

# Clinical significance and outcome of *Aeromonas* spp. infections among 204 adult patients

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Received: 25 October 2016 / Accepted: 7 February 2017 / Published online: 3 March 2017  
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**Abstract** The objectives of this investigation were to analyze the clinical patterns, risk groups, prognostic factors, and mortality of infections caused by *Aeromonas* spp. This was a retrospective study of adult patients with *Aeromonas* spp. isolates attended at the Hospital del Mar in Barcelona, Spain, between January 2006 and December 2012. Epidemiological data, antimicrobial susceptibility, clinical patterns, underlying illnesses, type of infection, admission to the intensive care unit (ICU), number of episodes, coinfection, antimicrobial therapy, and evolution were analyzed. A total of 221 clinical samples from 204 patients were positive for *Aeromonas* spp. The mean age of the patients was 67.6 years. The main clinical form of presentation was gastrointestinal (78.4%). Malignancy was the main risk group in 69 (33.8%) patients, and 48 (23.5%) were previously healthy. Twenty-one patients (10.3%) were admitted to the ICU. Infections were acquired in the hospital in 52.5% of the patients, and 28.9% were polymicrobial. The overall mortality (after 1 year of follow-up from the first positive culture) was 26.5%. Univariate analysis identified an association between increased mortality and the following variables: age  $\geq 80$  years, hospitalization, admission to the

ICU, malignancy, extraintestinal infection, and appropriate antimicrobial therapy. In the multivariate analysis, age  $\geq 80$  years [odds ratio (OR), 4.37 [95% confidence interval (CI), 1.68–11.35;  $p = 0.002$ ]], admission to the ICU (OR, 6.59 [95% CI, 2.17–19.99;  $p = 0.001$ ]), and malignancy (OR, 3.62 [95% CI, 1.32–9.90;  $p = 0.012$ ]) were significantly associated with mortality. *Aeromonas* infections are mainly gastrointestinal. The 1-year follow-up mortality rate was high. Old age (age  $\geq 80$  years), admission to the ICU, and malignancy were identified as independent risk factors for mortality.

## Introduction

*Aeromonas* spp. are Gram-negative rods, facultatively anaerobic, oxidase-positive, and non-spore-forming. Aeromonads are essentially ubiquitous in the microbial biosphere and they can be isolated from virtually every environmental niche where bacterial ecosystems exist, such as aquatic habitats, fish, foods, domesticated pets, birds, and natural soils [1–3]. The first classifications within the *Aeromonas* genus have been determined phenotypically (phenospecies), based on growth characteristics and biochemical tests. Nevertheless, there is great difficulty in identifying the different *Aeromonas* strains on the species level by these characteristics, due to the phenotypical heterogeneity and growing number of known species. One of the biggest steps forward in the taxonomic process has been the introduction and continuous use of genotypical methods (genospecies) [3–6]. With the use of molecular methods, 96% of the clinical isolates are represented by four species: *A. caviae* (29.9%), *A. dhakensis* (25.5%), *A. veronii* (22.0%), and *A. hydrophila* (18.0%) [7].

*Aeromonas* genus microorganisms are known as etiologic agents of a wide spectrum of diseases in humans [2–4, 7–10]: gastroenteritis, skin and soft tissue infection, and bacteremia

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are the most common manifestations. Other reported infections include pneumonia, liver abscesses, peritonitis, meningitis, endocarditis, urinary tract infections, otitis media, eye infections, and osteomyelitis. Infections occur mainly in immunosuppressed hosts (basically patients with cirrhosis, diabetes, or malignancy), but they may also develop in healthy individuals [3]. The role of *Aeromonas* species in some syndromes, such as bacterial gastroenteritis, is still speculative and the subject of much debate [3, 8, 11]. However, recently, the enteropathogenic role of *Aeromonas* has been re-evaluated and demonstrated [12].

Most of the data published refer to just a single clinical manifestation associated with *Aeromonas* spp. [13–16]. Epidemiological studies are very scarce, retrospective, and restricted to a few cases [7, 15]. We present an epidemiological study, undertaken in a single institution over an extended time period, with the aim of analyzing the different clinical presentations, prognostic factors, treatments, and outcomes associated with *Aeromonas* spp. infection. Patients were followed up for 1 year after the identification of microorganisms.

## Materials and methods

### Design, background, and samples

This retrospective study was carried out at the Hospital Universitari del Mar in Barcelona, a general hospital located on the Mediterranean coast with 440 beds, which covers a population of  $\approx 450,000$  inhabitants. All adult patients (aged over 18 years) with at least one positive culture for *Aeromonas* spp. during the period between 1st January 2006 and 31st December 2012 were reviewed and investigated. Clinical samples positive for *Aeromonas* spp. were identified from the Laboratori de Referència de Catalunya database.

