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Original Article

Clinical presentations, prognostic factors, and mortality in patients with *Aeromonas sobria* complex bacteremia in a teaching hospital: a 5-year experience

Chien-Yu Wang, Chih-Yu Chi, Mao-Wang Ho, Cheng-Mao Ho, Po-Chang Lin, Jen-Hsien Wang

Section of Infectious Diseases, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan

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Background and purpose: Bacteremia due to *Aeromonas sobria* complex is an uncommon clinical presentation, associated with a high mortality rate. This retrospective study reviewed the clinical manifestations and prognostic factors of *A. sobria* complex bacteremia.

Methods: From September 2001 to August 2006, all adult patients with *A. sobria* complex bacteremia treated at a tertiary medical center in Taiwan were included. Antibiotic susceptibility was tested by disc diffusion method.

Results: Of 33 patients with *A. sobria* complex bacteremia, 66.7% were men and 72.0% were older than 50 years. Most patients (72.7%) had community-acquired infection. The commonest associated conditions were liver cirrhosis (42.4%) and neoplasm (30.3%). With the exception of diarrhea, the clinical manifestations were similar to those of other *Aeromonas* spp. Secondary bacteremia occurred in 51.5% of patients, most of whom had either biliary tract infection (47%) or peritonitis (23.5%) as the major infection focus. Monomicrobial bacteremia was recorded in 23 patients. All isolates were susceptible to gentamicin, amikacin, ceftazidime, cefepime, and ciprofloxacin; 90.9% were susceptible to aztreonam and piperacillin-tazobactam, 87.9% to imipenem, and 78.8% to trimethoprim-sulfamethoxazole. The mortality rate was 39.4% and nearly 50% of deaths occurred within 96 h of admission. Hypotension, impaired renal function, and liver cirrhosis were significantly associated with a high mortality rate.

Conclusions: *A. sobria* complex bacteremia usually occurs in patients with liver cirrhosis or neoplasm. In patients with *A. sobria* complex bacteremia, a secondary infection focus should be considered. Adequate antibiotics should be given early, especially to patients with hypotension and impaired renal function.

Key words: *Aeromonas sobria*; Bacteremia; Liver cirrhosis; Neoplasms; Taiwan

Introduction

Members of the genus *Aeromonas* spp. are Gram-negative facultative anaerobes and are oxidase- and catalase-positive organisms. Members of this genus are ubiquitous inhabitants of aquatic ecosystems worldwide. The species can cause infections in human, frogs, pigs, cattle, birds, and marine animals [1]. There are currently 14 named species, but only 3, *Aeromonas hydrophila*, *Aeromonas caviae*, and *Aeromonas veronii* biovar *sobria*, are of major clinical importance [2]. Due to overlapping biochemical reactions and lack of a clear-cut phenotypic table, biochemical identification of *Aeromonas* spp. to complex level has been recommended [3]. Many studies have shown that these bacteria are responsible for infections in both immunocompromised and immunocompetent patients [4-8], and are able to cause human diseases, including gastroenteritis, septicemia, hepatobiliary tract infection, soft tissue infection, pleuropulmonary infection, indwelling device–related infection, meningitis, peritonitis, and hemolytic uremic syndrome [5]. *A. hydrophila* is the most commonly isolated species [4,7,8].

Corresponding author: Dr. Jen-Hsien Wang, Section of Infectious Diseases, Department of Internal Medicine, China Medical University Hospital, No. 2, Yude Rd., North District, Taichung 404, Taiwan.
E-mail: jerrywang6416@yahoo.com.tw

However, *A. sobria* has the highest fatality rate of this genus (56% for *A. sobria*, 33% for *A. hydrophila*, 17% for *A. caviae*) [4]. Furthermore, in an animal study, *A. sobria* was more virulent than either *A. hydrophila* or *A. caviae* [9]. To the authors' knowledge, there have been few reports focusing on *A. sobria* complex bacteremia [10]. This retrospective study was conducted to review the clinical characteristics, prognostic factors, and mortality of *A. sobria* complex bacteremia.

