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Outcomes of *Aeromonas* bacteremia in patients with different types of underlying disease

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Over a 6-year period, 42 patients with different underlying diseases developed *Aeromonas* bacteremia in our hospital. The male to female ratio was 2:1. The vast majority of these patients had underlying diseases, including various types of neoplasm (n = 14), liver cirrhosis (n = 11), biliary tract disorder (n = 10) and other illnesses (n = 7). Community-acquired bacteremia was predominant (33 cases, 79%). *Aeromonas hydrophila* was the most common species isolated (88%). Monomicrobial bacteremia was more common than polymicrobial bacteremia (64% vs 36%). Monomicrobial bacteremia was associated with neoplasm or liver cirrhosis in 80% of patients. Polymicrobial bacteremia was more common in patients with biliary tract disorder than in patients from other groups (60% vs 40%). *Escherichia coli* (60%) was the predominant concomitant organism isolated. The major clinical manifestations were fever (74%), jaundice (57%), and abdominal pain (45%). Recognized infection sites included biliary tract, soft tissue involvement, peritoneal involvement, while 50% of patients had no recognized infection site. Eight patients (80%) received cholecystectomy due to gall stone with acute cholecystitis. However, none of the cirrhotic patients with necrotizing fasciitis received surgical treatment. The mortality attributed to *Aeromonas* bacteremia was 70%. Patients with liver cirrhosis or malignancy had a higher acute mortality (death within 7 days after admission) than the other patients (89% vs 11%). We conclude that *Aeromonas* bacteremia can cause a rapidly fatal outcome and should be considered an important pathogen for septicemia in patients with liver cirrhosis or neoplasm.

Key words: *Aeromonas*, bacteremia, biliary tract disorder, liver cirrhosis, neoplasm

Aeromonas species are motile gram-negative nonspore forming bacilli with positive oxidase reaction [1]. The most common species responsible for human infection is *Aeromonas hydrophila* [2]. These organisms have wide natural distribution and cause diseases in both marine and warm-blooded animals [1]. Various studies have shown that these bacteria are responsible for opportunistic infections in immunocompromised patients such as those with malignancy, liver cirrhosis, and uremia undergoing hemodialysis [3-5]. The spectrum of human diseases caused by *Aeromonas* species includes gastroenteritis, cellulitis, necrotizing fasciitis, meningitis, bacteremia, and peritonitis [2]. Recently, new syndromes related to this genus have been identified including hemolytic uremic syndrome, burn-associated sepsis, and a variety of respiratory tract infections, including epiglottitis [2]. The various clinical manifestations are associated with the severity of underlying disease. Most *Aeromonas* infections in healthy persons are self-limited, but those in patients with immunocompromised condition are frequently associated with significant morbidity and mortality. The aim of this retrospective study was to compare the outcome of *Aeromonas* septicemia among patients with various underlying conditions.

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Patients and Methods

The medical charts of all cases of bacteremia due to *Aeromonas* species treated during a 6-year period from January 1994 to December 1999 at Tri-Service General Hospital, a 1400-bed teaching hospital in Taipei, were reviewed. Blood cultures were performed by means of BacT/Alert 240 (Organon Teknika Corp., Durham, USA). Positive blood cultures were subcultured on CNA (colistin-nalidixic acid) agar, heated (chocolated) blood agar and MacConkey agar. Isolated colonies on culture media were initially subjected to oxidase test and followed by analysis a commercial kit, the Vitek GNI system (Vitek Systems, Hazelwood, MO, USA). The

biochemical profiles were finally confirmed by standard biochemical manual methods [1].

Definitions

The following predefined criteria were used in the retrospective case review.

Onset of bacteremia was defined as the date when the first positive blood culture was obtained. Bacteremia was defined as nosocomial in origin if the blood culture was obtained at least 3 days after the time the patient was admitted to the hospital. Otherwise, the bacteremia was considered community acquired. Bacteremia was categorized as polymicrobial if microorganisms other than *Aeromonas* species were recovered in the blood cultures. Neutropenia was defined as an absolute neutrophil count less than 500 x 10^9/L at the time the specimen was collected. Septic shock was defined as a systolic blood pressure of less than 90 mmHg within 3 days of, prior to, or on the day of the specimen with a positive blood culture was collected. A cirrhotic patient was considered to have spontaneous bacterial peritonitis when at least two of the following criteria were met: an ascitic leukocyte count more than 500/mm^3, symptoms or signs of peritonitis, and a positive result of ascitic culture. The Child-Pugh score was used to assess the severity of the decompensation of hepatic function in cirrhotic patients.

