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Original Article

Clinical features and risk factors for mortality in *Aeromonas* bacteremic adults with hematologic malignancies

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Background and Purpose: *Aeromonas* spp. often cause infections in immunocompromised patients. To specifically understand the clinical features of *Aeromonas* bacteremic adults with hematologic malignancies, we investigated the demographic, clinical and microbiologic characteristics of *Aeromonas* bacteremia in this patient population.
Methods: Retrospective study performed in a tertiary medical center in southern Taiwan, in which adults with hematologic malignancies suffered from *Aeromonas* bacteremia admitted between 1995 and 2003 were included for study.
Results: There were 45 episodes of *Aeromonas* bacteremia in 41 adults with hematologic malignancies. Episodes of *Aeromonas* bacteremia which occurred at least 2 months apart were counted as separate cases in the analysis. A total of 30 men and 15 women (mean age: 53.2 years), with 4 patients experiencing 2 episodes, was included. The 3 leading underlying hematologic malignancies were acute myelogenous leukemia (37.8%), myelodysplastic syndrome (26.7%) and non-Hodgkin's lymphoma (17.8%). No cluster of *Aeromonas* bacteremia was found during the study period. Twenty nine (64.4%) of the 31 patients with nosocomial *Aeromonas* bacteremia had received recent antineoplastic chemotherapy. The 3 leading clinical manifestations were fever (88.9%), septic shock (40%), and altered consciousness (26.7%). Eleven (24.4%) episodes of bacteremia were polymicrobial. Sixteen (35.6%) patients died within 14 days of onset of bacteremia. The mean duration from sampling blood for culture to death was 3.81 days. Altered consciousness (odds ratio, 8.999; 95% confidence interval, 1.787-45.33; p=0.008) was the only independent prognostic factor for mortality. High resistance rates (11.1% to piperacillin and 35.6% to imipenem) among *Aeromonas* isolates were also noted.
Conclusion: In febrile patients with hematologic malignancies and suspected *Aeromonas* infections, particular attention to the development of alteration of consciousness is needed as it is an independent risk factor for mortality.

Key words: *Aeromonas*, bacteremia, hematologic neoplasms, microbial sensitivity tests, risk factors

Introduction

Aeromonas is the only genus in the family *Aeromonadaceae*. Members of *Aeromonas* are motile Gram-negative rods or coccoid cells, and are pathogenic for humans [1]. *Aeromonas* spp. are inhabitants of aquatic ecosystems worldwide, which include groundwater, drinking water at treatment plants, water distribution systems, reservoirs as well as clean or polluted lakes and rivers. *Aeromonas* spp. may also be found in marine environments but only in brackish water or water with low sodium content [1]. There are 2 subdivisions within the genus *Aeromonas* based on the temperature of bacterial growth [2]. Psychrophilic strains of *Aeromonas* cause diseases in fishes of economical importance as well as cold-blooded amphibians; mesophilic strains are notorious for their pathogenic roles in a broad spectrum of human diseases, including gastroenteritis, cellulitis, necrotizing fasciitis, septicemia, meningitis, hemolytic-uremic syndrome, peritonitis and respiratory tract diseases [2]. *Aeromonas* may cause illnesses in healthy persons, but these are

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often self-limited. Most infections caused by *Aeromonas* are found in immunocompromised hosts, especially patients with liver cirrhosis and malignancies [3]. The mortality rate of *Aeromonas* bacteremia is very high among immunocompromised hosts, ranging from 24% to 68% in different studies [3-5]. In previous studies, *Aeromonas* bacteremic patients were found to have mixed underlying diseases, mainly liver cirrhosis and solid tumors [3-5]. The inclusion of only a small number of patients with hematologic diseases in a previous study on *Aeromonas* bacteremic patients offered limited information on *Aeromonas* infection in this patient population [6]. This study investigated the demographic, clinical and microbiologic characteristics of *Aeromonas* bacteremia in patients with hematologic malignancies.