Methods

Patients and definitions

From September 2001 to August 2006, all patients who were older than 18 years and had *A. sobria* complex bacteremia at China Medical University Hospital, a 1700-bed tertiary teaching hospital in Taichung, Taiwan, were included. Patients were enrolled only if they had clinical symptoms/signs of *A. sobria* complex bacteremia plus ≥1 set of positive blood cultures. The patients' medical charts were thoroughly reviewed to collect the following data: demographic characteristics, clinical presentations, underlying diseases, laboratory data, outcomes, and duration of hospital stay. The seasonal distribution of *A. sobria* complex bacteremia was also reviewed. Hypotension was documented when the systolic blood pressure was <90 mm Hg within 3 days before and after obtaining blood cultures. Nosocomial bacteremia was defined as a positive blood culture obtained at least 3 days after admission; other infections were regarded as community-acquired. Bacteremia accompanied with other obvious infection foci due to the same pathogen was considered to be secondary bacteremia; other infections were regarded as primary bacteremia. In the first 48 h of onset of symptoms, empiric therapy with agents active in vitro against *A. sobria* complex was regarded as adequate antibiotic treatment; all other treatments were regarded as inadequate. Duplicated episodes of *A. sobria* complex bacteremia were excluded, and only the first isolate was included for further investigation.

Microbiology and antibiotic susceptibility tests

All blood specimens were incubated in aerobic and anaerobic media at 35°C and processed using the Bactec 9000 System (Becton Dickinson, Sparks, MD, USA). Positive specimens were subcultured on blood agar, heated (chocolated) blood agar and eosin-methylene blue agar, and the isolates were identified as *A. sobria* complex according to the previously described biochemical criteria [3]. API 20 E (bioMérieux, Inc. Hazelwood, MO, USA) was applied for further confirmation. The disc diffusion method was used to test the in vitro antibiotic susceptibilities of *A. sobria* complex [11]. Antibiotics selected for testing included gentamicin 10 μg, amikacin 30 μg, ceftazidime 30 μg, imipenem 10 μg, aztreonam 30 μg, piperacillin-tazobactam 100/10 μg, ciprofloxacin 5 μg, trimethoprim-sulfamethoxazole 1.25/23.75 μg, cefepime 30 μg, ampicillin-sulbactam 10/10 μg, and levofloxacin 5 μg. The interpretation of antibiotic susceptibility was based on the criteria proposed by the Clinical and Laboratory Standards Institute for *A. hydrophila* complex [12].

Statistical analysis

All statistical analyses were performed by using the Statistical Analysis System (version 9.1.2; SAS Institute, Inc., Cary, NC, USA). Categorical variables were compared with the chi-squared test or Fisher's exact test. Continuous variables were analyzed with the Student *t* test. Confounding factors were adjusted by multivariate logistic regression. A 2-tailed *p* value of <0.05 was considered statistically significant.

Results

Thirty three patients with *A. sobria* complex bacteremia were included. The demographic data and underlying diseases of these patients are summarized in Table 1. Twenty two patients (66.7%) were men and the median age was 58 years (range, 28-90 years). Most patients (n = 24; 72.7%) were older than 50 years, particularly the 50 to 60 years age group (n = 11; 33.3%). Liver cirrhosis (n = 14; 42.4%) was the leading underlying disease, followed by neoplasm, except hepatoma (n = 10; 30.3%), choledocholithiasis (n = 7; 21.2%), hepatoma (n = 6; 18.2%), and diabetes mellitus (n = 5; 15.2%). Among the 10 patients with neoplasm, 6 had hematologic malignancy and 4 had solid organ tumors, including pancreatic tumor, gastric tumor, and cervical cancer. One patient had both hepatoma and transitional cell carcinoma of the ureter.

The seasonal distribution of *A. sobria* complex bacteremia is shown in Figure 1. There was a trend towards more frequent occurrence during the warmer seasons (May to September; n = 23; 66.7%). Most patients (n = 24; 72.7%) had community-acquired infection. Among these patients, 11 (45.8%) had liver

Table 1. Demographic characteristics of 33 patients with *Aeromonas sobria* complex bacteremia.