### Variables

The electronic medical records of all patients were examined. A specific data collection sheet was designed (Access 2010®), on which the following data were recorded: age, sex, clinical group (medical, surgical, or trauma), type of surgery (digestive tract, biliary, others), clinical form of presentation, underlying diseases, immunosuppressive treatment, isolation source, type of infections (nosocomial or community-acquired), intensive care unit (ICU) stay, number of microorganisms in the different samples analyzed, date of hospital admittance, date of hospital discharge, department of origin (outpatient consulting, emergency <48 h, hospital-admitted patient), antibiotic administered (appropriate, inappropriate, not administered), antimicrobial susceptibility tests, and clinical outcome at discharge (survivor or died for any reason). All patients were followed

up for 1 year from the first positive culture. Information on mortality in this period, new identification of *Aeromonas* in case of readmission, and the source of the *Aeromonas* isolation were extracted from electronic databases.

### Definitions

Clinical features of *Aeromonas* infections were classified into two major groups: (1) gastrointestinal: including *Aeromonas* spp. in stools and presence of acute diarrhea (acute gastroenteritis: >3 stools/day for less than 14 days) or chronic (chronic gastroenteritis: diarrhea >14 days), with or without associated symptoms (fever, abdominal pain, and/or pathological products); and (2) extraintestinal, with the following patterns, (2a) skin and soft tissue infection: *Aeromonas* spp. isolation in soft tissue abscesses, ulcers, and purulent exudate in surgical wound with pain, erythema, and edema (cellulitis, ulcers, and wound); (2b) bacteremia: *Aeromonas* spp. isolated in at least one blood culture; (2c) intraabdominal infection: *Aeromonas* spp. isolated from bile samples (cholangitis), or peritoneal exudate or intraabdominal abscess pus (peritonitis); and (2d) pulmonary infection: *Aeromonas* spp. isolation from sputum, tracheobronchial aspirate, or lung biopsy (pneumonia).

All of the patients were included in one comorbidity condition (even if they had more than one underlying illness), stratified as follows: transplant patients >> human immunodeficiency virus (HIV) infection >> hematological malignancy >> solid tumor >> autoimmune disorder >> chronic disease. Patients without underlying illnesses were classified as previously healthy. For statistical purposes, four groups were considered: malignancy, chronic disease, miscellaneous, and previously healthy.

Immunosuppressive treatment was defined as treatment with corticosteroids during the preceding 3 months, chemotherapy, or radiotherapy, or drugs administered to prevent organ rejection.

Patients who did not require hospital admission were defined as outpatients (including patients who visited the outpatient clinic or the emergency department for less than 48 h and discharged home).

*Aeromonas* spp. infection was defined as nosocomial when a positive culture was obtained 72 h after hospitalization with a clinical picture that motivated the admission different from the one related to the posterior isolation of *Aeromonas* and as community-acquired when it was identified within 72 h of hospital admission or in outpatients. Infection was judged to be polymicrobial if microorganisms other than *Aeromonas* spp. were also isolated in the same clinical sample.

Inappropriate antibiotic use was considered as the use of an antimicrobial agent ineffective against *Aeromonas* spp., while antimicrobial treatment was considered appropriate if it was active in vitro against the *Aeromonas* strain responsible for the infection and administered for at least 72 h.

## Identification of isolates to the species level and antimicrobial susceptibilities

All strains ( $n = 221$ ) were initially assigned to the genus *Aeromonas*, as they were resistant to the vibriostatic agent 0/129 (150  $\mu\text{g}$ ), Gram-negative, and oxidase-positive; they were facultative anaerobes which produce acid from glucose and mannitol but not from meso-inositol, and by lack of growth in 6.5% NaCl. Each strain was then identified to the species level by conventional methods and further verified by the ID32 GN System (bioMérieux Vitek Inc., Durham, NC, USA) or the Vitek 2 ID-GNB identification card (bioMérieux Inc., Durham, NC, USA). Antimicrobial susceptibilities of the isolates to a battery of antimicrobial agents were determined using the agar dilution method as described by the Clinical and Laboratory Standards Institute (CLSI) criteria [17]. The strains in the intermediate category were classified as resistant.