Methods

This retrospective study included *Aeromonas* bacteremic adults with underlying hematologic malignancies admitted between November 1995 and August 2003 at Chang Gung Memorial Hospital-Kaohsiung, a 2300-bed tertiary teaching hospital in southern Taiwan. Malignancies were diagnosed based on the findings of histopathological studies by both hematologists and pathologists. All included patients had positive blood cultures for *Aeromonas* spp. which were presumptively identified based on recognition of microscopically Gram-negative bacilli, positive oxidase tests, glucose fermentation, motility and resistance to 150 μg vibriostatic agent O/129 (2,4-diamino-6,7-diisopropylpteridin; Rosco, Taastrup, Denmark) [7]. Isolates were further confirmed with the API 20NE (bioMérieux Vitek, Hazelwood, MO, USA) or ID 32 GN system (bioMérieux, Hazelwood, MO, USA). In vitro antibiotic susceptibilities of *Aeromonas* spp. were tested using the Kirby-Bauer disk diffusion method on a regular clinical service basis. Antibiotics selected for testing included cephalothin (30 μg per disk), cefuroxime (30), ceftriaxone (30), cefotaxime (30), ceftazidime (30), imipenem (10), trimethoprim-sulfamethoxazole (1.25/23.75), piperacillin (100), gentamicin (10), amikacin (30) and ciprofloxacin (10). The procedures and breakpoint concentrations for interpretation were in accordance with those of the National Committee for Clinical Laboratory Standards for *Enterobacteriaceae* [8].

Medical charts were reviewed to collect information on demographic characteristics, laboratory and clinical data, seasonal distribution of *Aeromonas* bacteremia, location of acquisition, as well as the timing before or after antineoplastic chemotherapy of *Aeromonas* infections. *Aeromonas* bacteremia was considered hospital-acquired if an *Aeromonas* sp. isolate was obtained from blood sampled after more than 72 h 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. Otherwise, the *Aeromonas* bacteremia was considered community-acquired. Polymicrobial bacteremia was defined as concurrent growth of pathogen(s) other than *Aeromonas* spp. in blood culture. Septic shock was defined as a systolic blood pressure ≤90 mm Hg or a systolic blood pressure lowered ≥40 mm Hg compared to the baseline systolic blood pressure. The cytotoxic antineoplastic regimen and antibiotic(s) were selected at the discretion of the attending physicians. Antibiotics first used continuously for at least 48 h after the onset of symptoms were regarded as the initial prescribed antibiotics in situations where antimicrobial agents were changed during the course of illness. *Aeromonas* bacteremia was considered the cause of death in patients with unrelenting sepsis who died within 14 days after collection of a sample with a positive blood culture. Differences between fatal cases and survivors were analyzed by Mann-Whitney *U* test for comparison of continuous variables, and chi-squared or Fisher's exact test for dichotomous variables. Variables with significant results in the univariate analyses were included in a multiple logistic regression to identify independent risk factors for mortality. A 2-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 12.0, SPSS Inc., Chicago, USA).

Results

A total of 41 individuals were included in this study, 4 of whom experienced 2 *Aeromonas* bacteremic episodes, which occurred at least 2 months apart in the same patient. Because of the substantial time lapses between bacteremic episodes in the same patient, each episode was counted separately in the analysis. Thus, 45 episodes of *Aeromonas* bacteremia were retrospectively analyzed; patients could contribute more than a single record in the analyses.

The patients included 30 men (66.7%) and 15 women (13.3%), with mean age of 53.2 years. The ages

of the majority of patients were between 50 and 80 years old. The underlying hematologic malignancies in decreasing order of frequency were acute myelogenous leukemia (17 cases; 37.8%), myelodysplastic syndrome (12 cases; 26.7%), non-Hodgkin's lymphoma (8 cases; 17.8%), acute lymphocytic leukemia (6 cases; 13.3%), chronic myelogenous leukemia in blastic transformation (1 case; 2.2%) and Hodgkin's disease (1 case; 2.2%). No cluster of *Aeromonas* bacteremia was found during the study period. *Aeromonas* bacteremia occurred throughout the year, but was at its highest frequency (42.2%) in the summer season between June and August. Among the 31 patients (68.9%) with nosocomial *Aeromonas* bacteremia, 29 had received antineoplastic chemotherapy either at an outpatient visit or during hospitalization. All patients who had received antineoplastic chemotherapies on an outpatient basis were admitted with the chief complaint of fever. The clinical manifestations of the patients are summarized in Table 1. Fever was the most commonly encountered presentation (88.9%), followed by septic shock (40%), altered consciousness (26.7%) and dyspnea (24.4%). Soft tissue involvement was rarely seen; ecthyma gangrenosum and cellulitis each occurred in a single patient. Respiratory failure requiring endotracheal intubation for mechanical ventilatory support was found in 3 patients (6.7%). Overt consolidations were found on chest radiographic films in 4 (8.9%) patients; however, no *Aeromonas* sp. was isolated from the sputum of these patients. Pleural empyema was diagnosed in 1 *Aeromonas* bacteremic patient whose pleural effusion grew the same pathogen. Polymicrobial bacteremia was found in 11 patients (24.4%). The concomitant non-*Aeromonas* bacteria isolates included *Staphylococcus aureus* (n = 3), *Staphylococcus epidermidis* (n = 1), *Escherichia coli* (n = 5), *Klebsiella pneumoniae* (n = 4), *Citrobacter freundii* (n = 1), and *Enterobacter cloacae* (n = 1). One of the *K. pneumoniae* isolates was an extended-spectrum beta (β)-lactamase-producing strain.