Acute mortality was defined as death within 7 days after admission. When the *Aeromonas* bacteremia was the main cause of death, mortality was defined as directly related. If the patient died more than 1 month later after the *Aeromonas* bacteremia, the mortality was considered unrelated to *Aeromonas* bacteremia, and the cause of death was categorized as indirectly related. The Chi-square test was used for the comparison of proportions.

Results

The medical records of a total of 42 patients with *Aeromonas* bacteremia, treated during the 6-year from January 1994 to December 1999, were reviewed. These patients were divided into four clinical groups on the basis of their underlying illnesses as follows: group I, neoplasm; group II, liver cirrhosis; group III, biliary tract disorder; group IV, other illnesses. Patients with malignancy involving the biliary tract were categorized in group I. The outcome was analyzed based on these groups.

Demographic features

The age of patients ranged from 35 years to 89 years (mean, 62 years). A male predominance (2:1) was noted. Among the cirrhotic patients, 91% were aged less than or equal to 60 years. Of the 42 cases, 33 (79%) were community-acquired and nine (21%) were nosocomial infection. Of the 20 patients (61%) with community-acquired *Aeromonas* bacteremia, 11 had liver cirrhosis and 10 had biliary tract disorder.

Underlying diseases

Table 1 summarizes the predisposing underlying conditions of the 42 patients. Eight had hematologic malignancy and six had solid organ tumor. One patient with pancreatic carcinoma and one with cholangiocarcinoma had biliary obstruction. Decompression of biliary obstruction was achieved by percutaneous transhepatic biliary drainage after admission in both of these patients. Liver cirrhosis was noted in 11 patients (26%) and biliary tract disorder in 10 patients (24%). Six patients had other types of underlying disease and these patients had no obvious source of infection. One patient with no evidence of underlying disease presented with *A. hydrophila* liver abscess which was confirmed by blood and abscess culture. Percutaneous transhepatic abscess drainage was performed after admission in this patient.

Clinical characteristics

The most common clinical features were fever (74%), jaundice (57%), abdominal pain (45%), septic shock

Table 1. Underlying diseases in 42 patients with *Aeromonas* bacteremia

Underlying disease	No. of cases (n = 42)
Liver cirrhosis	11
Biliary tract disorder	10
with gall stone	9
without gall stone	1
Hematologic malignancy	8
Acute lymphocytic leukemia	1
Acute myelocytic leukemia	4
Chronic lymphocytic leukemia	1
Non-Hodgkin's lymphoma	2
Solid organ tumor	6
Pancreatic carcinoma	1
Breast carcinoma	1
Tongue carcinoma	1
Cholangiocarcinoma	1
Ovary carcinoma	1
Gastric carcinoma	1
Other illnesses	7
Cardiac disease	2
Uremia with hemodialysis	2
Trauma	1
Colon polyposis	1
None identified	1

(45%), dyspnea (12%) and diarrhea (12%). Seven patients received chemotherapy before the bacteremic episode and two had neutropenia at the time of onset of *Aeromonas* septicemia. All patients with consciousness disturbance had liver cirrhosis. Seven patients, two with neoplasm and five with liver cirrhosis, had soft tissue infection. Among the cirrhotic patients with soft tissue infection, four had necrotizing fasciitis with hemorrhagic bullae at admission. Two patients with liver cirrhosis had spontaneous bacterial peritonitis. Acute esophageal varices hemorrhage occurred in five cirrhotic patients. The clinical characteristics of the 11 cirrhotic patients are shown in Table 2. Jaundice, right upper quadrant pain and fever were the most common manifestations in patients with biliary tract disorder. No infection site was identified in 50% of the patients.

Bacteriologic features

A. hydrophila was the predominant species isolated (88%), followed by *Aeromonas* spp. (10%) and *Aeromonas sobria* (2%) (Table 3). Monomicrobial bacteremia (64%) was more common than polymicrobial bacteremia (36%). Monomicrobial bacteremia was associated with neoplasm or liver cirrhosis in 80% (21/27) of the patients. Polymicrobial bacteremia was often found in 60% (9/15) of the patients with biliary tract disorder. Most (93%) of the concomitant organisms belonged to the *Enterobacteriaceae*. Organisms isolated in conjunction with *Aeromonas* were *Escherichia coli* (n = 9), *Klebsiella pneumoniae* (n = 3), *Citrobacter freundii* (n = 2), and glucose nonfermenting gram-negative bacilli (n = 1).

