfamethoxazole, and cefazolin showed inter-species variability. These findings agree with previous studies (10, 11). Besides, we observed that flomoxef was active to only about 50% isolates of *A. caviae* and *A. hydrophila*. Although flomoxef belongs to oxyimino-β-lactam and is considered as a kind of extended-spectrum cephalosporin, traditional extended-spectrum cephalosporins are more efficacious for treatment of *Aeromonas* bacteremia.

Although there were some limitations from different commercial identifying systems in our study, this study included large sample size and showed different clinical presentations of bacteremia among *A. hydrophila*, *A. veronii* biovar sobria and *A. caviae*. In conclusion, the severity of *A. caviae* bacteremia is lower than *A. hydrophila* bacteremia or *A. veronii* biovar sobria bacteremia.

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Different Clinical Characteristics Among *Aeromonas hydrophila, Aeromonas veronii* biovar sobria and *Aeromonas caviae* Monomicrobial Bacteremia

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This study aimed to evaluate the clinical presentations of 154 patients having *A. hydrophila*, *A. veronii* biovar sobria or *A. caviae* monomicrobial bacteremia by retrospective methods in Taiwan. The clinical presentation of *A. caviae* bacteremia was much different from *A. hydrophila* and *A. veronii* biovar sobria bacteremia. The patients with *A. caviae* bacteremia had less severity and lower mortality than those with *A. veronii* biovar sobria or *A. hydrophila* bacteremia.

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