Table 1. Clinical presentations of 45 patients with *Aeromonas* bacteremia[a]

Presentations	No. of cases (%)
Dyspnea	11 (24.4)
Abdominal pain	7 (15.6)
Fever (>38°C)	40 (88.9)
Shock	18 (40)
Altered consciousness	12 (26.7)
Diarrhea	4 (8.9)
Respiratory failure	3 (6.7)
Ecthyma gangrenosum	1 (2.2)
Cellulitis	1 (2.2)

[a]One patient might have more than 1 manifestation.

Table 2. Results of susceptibility testing of 45 *Aeromonas* isolates by the disk diffusion method

Antibiotic	No. of *Aeromonas* isolates (%)
Cephalothin	32 (71.1)
Cefuroxime	44 (97.8)
Ceftriaxone	44 (97.8)
Cefotaxime	44 (97.8)
Ceftazidime	44 (97.8)
Imipenem	29 (64.4)
Trimethoprim-sulfamethoxazole	37 (82.2)
Piperacillin	40 (88.9)
Gentamicin	45 (100)
Amikacin	45 (100)
Ciprofloxacin	42[a] (100)

[a]Only 42 isolates were tested.

Results of antimicrobial susceptibility testing by the disk diffusion method on the 45 *Aeromonas* clinical isolates are shown in Table 2. Briefly, the *Aeromonas* isolates were universally susceptible to aminoglycosides and ciprofloxacin and highly susceptible to second- and third-generation cephalosporins. Remarkably, only 88.9% of the *Aeromonas* isolates were susceptible to piperacillin and 64.4% to imipenem, the 2 most frequently prescribed antipseudomonal antibiotics for septic patients with hematologic malignancies.

Sixteen patients died, resulting in an overall fatality rate of 35.6%. The average duration from blood sampling for culture to death was 3.81 days (median, 3.50 days; range, 1-12 days). The demographic, clinical and laboratory data for these patients are summarized in Table 3. In the univariate analysis, septic shock (p=0.022) and altered consciousness (p=0.014) were significantly more frequent among patients who died. Only altered consciousness (odds ratio, 8.999; 95% confidence interval, 1.787-45.33; p=0.008) was an independent prognostic factor for mortality in *Aeromonas* bacteremic patients with hematologic malignancies.

Discussion

Members of the genus *Aeromonas* have frequently been taxonomically reclassified and a number of new species have been added in the past. At least 14 *Aeromonas* genomospecies have been identified [9]. In spite of the increasingly recognized numbers of *Aeromonas* species, more than 85% of clinical isolates

Table 3. Demographic, clinical and laboratory data of 45 *Aeromonas* bacteremic patients with hematologic malignancies

Variable	Total cases (n = 45)	Fatal cases (n = 16)	Nonfatal cases (n = 29)	p^a
Gender				0.271
Female (%)	15 (33.3)	7 (46.7)	8 (53.3)	
Male (%)	30 (66.7)	9 (30)	21 (70)	
Age (years)				0.660
<65 (%)	15 (33.3)	6 (40)	9 (60)	
≥65 (%)	30 (66.7)	10 (33.3)	20 (66.7)	
Septic shock				0.022
Yes (%)	18 (40)	10 (55.6)	8 (44.4)	
No (%)	27 (60)	6 (22.2)	21 (77.8)	
Altered consciousness				0.014
Yes (%)	12 (26.7)	8 (66.7)	4 (33.3)	
No (%)	33 (73.3)	8 (24.2)	25 (75.8)	
Serum creatinine (mg/dL)				0.225
<1.5 (%)	38 (84.4)	12 (31.6)	26 (68.4)	
≥1.5 (%)	7 (15.6)	4 (57.1)	3 (42.9)	
Place of acquisition				1.0
Hospital (%)	31 (68.9)	11 (35.5)	20 (64.5)	
Community (%)	14 (31.1)	5 (35.7)	9 (64.3)	
Antineoplastic chemotherapy				0.840
Yes (%)	29 (64.4)	10 (34.5)	19 (65.5)	
No (%)	16 (35.6)	6 (37.5)	10 (62.5)	
No. of bacteria species isolated from blood				1.0
Monomicrobial (%)	34 (75.6)	12 (35.3)	22 (64.7)	
Polymicrobial (%)	11 (24.4)	4 (36.4)	7 (63.6)	
Absolute neutrophil counts				0.820
>500/μL (%)	21 (46.7)	8 (38.1)	13 (61.9)	
≤500/μL (%)	23 (53.3)	8 (34.8)	15 (65.2)	