Therapy and outcome

Group III patients received cholecystectomy due to gall stone with acute cholecystitis in 80% of the cases. One patient developed the complication of gall bladder empyema, and his condition was improved after early surgical treatment. All patients with biliary tract disorder received first generation cephalosporins and aminoglycosides and recovered uneventfully. Patients in other groups received a combination of aminoglycoside and an extended-spectrum cephalosporin for *Aeromonas* septicemia. The overall mortality rate was 64% (27/42). Nineteen patients (70%) died within 7

Table 2. Clinical characteristics of 11 cirrhotic patients with *Aeromonas* bacteremia

Case no.	Age/sex	Etiology of liver disease	Associated infection	Child-Pugh class	Esophageal varices bleeding	Outcome (days from admission to death)
1	39/M	Chronic hepatitis B	Cellulitis, bilateral legs	B	No	Died (36)
2	37/M	Chronic hepatitis B	SBP[a]	C	No	Survived
3	55/F	Chronic hepatitis B	SBP[a]	C	No	Died (2)
4	83/F	Chronic hepatitis B	Necrotizing fasciitis with hemorrhagic bulla, bilateral legs (occurred 3 days later after admission)	B	No	Died (4)
5	46/M	Alcoholism	Primary[b]	C	Yes	Died (2)
6	42/M	Alcoholism	Necrotizing fasciitis with hemorrhagic bulla, right leg	C	Yes	Died (2)
7	56/M	Alcoholism	Primary[b]	C	No	Died (1)
8	59/M	Alcoholism	Primary[b]	C	Yes	Died (5)
9	43/M	Alcoholism	Necrotizing fasciitis with hemorrhagic bullae, bilateral legs	C	Yes	Died (3)
10	46/M	Alcoholism	Necrotizing fasciitis with hemorrhagic bulla, right leg	C	Yes	Died (2)
11	31/F	Glycogen storage disease	Primary[b]	C	No	Died (3)

[a]Spontaneous bacterial peritonitis.
[b]Primary *Aeromonas* bacteremia with unknown infectious site.

Table 3. Organisms isolated in 42 patients with *Aeromonas* bacteremia with different types of underlying diseases

	Neoplasm (n = 14)	Liver cirrhosis (n = 11)	Biliary tract disorder (n = 10)	Other illness (n = 7)	Total (n = 42)
Monomicrobial (n = 27)					
A. hydrophila	9	10		5	24
A. sobria	1				1
Aeromonas spp.		1	1		2
Polymicrobial (n = 15)					
A. hydrophila	3		8	2	13
A. sobria					0
Aeromonas spp.	1		1		2
Other bacteria isolated (n = 15)					
E. coli	1		8		9
K. pneumoniae	1			2	3
C. freundii	1		1		2
Nonfermentive gram-negative bacilli	1				1

Table 4. Outcome of monomicrobial and polymicrobial *Aeromonas* bacteremia

Group[a]	No. of cases	Death within 7 days after bacteremia	Death more than 1 month after bacteremia[b]	Survived 1 year after bacteremia
Group I				
Monomicrobial	10	7	3	0
Polymicrobial	4	1	3	0
Group II				
Monomicrobial	11	9	1	1
Polymicrobial	0	0	0	0
Group III				
Monomicrobial	1	0	0	1
Polymicrobial	9	0	0	9
Group IV				
Monomicrobial	5	2	0	3
Polymicrobial	2	0	1	1

[a]Group I: neoplasm, Group II: liver cirrhosis, Group III: biliary tract disorder, Group IV: other illnesses.
[b]Death does not relate to *Aeromonas* bacteremia.

days after the *Aeromonas* bacteremia (Table 4). Eight patients died more than 1 month after the *Aeromonas* bacteremia because of their underlying diseases. The acute mortality of patients with malignancy or liver cirrhosis was significantly higher than that of the patients in the other groups (68% vs 12%, $p = 0.0007$). The acute mortality of patients with monomicrobial bacteremia was higher than that of patients with polymicrobial bacteremia (67% vs 7%, $p = 0.0001$).