## Statistical analysis

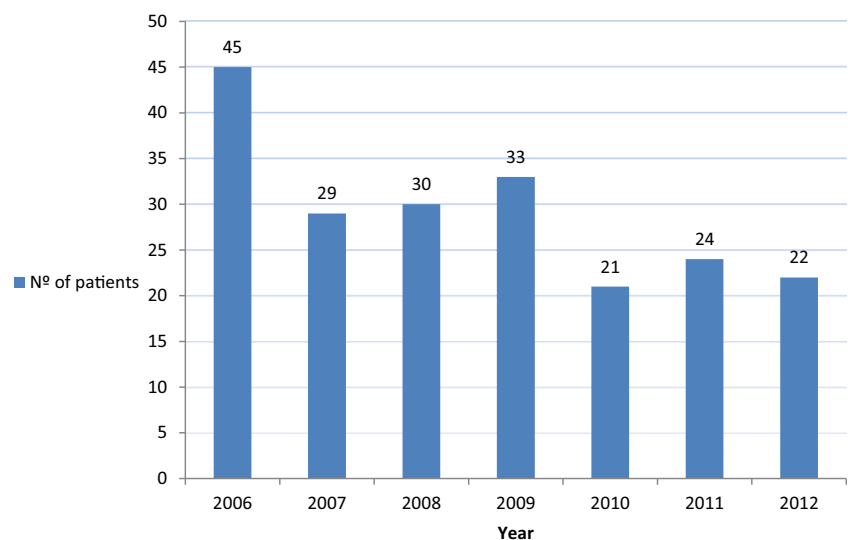
Continuous variables are reported as medians and interquartile range for non-parametric data (Wilcoxon test) or as means  $\pm$  standard deviation (SD) for variables with normal distribution (Student's *t*-test). Categorical variables were compared using the Chi-square test or Fisher's exact test, where appropriate. To identify factors associated with mortality, we first performed a univariate analyses. Variables with *p*-values  $< 0.05$  were considered as potential risk factors and candidates for the model selection process. Multivariate logistic regression modeling was performed in a stepwise manner to establish independent predictors for mortality at 1 year of follow-up from the first isolation. Statistical significance was defined as *p*-values  $< 0.05$ . Data analyses were performed using SPSS® version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

During the study period, a total of 221 clinical samples positive for *Aeromonas* spp. were identified to the phenospecies level in 204 patients. The number of patients with *Aeromonas* spp. infection identified every year are presented in Fig. 1. The clinical features of the 204 patients with *Aeromonas* spp. infection are summarized in Table 1. Gastroenteritis was diagnosed in 160 (78.4%) patients [including 101 (63.1%) patients with acute gastroenteritis and 59 (36.9%) with chronic diarrhea], peritonitis in 20 (9.8%) patients [including nine cases of secondary peritonitis, one case of spontaneous bacterial peritonitis, and nine cases of cholangitis], skin and soft tissue infection in 12 (5.9%) patients (of whom six cases with ulcers in legs and six with surgical or traumatic wound infection), bacteremia in 6 (2.9%) patients, and pneumonia in 6 (2.9%) patients. The patients ranged in age from 18 to 97 years (mean, 67.6 years). Seventy-four patients (36.3%) were aged  $< 65$  years old, 71 (34.8%) were between 65 and 79 years old, and 59 (28.9%) were  $> 80$  years old; 50.5% of the patients were male. Comorbidity conditions occurred in 76.5% of cases. Chronic disease (59, 28.9%) and solid tumor (58, 28.4%), of whom 33 (47.8%) had metastases, were the most frequent. Forty-eight (23.5%) were healthy. The complete list of 252 underlying illnesses (1.5% underlying illness per patient with comorbidities) is displayed in Table 2. Fifty-four (26.5%) were receiving immunosuppressive treatment.

Regarding the distribution according to reason for admission, 152 (74.5%) patients were included in the medical group, 46 (22.5%) in the surgical group (digestive tract surgery in 23 and biliary tract in 13 patients), and 6 (2.9%) in the trauma group. Fifty-six patients (27.5%) were seen in the outpatient clinic or in the emergency department, while 148 (72.5%) were admitted to hospital with a median length of