Demographic data	No. of patients (%)
Sex	
Male	22 (66.7)
Female	11 (33.3)
Age (years)	
>50	24 (72.7)
50-60	11 (33.3)
Acquisition	
Community	24 (72.7)
Nosocomial	9 (27.3)
Warm season distribution (May to September)	23 (66.7)
Underlying diseases	
Liver cirrhosis	14 (42.4)
Hepatoma	6 (18.2)
Neoplasm (except hepatoma)	10 (30.3)
Hematologic malignancy	6 (18.2)
Solid organ tumor	4 (12.1)
Choledocholithiasis	7 (21.2)
Diabetes mellitus	5 (15.2)
End-stage renal disease	2 (6.0)
Previous surgery[a]	8 (24.2)
Origin of infection	
Primary bacteremia	16 (48.5)
Secondary bacteremia	17 (51.5)
Biliary tract infection	7 (41.2)
Peritonitis	4 (23.5)
Necrotizing fasciitis	2 (11.8)
Pneumonia	2 (11.8)
Liver abscess	1 (5.9)
Intra-abdominal infection	1 (5.9)
Urinary tract infection	1 (5.9)

[a]Includes 4 patients (12.1%) with previous abdominal surgery.

cirrhosis, 8 (33.3%) had biliary tract diseases, and 6 (25.0%) had neoplasms. The proportion of underlying malignancies among patients with nosocomial infections was higher (n = 4; 44.4%). Only 2 patients (22.2%) in the nosocomial infection group had liver cirrhosis and 1 (11.1%) had biliary tract disease. There was no clustering of nosocomial bacteremia during the study period.

Seventeen patients (51.5%) had secondary bacteremia, among whom biliary tract infection (n = 7; 41.2%) was the most common primary infection site, followed by spontaneous peritonitis (n = 4; 23.5%), pneumonia (n = 2; 11.8%), necrotizing fasciitis (n = 2; 11.8%), liver abscess (n = 1; 5.9%), intra-abdominal infection (n = 1; 5.9%), and urinary tract infection (n = 1; 5.9%). More than half of the patients (n = 23; 69.7%) had monomicrobial bacteremia, and there was more association with neoplasm or liver cirrhosis than

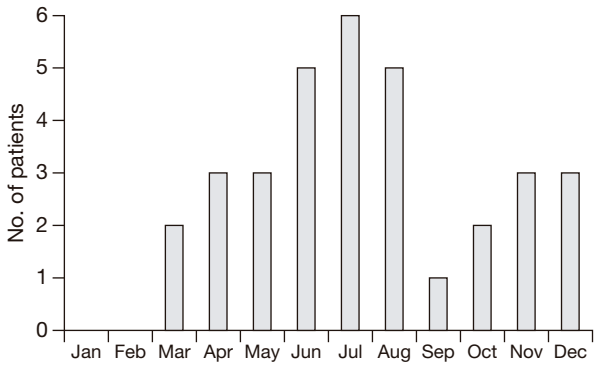

Figure 1. Monthly distribution of *Aeromonas sobria* complex bacteremia.

for those with polymicrobial bacteremia (78.3% vs 50.0%). Among patients with polymicrobial bacteremia, more biliary tract infections were noted (40% vs 13%), and concomitant bacteria included *Enterobacteriaceae*, *Enterococcus raffinosus* (n = 1), *Bacteroides distasonis* (n = 1), and *Streptococcus mutans* (n = 1). Among the *Enterobacteriaceae*, the most common isolates were *Escherichia coli* (n = 6), and *Klebsiella pneumonia* (n = 3). One of the *E. coli* isolates was an extended-spectrum β-lactamase–producing strain. All isolates were susceptible to gentamicin, amikacin, ceftazidime, cefepime, and ciprofloxacin, and 90.9% were susceptible to aztreonam and piperacillin-tazobactam, 87.9% to imipenem, and 78.8% to trimethoprim-sulfamethoxazole.

Table 2 summarizes the clinical manifestations of these patients. Fever (81.8%), jaundice (54.5%), hypotension (45.5%), and abdominal pain (39.4%) were

Table 2. Presenting signs and symptoms of 33 patients with *Aeromonas sobria* complex bacteremia

Manifestation	No. of patients (%)
Fever	27 (81.8)
Jaundice	18 (54.5)
Hypotension	15 (45.5)
Abdominal discomfort	15 (45.5)
Chills	12 (36.4)
Dyspnea	10 (30.3)
Altered consciousness	7 (21.2)
Diarrhea	7 (21.2)
Gastrointestinal bleeding	6 (18.2)
Weakness	6 (18.2)
Neutropenia[a]	5 (15.2)
Cough	5 (15.2)
Hypothermia	4 (12.1)
Abdominal discomfort	15 (45.5)

[a]Absolute neutrophil count <1000 cells/mm^3.

the most frequently encountered clinical presentations. Leukocytosis (>12,000/mm^3) was noted in 13 patients (39.4%), leukopenia (<4000/mm^3) in 10 (30.3%), and thrombocytopenia (<100,000/mm^3) in 21 (63.6%). Most patients had abnormal liver function profiles (71.9% had elevated aspartate aminotransferase levels, 80% had elevated alanine aminotransferase, 82.8% had elevated bilirubin) and elevated C-reactive protein levels (82.1%).

