Bacteremia Caused by *Aeromonas hydrophila* Complex in the Caribbean Islands of Martinique and Guadeloupe

Patrick Hochedez,* Emilie Hope-Rapp, Claude Olive, Muriel Nicolas, Gilles Beaucaire, and André Cabié

*Department of Infectious and Tropical Disease, and Department of Bacteriology, Fort de France Teaching Hospital, Martinique, France;
Department of Infectious and Tropical Disease, and Department of Bacteriology, Pointe à Pitre Teaching Hospital, Guadeloupe, France*

Abstract. *Aeromonas* species are Gram-negative bacilli of the water environment whose survival appears facilitated by warm climates. There have been no reports on *Aeromonas hydrophila* complex (*A. hydrophila*, *A. caviae*, *A. veronii*) in the Caribbean to date. Our aim was to describe clinical and bacteriological features in patients presenting with such bacteremia in Martinique and Guadeloupe. During a 14-year period, we retrospectively identified 37 patients. The mean age was 55 years and in 89% of cases underlying disease such as digestive diseases, cutaneous wounds, and malignancy were identified. One case was related to severe strongyloidiasis and one with snake bite. Polymicrobial bacteremia was identified in 38%, essentially with *Enterobacteriaceae*. All *Aeromonas* isolates were resistant to amoxicillin but extended-spectrum beta-lactam and fluoroquinolone were active against more than 95%. During hospitalization 10 patients died (27%). Older age, occurrence of multiorgan failure, and impaired renal function were associated with in-hospital mortality.

INTRODUCTION

Aeromonas species are oxidase-positive, flagellated non-sporulating Gram-negative bacilli with facultative anaerobic metabolism whose natural habitat is freshwater and brackish water.[1] Isolates have been recovered from lakes, rivers, fish tanks, swimming pools, soil, tap water including hospital water supplies, and foods. Although discovered over 100 years ago and being associated with fish, reptile, and amphibian pathogens for a long time, their role in human infection has been proven only in the last three decades and is still subject to debate in gastroenteritis. The three most common human infections caused by *Aeromonas* species are gastrointestinal infection, skin and soft-tissue infection, and bacteremia in immunocompromised individuals.[1,2] It has also been implicated as a cause of peritonitis, cholangitis, meningitis, septic arthritis, osteomyelitis, myositis, ocular infections, urinary tract infections, pneumonia, and hemolytic uremic syndrome.[1,3]

Warm climates are favorable to the survival of *Aeromonas* species in the environment and numerous series of *Aeromonas* bacteremia published in the literature report cases, which occurred in tropical and subtropical countries.[1,4–7] Among the different *Aeromonas* species recognized as human pathogens, the three species mainly isolated during septicaemia belong to the *Aeromonas hydrophila* complex: *A. hydrophila*, *A. veronii*, and *A. caviae*.[1] *Aeromonas hydrophila* is predominantly isolated in monomicrobial bactaeraemia, followed by *A. veronii* and *A. caviae*.[4,8] There have been several reports on *Aeromonas* bacteremia from Asia and the United States but none to date in the Caribbean.[4,8] Our primary objective was to describe clinical, bacteriological, and epidemiological features of bacteremia caused by *A. hydrophila* complex in the Caribbean islands. We describe a series of 37 bacteremia, which occurred in the French Caribbean islands of Martinique and Guadeloupe, and report on underlying diseases, antibiotic susceptibility testing, and factors associated with death.