**Fig 1** Annual distribution of *Aeromonas* spp. isolated from clinical samples recovered from 204 patients



**Table 1** Clinical features of 204 patients with *Aeromonas* spp. infections

Variables (total no.)	Extraintestinal group				
	Gastroenteritis, <i>n</i> = 160 <i>n</i> (%)	Intraabdominal, <i>n</i> = 20 <i>n</i> (%)	Skin and soft tissue, <i>n</i> = 12 <i>n</i> (%)	Lung, <i>n</i> = 6 <i>n</i> (%)	Bacteremia, <i>n</i> = 6 <i>n</i> (%)
<b>Gender</b>					
Female (101)	84 (52.5)	6 (30.0)	5 (41.7)	2 (33.3)	4 (66.7)
Male (103)	76 (47.5)	14 (70.0)	7 (58.3)	4 (66.7)	2 (33.3)
<b>Age group, years</b>					
<65 (74)	59 (36.9)	4 (20.0)	6 (50.0)	3 (50.0)	2 (33.3)
65–79 (71)	54 (33.8)	9 (45.0)	5 (41.7)	3 (50.0)	0
≥80 (59)	47 (29.4)	7 (35.0)	1 (8.3)	0	4 (66.7)
<b>Comorbidity conditions</b>					
Solid organ transplant (10)	9 (5.6)	0	1 (8.3)	0	0
HIV infection (8)	6 (3.8)	0	1 (8.3)	0	1 (16.7)
Hematological malignancy (11)	10 (6.3)	0	1 (8.3)	0	0
Solid tumor (58)	41 (25.6)	11 (55.0)	2 (16.7)	3 (50.0)	1 (16.7)
Autoimmune disorder (10)	10 (6.3)	0	0	0	0
Chronic disease (59)	48 (30.0)	4 (20.0)	2 (16.7)	3 (50.0)	2 (33.3)
Healthy (48)	36 (22.5)	5 (25.0)	5 (41.7)	0	2 (33.3)
<b>Immunosuppressant drugs</b>					
Yes (54)	43 (26.9)	3 (15.0)	4 (33.3)	3 (50.0)	1 (16.7)
No (150)	117 (73.1)	17 (85.0)	8 (66.7)	3 (50.0)	5 (83.3)
<b>Type of patient</b>					
Outpatient (56)	49 (30.6)	0	6 (50.0)	1 (16.7)	0
Hospitalized (148)	111 (69.4)	20 (100.0)	6 (50.0)	5 (83.3)	6 (100.0)
Medical (152)	134 (83.8)	3 (15.0)	6 (50.0)	4 (66.7)	5 (83.3)
Traumatic (6)	3 (1.9)	0	3 (25.00)	0	0
Surgical (46)	23 (14.4)	17 (85.0)	3 (25.0)	2 (33.3)	1 (16.7)
<b>Type of surgery</b>					
Digestive tract (23)	12 (7.5)	9 (45.0)	1 (8.3)	1 (16.7)	0
Hepatobiliary (13)	3 (1.9)	8 (40.0)	1 (8.3)	0	1 (16.7)
Others (10)	8 (5.0)	0	1 (8.3)	1 (16.7)	0
<b>ICU admission</b>					
Yes (21)	8 (5.0)	6 (30.0)	2 (16.7)	3 (50.0)	2 (33.3)
No (183)	152 (95.0)	14 (70.0)	10 (83.3)	3 (50.0)	4 (66.7)
<b>Number of samples with positive culture</b>					
1 (190)	154 (96.3)	17 (85.0)	9 (75.0)	6 (100.0)	4 (66.7)
>1 (14)	6 (3.8)	3 (15.0)	3 (25.0)	0	2 (33.3)
<b>Monomicrobial vs. polymicrobial</b>					
Monomicrobial (145)	137 (85.6)	2 (10.0)	3 (25.0)	0	3 (50.0)
Polymicrobial (59)	23 (14.4) <sup>a</sup>	18 (90.0) <sup>b</sup>	9 (75.0) <sup>c</sup>	6 (100.0) <sup>d</sup>	3 (50.0) <sup>e</sup>
<b>Acquisition</b>					
Nosocomial (107)	87 (54.4)	11 (55.0)	5 (41.7)	2 (33.3)	2 (33.3)
Community (97)	73 (45.6)	9 (45.0)	7 (58.3)	4 (66.7)	4 (66.7)
<b>Antimicrobial treatment</b>					
Appropriate (76)	48 (30.0)	14 (70.0)	4 (33.3)	6 (100.0)	4 (66.7)
Not appropriate (44)	33 (20.6)	4 (20.0)	5 (41.7)	0	2 (33.3)
None (84)	79 (49.4)	2 (10.0)	3 (25.0)	0	0
<b>Outcome</b>					
Survival (150)	123 (76.9)	13 (65.0)	11 (91.7)	1 (16.7)	2 (33.3)
Mortality (54)	37 (23.1)	7 (35.0)	1 (8.3)	5 (83.3)	4 (66.7)

**Table 1** (continued)

Variables (total no.)	Gastroenteritis, n = 160 n (%)	Extraintestinal group			
		Intraabdominal, n = 20 n (%)	Skin and soft tissue, n = 12 n (%)	Lung, n = 6 n (%)	Bacteremia, n = 6 n (%)
During hospitalization (24)	11 (6.9)	4 (20.0)	1 (8.3)	5 (83.3)	3 (50.0)
During follow-up (30)	26 (16.3)	3 (15.0)	0	0	1 (16.7)