Discussion

As previous studies have reported [3,6], the vast majority (98%) of our patients with *Aeromonas* septicemia had an underlying disease, most frequently including various types of neoplasm (n = 14; 33%), liver cirrhosis (n = 11; 26%) and biliary tract disorder (n = 10; 24%). Other less frequent underlying diseases included uremia (n = 2; 5%), cardiac disease (n = 2; 5%), trauma (n = 1; 2%), and other types of gastrointestinal diseases (n = 2; 5%). In contrast to previous studies [3,7], neoplasm (33%) was more common than cirrhosis of the liver (26%) in our series. Thirty-three cases (79%) of *Aeromonas* bacteremia were community-acquired. Unlike some previously described patients with community-acquired infection who had antecedent trauma or recent exposure to freshwater [9], only one patient in our series who had head injury but without soft tissue infection and none of the 33 patients with community-acquired bacteremia had been exposed to fresh or salt water or consumed undercooked seafood.

Nine patients (21%) acquired their infections after being hospitalized for periods ranging from 5 days to 2 weeks. Although *A. hydrophila* has been isolated from the water supplies in hospital [10,11], the sources of nosocomial *Aeromonas* bacteremia were unclear in this retrospective study.

There are currently 14 named species of *Aeromonas*, but only five (*A. hydrophila*, *A. caviae*, *A. veronii*, *A. jandaei*, and *A. schubertii*) are of major clinical importance [2]. *A. hydrophila* (88%) was the predominant species among clinical isolates in our series. Some investigators reported that *A. hydrophila* was most often monomicrobic and associated with less serious underlying disease [12]. However, in our series, 100% of liver cirrhosis patients with *Aeromonas* septicemia were monomicrobic and the acute mortality in these patients was 82%. The virulence factors of the infecting strain and the immunologic status of the host may be more important than the infectious dose in the outcome of *Aeromonas* septicemia [13]. Several potential virulence factors elaborated by *Aeromonas* spp. from patients with bacteremia have been described, including cytotoxin, hemolysin and cholera toxin-like factor [14]. The key factors regulating invasion from the gastrointestinal tract have not been identified. Some factors such as resistance to complement-mediated lysis, elevated levels of protease and hemolysin activity, and the ability to elaborate siderophores were correlated with a higher virulence [13].

Recent advances in antineoplastic agents and general supportive care have contributed to the survival of patients with neoplasm. However, in parallel with the adoption of these new techniques, the incidence of opportunistic infections has greatly increased in these compromised hosts. In this series, of the 14 patients with neoplasm, eight had hematologic malignancy, and six had solid tumors. All patients with hematologic malignancy had undergone several courses of cancer chemotherapy but none of them were in remission. Primary *Aeromonas* bacteremia is a common manifestation of patients with neoplasm. The portal of entry or the exact pathogenesis of *Aeromonas* bacteremia is uncertain. Drugs used in cancer chemotherapy are often toxic to the gastrointestinal mucosa, causing ulceration and increased permeability. In addition to a deficiency in the number of neutrophils, depression in polymorphonuclear leukocytes secondary to cytotoxic chemotherapy and the lack of specific opsonizing antibody were the possible factors in the development of *A. hydrophila* infection [15]. In a previous study, autopsy revealed ulcerative lesions of the gastrointestinal tract but *Aeromonas* organism was not identified [16]. Despite the possible gastrointestinal source, only three patients in our series presented with diarrhea. Gastroenteritis caused by *Aeromonas* species has been described [17], but there is controversy as to whether this species is a normal part of the human stool flora. *Aeromonas* species are uncommon (4.2-5%) in routine stool specimens [18-19]. Although a number of studies reported that *Aeromonas* bacteremia was common in cancer patients, few of these studies performed stool culture before or at the same time of bacteremia [20-21]. In one report of three cases of *Aeromonas* septicemia in patients with leukemia, fecal cultures were negative for the organism [22]. Therefore, it is presently unclear whether the gut is the portal of entry of the organism. Further studies to determine the portal of entry of *Aeromonas* are needed.