MATERIALS AND METHODS

Cases of bacteremia caused by *A. hydrophila* complex from January 1995 to May 2009 were identified from the records of blood cultures in the Microbiology Laboratory of the Fort-de-France Teaching Hospital, Martinique and from the Pointe-à-Pitre Teaching Hospital, Guadeloupe. Microbiologic and clinical data collection took place in 2009. Hospitals microbiology laboratory databases were reviewed to determine the number of *Aeromonas* species bacteremia and gram-negative bacteremia during the study period. The bacteremia were detected by the automated blood culture BACTEC 9240 (BD; Franklin Lakes, NJ) or BACTALERT (BIOMERIEUX, France). Both patients with bacteremia solely caused by *A. hydrophila* complex and those presenting with polymicrobial bacteremia were included in the study. The patient was diagnosed to have a polymicrobial infection if microorganisms other than *Aeromonas* spp. were also isolated in the same blood culture. Bacteremia caused by *A. hydrophila* complex (*A. hydrophila*, *A. veronii*, and *A. caviae*) were identified by the positive oxidase test, glucose fermentation, salt tolerance, motility, and phenotypic characteristics studied by the API 20NE system (BIOMERIEUX; Marcy-I'Etoile, France) or Neg Non-Fermenter Combo Panel Type 48 system (MICROSCAN WALKAWAY; SIEMENS, Deerfield, IL). Antimicrobial susceptibilities of all isolates were determined by the disk diffusion methods described by the Antibiogram Committee of the French Society for Microbiology.[9] The inhibition zone diameters of each drug for each isolate were determined after overnight incubation at 35, 8°C in ambient air. The interpretive criteria of inhibition zone and minimum inhibitory concentrations (MICs) were in accordance with those of the Antibiogram Committee of the French Society of Microbiology.

Data on clinical and demographic characteristics were obtained retrospectively by review of patient medical records. Underlying diseases, clinical presentation, and laboratory test results, bacterial identification in cases of multiple bacteremia, antimicrobial susceptibilities, antibiotic regimen, clinical outcome, and the cause of death were also recorded. Cases were identified as community-acquired if the infection was present at the time of admission or became evident within 72 h after admission. Healthcare-associated infections were defined as the bacteraemic episodes detected at least 72 h after

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* Address correspondence to Patrick Hochedez, Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Fort de France, BP 632, 97261 Fort de France, Martinique, France. E-mail: patrick.hochedez@chu-fortdefrance.fr

admission in patients without signs and symptoms of infection at the time of admission. Subsequent isolation of *A. hydrophila* complex strains during the therapy of bacteremia was also recorded with the information about antimicrobial susceptibilities to detect emergence of resistant strains during treatment. The focus of infections was determined on the basis of clinical findings or bacterial culture results. Primary bacteremia was defined as septicaemic episodes without any concomitant attributable focus of infections. The choice of antibiotic regimen was at the discretion of the attending clinicians. Antimicrobial regimens given before the results of susceptibility tests that became available were defined as empirical. Antimicrobial regimens subsequently adjusted according to the susceptibility data were defined as definitive. Appropriate antibiotics were those which had demonstrable *in vitro* activity against the causative strains and were given for at least 72 h. The endpoint was survival or death during the hospitalization consequent to the positive blood culture. Death resulting from *Aeromonas* bacteremia without any concomitant events other than septicaemia was considered as directly related to the bacteremia; otherwise, they were not considered as directly related to bacteremia.

For comparison of categorical variables, the χ^2 test or two-tailed Fisher's exact test was used, and Student's *t* test was used for continuous variables. A *P* value < 0.05 was considered to be statistically significant.

RESULTS

During the 14-year period over which data were collected, there were 41 episodes of bacteremia caused by *A. hydrophila* complex in 41 patients. With the exclusion of four cases whose medical records were incomplete, this study included 37 cases. In total, 25,625 bacteremia were identified during the study period and among them 12,266 Gram-negative bacilli bacteremia in Martinique and Guadeloupe. Overall, bacteremia caused by *A. hydrophila* complex accounted for 0.3% of Gram-negative bacilli bacteremia.