ICU intensive care unit

<sup>a</sup> *Clostridium difficile* (n = 11), *Campylobacter jejuni* (n = 7), *Blastocystis hominis* (n = 3), *Salmonella* spp. (n = 2), *C. botulinum* (n = 1), *Enterococcus casseliflavus* (n = 1), *Escherichia coli* (n = 1)

<sup>b</sup> *E. coli* (n = 6), *Klebsiella* spp. (n = 4), *Bacteroides fragilis* (n = 3), *Streptococcus viridans* (n = 3), *E. casseliflavus* (n = 2), *E. faecium* (n = 2), other (n = 7)

<sup>c</sup> *B. fragilis* (n = 3), *Enterobacter cloacae* (n = 2), *E. coli* (n = 2), *Pseudomonas aeruginosa* (n = 2), other (n = 5)

<sup>d</sup> *Candida* spp. (n = 3), *Pseudomonas* spp. (n = 3), other (n = 5)

<sup>e</sup> *E. coli* (n = 2), *E. faecium* (n = 1), *S. bovis* (n = 1)

stay of 12 days (range 8–21). Among those 148 patients hospitalized, 21 (14.2%) required ICU admission.

Fourteen patients (6.9%) showed more than one positive culture for *Aeromonas* spp., with a total of 17 samples and nine different sources (in seven patients, *Aeromonas* spp. was recovered from different combinations of sources: bile + sputum; stool + urethral exudate; blood + bile + peritoneal exudate; blood + central venous catheter; stool + peritoneal exudate; abscess + surgical wound; and peritoneal exudate + surgical wound + abscess). In the remaining seven patients, *Aeromonas* was recovered sequentially from one source (stools in four patients with eight positive cultures, ulcers in two patients with five positive cultures, and one patient with two positive cultures from exudate of surgical wound). At least one blood culture was performed in 38 (23.7%) patients out of 160 patients with gastroenteritis and a positive fecal culture for *Aeromonas* spp. Of these, five (13.2%) patients developed bacteremia, for *Enterococcus faecalis* in two cases, *Salmonella enterica typhimurium* in two cases, and *Staphylococcus aureus* in one case. No patient developed bacteremia by *Aeromonas* spp. among patients with gastroenteritis. The infection was monomicrobial in 145 cases (71.1%) and polymicrobial in 59 patients (28.9%), mainly enteropathogens. Coinfection with more than one enteric pathogen occurred in 23 (14.4%) patients with gastroenteritis. The predominant microorganisms species found from stool cultures were *Clostridium difficile* (in 11 cases) and protozoa (in ten cases). The infection by *Aeromonas* spp. was considered community-acquired in 97 patients (47.5%) and nosocomial in 107 (52.5%). In 128 patients (62.7%), *Aeromonas* spp. was considered to be non-treated. Forty-four patients (21.6%)

received treatment that was considered inappropriate, and 84 patients (41.2%) did not receive antibiotic treatment; in 76 patients (37.3%), the treatment was appropriate.

The results of in vitro susceptibility testing of clinical *Aeromonas* isolates against various antimicrobial agents are shown in Table 3. The most active agents against *Aeromonas*, with sensitivity rates exceeding 90%, were amikacin, aztreonam, cefepime, cefotaxime, ceftazidime, gentamicin, and tobramycin. *Aeromonas* showed 100% sensitivity to tigecycline. *Aeromonas* showed a high frequency of resistance to two classes of antimicrobial agents, including amoxicillin/clavulanic acid and ampicillin (each with a resistance rate exceeding 90%). *Aeromonas* had susceptibility rates ranging between 72.5 and 76% to ciprofloxacin, imipenem, and piperacillin + tazobactam.

In-hospital and 1-year follow-up mortalities were 11.7% (24/204 patients) and 14.7% (30/204 patients), respectively, with an overall mortality of 26.5% (54/204 patients). Mortality during follow-up among patients with gastroenteritis was 2.5 times higher than in patients who died during hospitalization (16.3% vs. 6.9%). The highest mortality occurred among patients with lung infection (83.3%), all of them during hospitalization, and bacteremia (66.7%). Mortality of intraabdominal *Aeromonas* infection was 35% (20% during hospitalization and 15% during 1-year follow-up).

Univariate analysis was performed to identify variables associated with mortality. Age, age group, in-hospital patient, ICU stay, extraintestinal presentation, malignancy, and appropriate antimicrobial treatment were significantly associated with an increased mortality compared with survivors (Table 4).