All but 2 patients received antibiotic treatment. The overall mortality rate was 39.4% (n = 13), with a high proportion of deaths occurring within 96 h of obtaining blood cultures (n = 6; 46.2%). The prognostic factors are listed in Table 3. Age, sex, acquisition, neoplasm (except hepatoma), diabetes mellitus, choledocholithiasis, diarrhea, and poly-/monomicrobial infection were not related to prognosis. Most of the patients who died had liver cirrhosis (n = 8; 61.5%) or neoplasms (n = 4; 30.8%). A lower incidence of these 2 underlying diseases was recorded among the patients who survived (liver cirrhosis, 6/20 [30%]; neoplasm: 5/20, [25%]; total: 11/20 [55%]). There were a statistically significant differences in rates of liver cirrhosis and neoplasm between patients who died and those who survived (92.3% vs. 55%; $p < 0.05$). Other prognostic factors associated with mortality by univariate analysis were hypotension, altered consciousness, peritonitis, and impaired renal function (creatinine, ≥1.4 mg/dL).

Table 3. Prognostic factors for patients with *Aeromonas sobria* complex bacteremia.

Characteristic	Fatality (n = 13) No. (%)	Survival (n = 20) No. (%)	*p*
Age (years)			
≤60	7 (53.9)	13 (65.0)	0.5217
>60	6 (46.2)	7 (35.0)	
Sex			
Male	8 (61.5)	14 (70.0)	0.7136
Female	5 (38.5)	6 (30.0)	
Acquisition			
Community	9 (69.2)	15 (75.0)	1.0000
Nosocomial	4 (30.8)	5 (25.0)	
Underlying diseases			
Neoplasm[a]	4 (30.8)	5 (25.0)	0.9625
Liver cirrhosis	8 (61.5)	6 (30.0)	0.0733[b]
Neoplasm[a] or liver cirrhosis	12 (92.3)	11 (55.0)	0.0495[c]
Diabetes mellitus	1 (7.7)	4 (20.0)	0.6253
Choledocholithiasis	1 (7.7)	6 (30.0)	0.2018
Origin of infection			
Primary bacteremia	6 (46.2)	10 (50.0)	0.8290
Secondary bacteremia	7 (53.9)	10 (50.0)	0.8290
Biliary tract infection	0 (0)	7 (35.0)	0.0266[c]
Peritonitis	4 (30.8)	0 (0)	0.0175[c]
Necrotizing fasciitis	1 (7.7)	1 (5.0)	1.0000
Pneumonia	2 (15.4)	0 (0)	0.1477
Symptoms and signs			
Hypotension	10 (77.0)	5 (25.0)	0.0034[b,c]
Altered consciousness	6 (46.2)	1 (5.0)	0.0084[c]
Diarrhea	2 (15.4)	5 (25.0)	0.6756
Laboratory data			
Renal function impairment (creatinine, ≥1.4 mg/dL)	11 (84.6)	5 (25.0)	0.0008[b,c]
Polymicrobial infection	4 (30.8)	6 (30.0)	0.9625
Monomicrobial infection	9 (69.2)	14 (70.0)	0.9625
Death within 4 days by antibiotic treatment			
Adequate	1 (14.3)		0.0291[c]
Inadequate	5 (83.3)		

[a]Except hepatoma.

[b]Multivariate analysis.

[c]Univariate analysis.

Table 4. Comparison of patients who died according to antibiotic treatment.

Time to death (days)	Inadequate antibiotic treatment (n = 6)	Adequate antibiotic treatment (n = 7)	*p*
<4	5 (83.3)	1 (14.3)	0.0291[a]
≥4	1 (16.7)	6 (85.7)	

[a]Univariate analysis.

Biliary tract infection was associated with a better prognosis. By multivariate logistic regression, only renal impairment (odds ratio [OR], 81.2; 95% confidence interval [CI], 2.4->999.9; $p = 0.0140$), hypotension (OR, 40.0; 95%CI, 2.0-782.0; $p = 0.0150$), and liver cirrhosis (OR, 26.8; 95% CI, 1.0-703.6; $p = 0.0483$) were statistically significant independent prognostic factors.