Patients with bacteremia caused by *A. hydrophila* complex ranged in age from 19 to 87 years, with a mean age (±SD) of 54.6 years (±19). Characteristics of 37 patients are reported in Table 1. Male patients were predominant (26 cases, 70%). One or more of the three following underlying diseases were present in 33 (89%) patients: 12 (32%) had hepatobiliary or pancreatic diseases, 12 presented with a recent trauma or wound (32%), and 11 were immunocompromised by malignant neoplasia or human immunodeficiency virus (HIV) infection (30%). Two of those 33 patients have two underlying diseases, namely hepatobiliary diseases associated with trauma or immunosuppressive condition. In particular, liver and pancreatic diseases resulting from chronic alcohol-related hepatopathy were present in eight patients. Three patients had hepatic cirrhosis and one patient had acute alcohol-related pancreatitis. Both conditions were present in two patients. The last patient presented with rapid-onset abdominal pain with signs of inflammation related to a massive *Strongyloides stercoralis* infestation. Trauma and wounds were related to six car accidents, two falls, one knife injury, one diabetic chronic ulceration, one snake bite, and one catheter-related infection in a pregnant woman. Malignant neoplasia were solid cancer in five cases (stomach for two, bladder, pancreas or disseminated for one each) leukemia in two cases, lymphoma in two cases,

Characteristics of 37 patients with bacteremia caused by *Aeromonas hydrophila* complex*

Age (mean ± SD)	54.6 years (±19)
Male sex	26 (70%)
Warm season (May–October)	17 (46%)
Underlying diseases	
Recent trauma or wound	12 (32%)
Hepatobiliary or pancreatic diseases	12 (32%)
Chronic immunosuppressive condition (malignancy or HIV infection)	11 (30%)
Length of time from initial presentation at hospital to *A. hydrophila* complex bacteremia (median)	2 [range 1–38]
Community-acquired infections	27 (73%)
Bacteremia detected within 72 h	20 (54%)
Accompanying infection focus (bacteriologically confirmed)	12 (32%)
Skin	7
Urine	3
Lungs	2
Polymicrobial bacteremia	14 (38%)
A. hydrophila complex and *Enterobacteriaceae*	10
Appropriate initial antibiotic therapy	26 (72.2%)

* HIV = human immunodeficiency virus.

idiopatic bone aplasia and multiple myeloma in one case each. One patient had HIV infection. Only four patients (11%) had either hepatobiliary disease, recent trauma, or chronic immunosuppressive condition. There was one pregnant woman, two patients had ischemic arterial diseases of the lower limbs (one of them had also diabetes mellitus) and one had prostatic adenoma. However, diabetes mellitus and pregnancy should be seen as immunocompromised states albeit transiently. Overall, four patients had diabetes mellitus.

The length of time from initial presentation at the hospital to bacteremia, caused by *A. hydrophila* complex, ranged from 1 to 38 days (median 2 days). Twenty-seven (73%) cases were considered as community-acquired, of whom 20 (54%) had their bacteremic episodes detected within 72 h. The seven others had their bacteremic episodes detected after 72 h but presented with environmental-associated traumatic wounds with clinical signs of infection at the time of admission. Cutaneous samples were available for three of these seven patients and were positive for *A. hydrophila* complex. For the 10 other patients, underlying diseases such as chronic hepatopathy or malignant neoplasia were present. No clustering of cases was noted during hospitalization in the study period. Clinical presentation for the 37 patients is reported in Table 2. The five most common symptoms were fever, asthenia, chills, anorexia, and abdominal pain. The median temperature was 39° [35.5–40]. Concerning the two patients with bloody diarrhea, both of them had alcohol-related hepatic cirrhosis and bloody diarrhea were recorded at admission, together with the bacteremia. The three main biological disorders were anemia, leucocytosis, and increased C-reactive protein (CRP). At the time of bacteremia, an accompanying infection focus was bacteriologically confirmed in 12 cases (32%) with positive *A. hydrophila* complex samples. The infection focus was cutaneous in seven cases, six patients with recent traumatic wounds and one pregnant woman with catheter-related infection. In three cases the focus of infection was urinary: one with bladder cancer, one with prostatic adenoma, and one pregnant woman who had a fetal death. Finally, the focus of infection was pulmonary for two patients: one HIV-positive patient who also had chronic alcohol-related hepatopathy and one was a traumamatic car accident.