**Table 2** Underlying illnesses observed among 156 patients with *Aeromonas* infection (previously healthy patients excluded)

Illness	No. of patients <sup>a</sup>
Diabetes mellitus	40
Liver cirrhosis	30
Heart failure	27
COPD	15
End-stage renal disease	15
Autoimmune diseases <sup>b</sup>	11
Solid organ transplant	10
HIV infection	8
Asthma	5
Solid malignancies	
Colonic	16
Gastric	8
Hepatobiliary	7
Other digestive tract malignancies	9
Gynecological malignancies	6
Urinary bladder malignancies	7
Other urological malignancies	6
Breast cancer	6
Lung cancer	6
Other solid malignancies	4
Hematological malignancies	
Chronic lymphatic leukemia	5
Other hematological malignancies <sup>c</sup>	9
Miscellaneous <sup>d</sup>	2

COPD Chronic obstructive pulmonary disease; HIV human immunodeficiency virus

<sup>a</sup> Most patients had multiple underlying illnesses

<sup>b</sup> Rheumatoid arthritis: 4; Crohn's disease: 4; ulcerative colitis: 3

<sup>c</sup> Non-Hodgkin lymphoma: 3; Hodgkin lymphoma: 1; acute myelomonocytic leukemia: 1; primary myelofibrosis: 1; multiple myeloma: 3

<sup>d</sup> Sarcoidosis: 1; amyloidosis: 1

Finally, the multivariate analysis disclosed three independent predictors of 1-year follow-up mortality among patients with infection by *Aeromonas* spp.: age  $\geq 80$  years [odds ratio (OR), 4.37 [95% confidence interval (CI), 1.68–11.35;  $p = 0.002$ ], admission to ICU (OR, 6.59 [95% CI, 2.17–19.99;  $p = 0.001$ ], and malignancy (OR, 3.62 [95% CI, 1.32–9.90;  $p = 0.012$ ]) (Table 5).

## Discussion

We studied the features of *Aeromonas* spp. infection in a series of 204 adult patients; to our knowledge, this is the largest clinical series published so far. In humans, *Aeromonas* spp. is recognized as an opportunistic pathogen that can affect both

immunocompromised and immunocompetent individuals [2–4]. In our series, 80% of patients had at least one underlying disease, with malignancy and chronic disease being the most common. Interestingly, 22% of patients in our study were previously healthy. In our cohort, gastroenteritis was the most prevalent infection. In several reported studies throughout the world, *Aeromonas* spp. has been isolated at a rate of 0.6–10% from patients with diarrhea, predominantly from infants and children [3, 7, 8, 11, 18]. In Spain, *Aeromonas* occupied the fourth place among microbiological causes of all gastrointestinal diseases reported each year during the period from 1997 to 2006 [19]. The high incidence of *Aeromonas* spp. gastroenteritis in our series of adult patients is not in agreement with data from France and countries of south-east Asia, which reported that *Aeromonas*-associated diarrhea was the third clinical form of presentation, with 19 and 15%, respectively [9, 20, 21]. This variation may be due to the geographical difference in that south-east of Asia is endemic for *Aeromonas*, but also other factors may explain these differences, such as dietetic habits, processing method adopted for isolation and identification of *Aeromonas* species, and the ecology of this microorganism [3, 4, 20, 22].

The role of *Aeromonas* as a gastrointestinal pathogen has been controversial, as 1–4% of asymptomatic individuals carry *Aeromonas* spp. in their gut [3, 4, 18]. Enterotoxins, cytotoxins, and hemolysins have been studied to elucidate a mechanism by which *Aeromonas* spp. produce diarrhea, but no convincing causal relationship has been established so far [23]. It is generally assumed that the virulence of *Aeromonas* is multifactorial and that only a subset of *Aeromonas* strains can cause gastroenteritis in humans. Moreover, the intestine is a complex ecosystem and in this complex “host-enteric pathogen ecosystem,” a variety of both direct and indirect interactions between enteric pathogens, their host, and the circumstances must be taken into account [12, 24, 25]. In the present series, up to 80% of patients with *Aeromonas* gastroenteritis suffered from severe comorbidities. Therefore, *Aeromonas* gastrointestinal tract involvement appears to develop in patients predisposed to bowel infection either due to local immune deficiency or by nutritional factors. Unfortunately, we did not explore the pathogenicity and infectivity at a genetic level to establish the role of *Aeromonas* as an important enteropathogen. The prevalence of coinfection in our series was 14.4% in patients with gastroenteritis, with *C. difficile* followed by protozoa as the most common pathogens. Thus, it is difficult, in mixed infections, to assess the true contribution of *Aeromonas* to disease. Bloodstream invasion in patients with gastroenteritis is extremely uncommon and occurs preceding or concurrent with the onset of bacteremia in 9–14% of cases [26]. In our series, no case was recorded, while five patients developed bacteremia in the course of gastroenteritis by other enteropathogens yielded in the same fecal sample. It is possible that *Aeromonas* requires a huge inoculum