[a]For univariate analyses comparing fatal cases and survivors.

belong to 1 of the 3 clinically pathogenic *Aeromonas* genomospecies, namely, *Aeromonas hydrophila*, *Aeromonas veronii* bv. sobria and *Aeromonas caviae* [2, 9]. Almost all invasive infections caused by *Aeromonas* spp. were reported in hosts with an underlying disease that compromises immunity, such as solid tumors, hematologic malignancies, liver cirrhosis and diabetes mellitus [3,10]. Previous studies of *Aeromonas* bacteremia provided limited information on the effects of immunocompetency due to specific underlying disease states, and thus little information was obtained for antimicrobial treatments of *Aeromonas* sepsis in variably immunocompromised patients accordingly.

Most clinical presentations of *Aeromonas* bacteremia in this series were nonspecific (Table 1). Univariate analysis of the clinical presentations revealed that patients with shock and patients with altered consciousness were at significantly higher risk of mortality. However, multivariate analysis revealed that altered consciousness was the only factor independently associated with mortality. In the absence of brain abscess, other central nervous system infection, or any bacterium-specific neurotoxin, sepsis associated brain hypoperfusion is the most likely cause of disturbed consciousness. A subtle decrease in brain tissue perfusion may not be accompanied by a decrease in the host's systemic blood pressure that fulfills the criteria for septic shock. This finding emphasizes the need for special attention to consciousness disturbance in this patient population.

The most common infection caused by *Aeromonas* spp. is gastroenteritis, followed by soft tissue infection [2]. Portals of entry in patients with bacteremia include the gastrointestinal tract and skin lesions resulting from traumatic injury [2,11]. Because outdoor physical activities are likely to be limited in patients with hematologic malignancies, environmental or recreational exposure-associated soft tissue trauma is uncommon and it is logical to assume that the gastrointestinal lumen is the major *Aeromonas* infection source in this patient population. It was hypothesized that disintegrated gastrointestinal mucosa resulting from antineoplastic chemotherapies are an important portal of entry of

bacteria in patients with malignancies [12]. A previous study suggested that patients with hematologic malignancies are more prone to gastrointestinal colonization with *Aeromonas* spp. than persons with other underlying conditions [11]. One study performed in 1993 disclosed that *Aeromonas* spp. were found in 88% of seafood from retail markets and supermarkets in Taipei, the largest city in northern Taiwan [13]. There is a substantial market for seafood and freshwater fish island-wide in Taiwan, much of which is harvested and dispensed from southern Taiwan. The well-developed aquaculture and subtropical climate in southern Taiwan lead to a year-round abundance of *Aeromonas* spp. in the local biological surroundings. Further studies are needed to clarify the association between this biological background and the development of *Aeromonas* bacteremia in Taiwan.

As the antibiotic susceptibility patterns of *Aeromonas* spp. differ considerably from one geographic locale to another [1,11,14], information about the local susceptibility patterns is essential for selecting appropriate empirical antimicrobial treatment for patients with suspected *Aeromonas* sepsis. All but one of the *Aeromonas* isolates in this series were susceptible to third-generation cephalosporins. In contrast, 11% and 36% of these isolates were resistant to piperacillin and imipenem, respectively. *Aeromonas* spp. may express β-lactam-induced chromosomal β-lactamases in general and carbapenemases in particular, which may make the pathogens resistant to carbapenems [15]. Piperacillin and imipenem are often used in the empirical treatment of febrile neutropenic patients with an underlying hematologic malignancy for coverage of Gram-negative bacilli inclusive of *Pseudomonas aeruginosa* [16]. The susceptibility profiles of *Aeromonas* isolates in this series suggest the need for continuous monitoring of the susceptibility patterns of these pathogens, especially their susceptibilities to antipseudomonal drugs, which are frequently prescribed as empiric treatment for septic patients with a hematologic disease who are also at high risk of *Aeromonas* infections. Clinicians should pay special attention to the development of altered consciousness in an *Aeromonas* bacteremic patient, since it is an independent risk factor for mortality in this patient population.

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