TABLE 2
Clinical presentation of 37 patients with bacteremia caused by *Aeromonas hydrophila* complex

Clinical signs and symptoms (number of patients evaluated)	Number of cases (%)
Temperature (35)	
< 36.5	4 (11)
> 38	28 (80)
Asthenia (32)	26 (81)
Chills (30)	22 (73)
Anorexia (30)	15 (50)
Abdominal pain (33)	16 (48)
Dyspnea (31)	11 (35)
Cutaneous wounds (36)	11 (30)
Confusion (36)	9 (25)
Vomiting (34)	8 (23)
Diarrhea (32)	7 (22)
Myalgia (21)	3 (14)
Cephalagia (24)	3 (12)
Ascitis (34)	4 (12)
Shock (37)	4 (11)
Bloody stool (33)	2 (6)

Twenty-three patients (62%) had monomicrobial infection. For the 14 patients with polymicrobial bacteremia, *Enterobacteriaceae* were isolated in 10 cases (71%). The *Enterobacteriaceae* involved were *Escherichia coli* (4 cases), *Enterobacter cloacae* (4 cases), *Klebsiella pneumoniae* (3 cases), and *Morganella morganii*. The other species involved were *Acinetobacter baumannii* (2 cases), *Staphylococcus aureus* (2 cases), *Pseudomonas aeruginosa*, group B *Streptococcus*, and group D *Streptococcus* (in one case each). Antibiotic susceptibility data were available for 36 different strains of *A. hydrophila* complex isolated. All strains were resistant to amoxicillin and 85.7% and 79.4% of strains were resistant to cefazolin and cefoxitin, respectivly. Cefotaxime and ceftazidime were active against 94% of isolates, whereas piperacillin-tazobactam, ciprofloxacin, and gentamicin were active against 97% of isolates each. Cefepime and fosfomycin were active against 100% of isolates.

Except for one patient who underwent incision and drainage of an abscess related to snake bite, all other patients were treated exclusively with antibiotics. Beta-lactams antibiotics were predominantly given as empirical treatment (34 cases; 91.9%), in association with aminoglycosides in 22 cases (59.4%) and fluoroquinolones in six cases (16.2%). Overall, eight patients received empirical monotherapy, five with beta-lactam agents and three with fluoroquinolones. According to antibiotic susceptibility available for 36 strains, appropriate empirical treatment were administered in 26 cases (72.2%), including patients with multiple bacteremia. Twenty patients with an extended-spectrum cephalosporin-sensitive *A. hydrophila* complex strain received a cephalosporin empirical treatment of at least 72 h and two of them (10%) were later infected with a resistant strain of the *A. hydrophila* complex. For one patient with a spinal injury caused by a car accident and who received an appropriate empirical treatment by cefotaxime, two strains of *A. hydrophila* complex were identified at the spinal focus of infection 1 week apart. Although the first strain isolated was identical to the strain identified in bacteremia, the second, isolated after one week of cefotaxime therapy, became resistant to cefotaxime, piperacilin, and ceftazidime. This patient was secondarily successfully treated with fluoroquinolone. For a second patient with HIV infection presenting with *A. hydrophila* complex lung infection and who received an appropriate empirical treatment with ceftazidime, the strain isolated in bacteremia 1 week apart was resistant to ceftazidime, cefotaxime, and piperacilin-tazobactam. This patient was also secondarily successfully treated with fluoroquinolone.

During hospitalization, 10 patients died (27%). Prognostic factors for in-hospital mortality among 37 patients with bacteremia caused by *A. hydrophila* complex are reported in Table 3. The following data are related to these 10 patients. There were nine men and the median period for positive blood culture was 11.5 days [IQR 25–75: 5–23]. Older age, occurrence of multiorgan failure, and impaired renal function were associated with in-hospital mortality. On the other hand, none of the following factors were associated with death during hospital stay: sex, underlying disease, multiple bacteremia, antibiotic choice, or use of aminoglycoside.