**Table 3** In vitro susceptibilities of 221 clinical isolates of *Aeromonas* species

Antimicrobial agent	No. of isolates	Susceptible, <i>n</i> (%)	Resistant, <i>n</i> (%)	Breakpoints	
				S	R
Amikacin	207	203 (98.1)	4 (1.9)	≤8	>16
Co-amoxiclav	162	10 (6.2)	152 (93.8)	≤4/2	≥8/2
Ampicillin	162	2 (1.2)	160 (98.8)	≤8	≥32
Aztreonam	159	156 (98.1)	4 (1.9)	≤8	≥32
Cefepime	208	203 (97.6)	5 (2.4)	≤8	≥32
Cefotaxime	187	182 (97.3)	5 (2.7)	≤8	≥32
Cefoxitin	65	40 (61.5)	25 (38.5)	≤8	≥32
Ceftazidime	201	194 (96.5)	7 (3.5)	≤8	≥32
Cefuroxime	63	51 (81)	12 (19.0)	≤8	≥32
Ciprofloxacin	211	160 (75.8)	51 (24.2)	≤1	≥4
Cotrimoxazole	174	146 (83.9)	28 (16.1)	≤2/38	>4/76
Gentamicin	205	192 (93.7)	22 (10.7)	≤2	>4
Imipenem	25	19 (76)	7 (28.0)	≤2	>8
Nalidixic acid	38	23 (60.5)	15 (39.5)	≤16	≥32
Piperacillin	119	96 (80.7)	32 (26.9)	≤16	≥128
Piperacillin + tazobactam	109	79 (72.5)	21 (27.5)	<16/4	≥128/4
Tigecycline	42	42 (100)	0	≤1	>2
Tobramycin	93	85 (91.4)	8 (8.6)	≤2	>4

into the lumen of the gastrointestinal tract to spread to the bloodstream. The association of *Aeromonas* with inflammatory bowel disease (IBD) is of particular interest [10]. All of the patients with an autoimmune disorder (most of them with IBD) developed acute gastroenteritis as the clinical presentation of infection by *Aeromonas*. It is well known that *Aeromonas* has a variety of implications in patients with IBD, as a trigger of the IBD onset or of a relapse, or *Aeromonas* can cause gastroenteritis without any effect on the IBD course [10]. Remarkable findings among patients with *Aeromonas*-associated gastroenteritis in our cohort were that 72.5% had been hospitalized and 26.9% of patients received immunosuppressant drugs. In half of the patients with gastroenteritis, the infection was nosocomial. It's possible that *Aeromonas*-associated diarrhea appeared as a consequence of proliferation and mucosal invasion of patients previously colonized, under aggressive therapies, and with certain comorbidity conditions.

*Aeromonas* has also been implicated as a cause of various extraintestinal manifestations like peritonitis, cholangitis, skin and soft tissue infections, and others [15, 27–30]. Peritonitis caused by *Aeromonas* spp. is rare and, in our series, was the second cause of infection, together with cholangitis. In southeast Asia, *Aeromonas* peritonitis is more prevalent, presenting as secondary peritonitis, spontaneous bacterial peritonitis (SBP), or cholangitis. In this geographical area, the higher prevalence of cirrhosis caused by hepatitis B virus and biliary diseases, in association with dietary habits and wet climate combined with the higher frequency of *Aeromonas* intestinal

carriage, could explain the observed difference with western countries and our series [15, 16, 22, 31].

Wound and skin and soft tissue infections caused by *Aeromonas* have had a very low incidence in our series. By contrast, in Lamy et al.'s study [9], this clinical presentation was the most prevalent. Individuals become infected with *Aeromonas*, subsequent to trauma and environmental exposure, as this organism has been found in a variety of aquatic environments and soil [14, 32–34]. In our series, these infections mainly occurred in patients with several comorbidities, whereas in the study of Lamy et al. [9], they mainly occurred in healthy patients. It was notable that these infections were predominantly polymicrobial, typically involving other Gram-negative bacilli. Surgical site infection due to *Aeromonas* spp. is rare. Only 21 cases had been reported up to 2009, and the infections have a probable endogenous source after abdominal or pelvic surgery [35]. No case of cellulitis or necrotizing fasciitis was observed in our series.