Among the patients who died, those who did not receive appropriate antibiotic treatment had a more fulminant clinical course than those given adequate antibiotics; the mean days to death were 4.67 days and 15.57 days, respectively ($p = 0.048$). Among the patients who died who did not receive appropriate antibiotic treatment, most (83.3%) died within 4 days of the onset of symptoms compared with 14.3% of patients who died who were given adequate antibiotics ($p = 0.0291$) [Table 4].

Discussion

Aeromonas bacteremia is a relatively uncommon disease, comprising only 1.8% of all cases of Gram-negative bacilli bacteremia [13]. Of the *Aeromonas* spp., *A. sobria* is the second most common organism isolated in most reports after *A. hydrophila* [4,8,14]. *A. sobria* was more virulent than either *A. hydrophila* or *A. caviae* in an animal study [9].

In this study, most patients with *A. sobria* complex bacteremia were men and older than 50 years, these observations are similar to previous reports [4,6,8,15-17]. As in other series of *Aeromonas* infections [4,15], most patients acquired the infection in the community, and there was a trend towards case distribution in the warmer seasons (66.7%). In other studies, liver cirrhosis and neoplasm were the most common underlying diseases [4,6,8,14,15], which is similar to the observations from this study. In patients with community-acquired disease in this study, liver cirrhosis was the leading underlying disease (45.8%), and malignancy, except hepatoma, (44.4%) was the leading underlying disease in the nosocomial infection group. These disease patterns are similar to other studies [6,8,15].

The percent of patients in this study presenting with fever, hypotension, or jaundice is similar to previous studies [4,14-16]. In contrast to other studies [4,8,14-16], diarrhea (21.2%) was a more frequent presenting symptom. One possible explanation of this high incidence of diarrhea in patients with *A. sobria* complex bacteremia might be virulence factors such as cytolytic enterotoxin and hemolysin in these pathogens [18,19].

As reported by Ko et al, secondary bacteremia accounted for most cases of *A. sobria* bacteremia (51.5%) [6]. The most frequent source of secondary bacteremia in the present study was biliary tract infection (8/17 patients; 47.1%), followed by spontaneous bacterial peritonitis (4/17 patients; 23.5%), which is different from Ko et al's study [6]. In their report, spontaneous bacterial peritonitis (51.1%) was the most common major infection focus, followed by soft tissue infections. A possible explanation for this difference is that the patient population in Ko et al's study was limited to those with monomicrobial bacteremia only [6]. If the focus was primarily on patients with monomicrobial bacteremia, spontaneous bacterial peritonitis (33.3%) became the most common infection source, followed by biliary tract infection (25%). It is interesting to note that all patients with spontaneous bacterial peritonitis had monomicrobial bacteremia. Based on this study and Ko et al's [6] observations, spontaneous bacterial peritonitis should be considered in patients with monomicrobial *A. sobria* complex bacteremia. In patients with polymicrobial bacteremia, biliary tract infection should be considered. Similar to other studies [4,8,14,16], *Enterobacteriaceae*, especially *E. coli* and *K. pneumoniae*, were the commonest concomitant pathogens.

The mortality rate for *A. sobria* infection varies from 20% to 56% [4,10,14,17], which is similar to the rate of 39.4% in this study. Nearly all (92.3%) of the patients who died in this study had liver cirrhosis or neoplasm, which is different to the studies by Ko and Chuang [4] and Lau et al [8]. In their reports, only 66% to 68% of patients had liver cirrhosis or neoplasm [4,8]. A possible explanation of this dissimilarity is the different patient populations. Hypotension, impaired renal function, and liver cirrhosis were

additional prognostic factors in this study, and these prognostic factors have also been described in other studies [4,6]. Furthermore, 46.2% of deaths occurred within 96 h of obtaining blood cultures; this rate was higher (83.3%) for those patients who did not receive adequate antibiotic therapy. This fulminant clinical course has also been observed by other researchers [4,6,8,15,16]. Early and adequate antibiotic therapy may improve the patients' outcomes.

In conclusion, *A. sobria* complex bacteremia is a severe disease with a high mortality rate. Clinicians should be aware of this disease in patients with septicemia who have underlying diseases such as liver cirrhosis or neoplasms. Early and adequate antibiotic treatment may improve the outcomes, especially for patients with hypotension and impaired renal function.

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