DISCUSSION

This report is the first description, to our knowledge, of a series of 37 bacteremia caused by *A. hydrophila* complex in the Caribbean islands with a report on underlying diseases, antibiotic susceptibility testing, and factors associated with death. The most frequent underlying conditions were hepatobiliary and pancreatic diseases, recent trauma or wound, and malignancy. During hospitalization, the gross mortality rate was 27% and older age, occurrence of multiorgan failure, and impaired renal function were associated with in-hospital mortality.

The low proportion of bacteremia caused by *A. hydrophila* was also reported during a 5-year prospective study of blood culture positive bacteremia in Hong Kong where the incidence of *Aeromonas* bacteremia was 1.8%.[10] Although *Aeromonas* species are widespread in nature, *Aeromonas* infections seem to occur more frequently in warmer climates, either in tropical and subtropical areas or during the summer in temperate countries.[3–7] It has been suggested that persons from tropical and subtropical climates could have higher *Aeromonas*

TABLE 3
Prognostic factors for in-hospital mortality among 37 patients with bacteremia caused by *Aeromonas hydrophila* complex*

	Survivors (%) (N = 27)	Non-survivors (%) (N = 10)	P value
Male	17 (63%)	9 (90%)	0.22
Age > 60	8 (30%)	8 (80%)	**0.009**
Underlying disease			
Recent trauma or wound	11 (41%)	1 (10%)	0.12
Hepatobiliary or pancreatic diseases	7 (26%)	5 (50%)	0.24
Malignancy or AIDS	8 (29%)	3 (30%)	1
Polymicrobial bacteremia	10 (37%)	4 (40%)	1
Multi-organ failure	0	6 (60%)	**< 0.0001**
Appropriate initial antibiotic therapy	20 (77%)	6 (60%)	0.41
Use of aminoglycoside	17 (63%)	5 (50%)	0.7
Biological features (median, IQR 25–75)			
Leucocytosis (G/L)	10 [7–15]	16 [8.8–18]	0.29
Hemoglobin (g/dL)	9.1 [7.6–11.5]	9.4 [8.4–11.4]	0.51
Platelets (G/L)	162 [72–280]	131 [94–172]	0.63
Creatinine (µmol/L)	85 [69–106]	104 [103–138]	**0.04**
ALAT (IU/L)	45 [23–74]	46 [33–236]	0.67
CRP (mg/)	134 [78–257]	185 [140–291]	0.39

*AIDS = acquired immunodeficiency syndrome; IQR = interquartile range; ALAT = alanine aminotransferase; CRP = C-reactive protein.

colonization rates than in temperate regions, in relation with higher exposure to contaminated environment or food.[11,12] In our study, critical epidemiological information such as exposure to water and consumption of seafood or fish, were not available in medical files.

According to what has been reported in others series, *Aeromonas* infection occurred mainly in patients with underlying diseases, such as hepatobiliary and pancreatic diseases, recent trauma or wound, and neoplasia.[4,5,8] Although neither a specific environment study nor a systematic stool culture were performed during the study period, the source of infection was presumed to be mainly gastrointestinal or cutaneous after environmental exposure. Infection or transient colonization of the gastrointestinal tract as a source of *Aeromonas* infection has been suggested by several studies.[1,4,5] Twenty-seven (73%) cases were considered as community-acquired. There was no clustering of cases for the 10 others and the source of infection in so-called "healthcare-associated" cases is presumed to be infection or transient colonization of their gastrointestinal tract rather than hospital environment.[1,4] To our knowledge, we report the first case of bacteremia caused by *A. hydrophila* complex associated with severe strongyloidiasis. Severe strongyloidiasis is a life-threatening disseminated infection frequently associated with enteric gram-negative bacteremia. As in our case, the postulated mechanism for sepsis is transmission of enteric bacteria through the bowel wall by invading filariform larvae.[13]