Ko and Chuang reported that the 36% of patients with *Aeromonas* bacteremia had hepatic cirrhosis [3]. Among the 12 cirrhotic patients in their series, the common manifestations were spontaneous bacterial peritonitis, altered mental status, and jaundice [3]. Kuo *et al* demonstrated that fever and melena were also the common presentations of *Aeromonas* infection in cirrhotic patients [23]. Conn reported that two patients with *Aeromonas* sepsis and peritonitis had evidence of obstructive biliary tract disease [24]. In our study, all cirrhotic patients (n = 11) were febrile and had jaundice, and half of these patients had altered mental status while none of them had evidence of obstructive biliary tract disease. All of our cirrhotic patients were monomicrobial and had community-acquired bacteremia similar to the findings of a previous report [3]. The reason of why cirrhotic patients are more susceptible to severe forms of *Aeromonas* infection is not known. In patients with liver cirrhosis, the presence of portal hypertension, defective function of hepatic reticuloendothelial system, bowel wall congestion and inflammation can lead to significant degeneration of the intestinal mucosa. Under these circumstances, intestinal bacteria can easily invade the bloodstream and cause bacteremia. It is suggested that hematogenous spread from the gastrointestinal tract is the cause of spontaneous bacterial peritonitis [24].

Various clinical presentation of skin and soft tissue infections has been described in patients with *Aeromonas* sepsis [9]. In immunocompromised hosts, soft tissue infection and sepsis have occurred even in cases without skin lesion at the initial presentation. One of our cirrhotic patients presented a hemorrhage bulla and leg edema 3 days after admission. The lesion progressed rapidly and evolved to extensive necrotizing fasciitis. Furusu *et al* reported that the fatality rate of

A. hydrophila soft tissue infection in immunocompromised hosts was significantly higher (70%) among septicemic cases [4]. A combination of medical and surgical therapy is most often required for the successful management of *Aeromonas* soft tissue infection. However, none of our cirrhotic patients with soft tissue infection received surgical treatment. The absence of surgical treatment may have been due to two reasons. First, because the initial presentation of the soft tissue lesion was similar to cellulitis, it is likely that physicians treated it as cellulitis and were not alert to the possibility of deep soft tissue infection. Not until the lesion and the hemodynamics had deteriorated, and the risk associated with surgical intervention would be increased were these lesions properly diagnosed. Second, the presence of complications of underlying cirrhotic conditions, and also that three cirrhotic patients had acute esophageal varicose vein bleeding on admission further hindered the use of a surgical approach. All five cirrhotic patients with soft tissue infection died within 3 days and two patients with neoplasm died within 1 week after admission. Early surgical intervention is probably essential to save the life of patients with *Aeromonas* septicemia with deep soft tissue infection. Some investigators have reported that amputation saved the lives of patients with *Aeromonas* soft tissue infection [25], while others have reported patients who died eventually because of delay in removal of necrotic lesions by surgery [26].

Although the prevalence of biliary sepsis caused by *Aeromonas* species is very low (< 3%) [27], patients with impaired hepatobiliary function secondary to cholelithiasis and cholangiocarcinoma are at increased risk of developing *Aeromonas* septicemia [3,27]. Ko *et al* reported five out of 58 patients with *Aeromonas* infection had cholelithiasis and three had cholangiocarcinoma [3]. All 10 patients of our series with biliary tract disorder had gall bladder stones, one of whom had cholangiocarcinoma and one pancreatic carcinoma. The source of *Aeromonas* in biliary sepsis is often thought to be in the gastrointestinal tract [28]. Despite of the same endogenous gastrointestinal origin, the reason for different bacteremic patterns in different clinical settings, monomicrobial bacteremia occurred among the patients with neoplasm or liver cirrhosis and polymicrobial bacteremia in biliary tract infection, was still unclear. The complication of *Aeromonas* septicemia secondary to biliary tract infection was very rare [29]. Chan *et al* reported only 10% mortality of *Aeromonas* infection in biliary sepsis and all deaths were related to terminal malignancy or end-stage hepatic failure [27]. The results obtained by Chan *et al* and also in this series indicate that prompt drainage of biliary obstruction or surgical intervention in combination with appropriate antibiotic is most effective for the management of the *Aeromonas*-associated biliary sepsis.

In this series, even with early use of the combination of an extended-spectrum cephalosporin and an aminoglycoside and intensive supportive care, the course of *Aeromonas* bacteremia in immunocompromised patients was fulminant. Among the patients with liver cirrhosis or neoplasm, acute mortality due to *Aeromonas* septicemia (68%) was higher than in previous studies (28%-50%) [3,5-7,16]. This probably reflects the advanced stage and more severity of the disease in our series of patients.

This study has clearly demonstrated that the mortality rate of *Aeromonas* bacteremia was significantly different in patients with different underlying conditions. *Aeromonas* must be included in the differential diagnosis of septicemia, especially in patients with liver cirrhosis and neoplasm.

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