Wounds are the second most common source of clinical specimens yielding *Aeromonas*, following the gastrointestinal tract.[1] The individuals may be infected after abrasion or penetrating injury that results in exposure to an environmental contaminated source, or after more severe traumas such as automobile accidents.[3,7] Meanwhile, catheter-related infections are rarely caused by *Aeromonas* species.[3] For the 12 (32%) of our patients who presented with a recent trauma or wounds, skin was considered as the probable source of infections, although confirmed by bacterial culture in only seven cases. One of those patients was infected after being bitten on the hand by a snake *Bothrops lanceolatus*, a snake of the *Viperidae* family, which is endemic to the Caribbean island of Martinique.[14] Interestingly, *A. hydrophila* wound infections have not only been reported after snake bites but after many wild animals bites, like alligator, tiger, or shark-bites in warm climate.[1,15,16]

The antibiotic susceptibility patterns of our *A. hydrophila* complex isolates are similar to those reported by others in different tropical or subtropical locations.[4,5,17] In our series, antibiotic susceptibility testing revealed that piperacillin-tazobactam, cefotaxime, ceftazidime, imipenem, gentamicin, and ciprofloxacin had the highest activity against the *A. hydrophila* complex strains isolated with greater than 90% of the strains susceptible to these antibiotics. The major mechanism of beta-lactam resistance in *A. hydrophila* are chromosomally mediated inducible beta-lactamases.[18] The use of a beta-lactamase inhibitor may not restore antibiotic susceptibility.[4,5,19] Inducible chromosomally encoded beta-lactamases mediating resistance to extended-spectrum beta-lactam agents have been reported in *A. hydrophila* as it has been reported in other Gram-negative bacilli.[20] The emergence of cephalosporin-resistant mutants from a wild-type strain during the treatment of invasive *A. hydrophila* complex infections, as reported in our series, raises concerns to the use of cephalosporins in this setting and the need of close follow-up when bacteraemic patients are treated with these drugs.[4,20] Moreover, no benefit of simultaneous administration of aminoglycosides for the clinical outcome was identified in the largest monomicrobial *Aeromonas* bacteremia series published.[4]

During hospitalization, the gross mortality rate among our patients with bacteremia caused by *A. hydrophila* complex was 27%. In recent studies, the bacteremia related mortality rate for *Aeromonas* species have been ~30% and some have reported higher mortality rates among patients with malignancy compared with those with other underlying diseases.[4,5,8,21] We were not able to determine whether death was directly associated with *Aeromonas* infection in these episodes and not able to assess the contribution of each bacteria in patients with polymicrobial infection. Our study was impaired by the small number of patients and the exclusion of four cases because of missing data and the retrospective collection of information. Finally, only older age, occurrence of multiorgan failure, and impaired renal function were the underlying condition that we identified as factors associated with death during hospital stay.

Our results and other series suggest that patients with identified bacteremia caused by *A. hydrophila* complex can be treated with extended-spectrum beta-lactam agents such as extended-spectrum cephalosporins, piperacillin-tazobactam, imipenem, or a fluoroquinolone. Clinicians should be aware of the risk of emergence of cephalosporin-resistant mutants from a wild-type strain during the treatment of invasive *A. hydrophila* complex infections. The benefit of simultaneous administration of aminoglycosides for the prevention of emergence of cephalosporin resistance during therapy remains unknown in this setting.

Authors' addresses: Patrick Hochedez and André Cabié, Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Fort de France, Fort de France, Martinique, France, E-mails: patrick.hochedez@chu-fortdefrance.fr and andre.cabie@chu-fortdefrance.fr. Emilie Hope-Rapp and Gilles Beaucaire, Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Pointe à Pitre/Abymes, Pointe-à-Pitre, Guadeloupe, France, E-mails: emilie.hope-rapp@chu-guadeloupe.fr and gilles.beaucaire@chu-guadeloupe.fr. Claude Olive, Service de Bactériologie, Centre Hospitalier Universitaire de Fort de France, Fort de France, Martinique, France, E-mail: claude.olive@chu-fortdefrance.fr. Muriel Nicolas, Service de Bactériologie, Centre Hospitalier Universitaire de Pointe-à-Pitre/Abymes, Pointe-à-Pitre, Guadeloupe, France, E-mail: muriel.nicolas@chu-guadeloupe.fr.

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