Pneumonia due to *Aeromonas* spp. is uncommon [3, 9, 13, 36]. *Aeromonas* spp. has been reported as a causative pathogen in cases of near-drowning-associated pneumonia [37]. In our ICU, we have attended 21 patients with acute respiratory failure after near-drowning during the period between 2006 and 2012, and no case of pneumonia by *Aeromonas* spp. was identified (data unpublished). In our series, pneumonia was related to aspiration of vomitus in patients with *Aeromonas* colonizing their gut [38]. The possibility that the infection was acquired either via the ventilator or as a cross-infection during

**Table 4** Univariate analysis of mortality and associated risk factors during the 1-year follow-up period in 204 patients with *Aeromonas* spp. infection

Variable	Survivors, <i>n</i> = 150 (%)	Dead, <i>n</i> = 54 (%)	<i>p</i> -Value
Gender			
Female	78 (77.2)	23 (22.8)	N.S.
Male	72 (69.9)	31 (30.1)	
Age group (years)			
<65	61 (82.4)	13 (17.6)	<b>0.02</b>
65–79	53 (74.6)	18 (25.4)	
≥80	36 (61.0)	23 (39.0)	
Comorbidity condition			
Solid organ transplant	9 (90.0)	1 (10.0)	N.S.
HIV infection	6 (75.0)	2 (25.0)	
Hematological malignancy	8 (72.7)	3 (27.3)	
Solid tumor	35 (60.3)	23 (39.7)	
Autoimmune disorder	9 (90.0)	1 (10.0)	
Chronic disease	43 (72.9)	16 (27.1)	
Previously healthy	40 (83.3)	8 (16.7)	
Comorbidity condition (regrouped)			
Previously healthy	40 (83.3)	8 (16.7)	<b>0.03</b>
Malignancy <sup>a</sup>	43 (62.3)	26 (37.7)	
Chronic disease	43 (72.9)	16 (27.1)	
Miscellaneous <sup>b</sup>	24 (85.7)	4 (14.3)	
Immunosuppressant drugs			
No	114 (76.0)	36 (24.0)	N.S.
Yes	36 (66.7)	18 (33.3)	
Type of patient			
Medical	113 (74.3)	39 (25.7)	N.S.
Surgical	32 (69.6)	14 (30.4)	
Traumatic	5 (83.3)	1 (16.7)	
Clinical presentation			
Bacteremia	2 (33.3)	4 (66.7)	<b>0.001</b>
Gastroenteritis	123 (76.9)	37 (23.1)	
Intraabdominal infection	13 (65.0)	7 (35.0)	
Skin and soft tissue infection	11 (91.7)	1 (8.3)	
Lung infection	1 (16.7)	5 (83.3)	
Others	27 (61.4)	17 (38.6)	
Hospitalization			
Outpatient	48 (85.7)	8 (14.3)	<b>0.015</b>
Hospitalized	102 (68.9)	46 (31.1)	
ICU			
No	142 (77.6)	41 (22.4)	<b>0.001</b>
Yes	8 (38.1)	13 (61.9)	
Multiple episodes			
No	142 (74.7)	48 (25.3)	N.S.
Yes	8 (57.1)	6 (42.9)	
Mono vs. poly			
Monomicrobial	108 (74.5)	37 (25.5)	N.S.
Polymicrobial	42 (71.2)	17 (28.8)	
Acquisition			
Community-acquired	73 (75.3)	24 (24.7)	N.S.
Nosocomial	77 (72.0)	30 (28.0)	
Antimicrobial treatment			
Appropriate	48 (63.2)	28 (36.8)	<0.03
Inappropriate	36 (81.8)	8 (18.2)	
None	66 (78.6)	18 (21.4)	

<sup>b</sup> Miscellaneous: includes organ solid transplant (*n* = 10), HIV infection (*n* = 8), and autoimmune disorder (*n* = 10)

<sup>a</sup> Malignancy: includes solid tumors (*n* = 58) and hematological malignancies (*n* = 11)

hospitalization was dismissed because of the absence of a cluster of cases and because the infection was community-acquired. Interestingly, *Aeromonas* pneumonia was polymicrobial in all of the patients.

The prevalence of bacteremia due to *Aeromonas* spp. in Spain ranges between 0.3 and 12% [11, 15, 39]. The prevalence in our series was lower (2.94%), as also compared with other series reported in the last several years, both in south-



**Table 5** Logistic regression analysis of independent risk factors related to mortality during the 1-year follow-up period in 204 patients with *Aeromonas* spp. infection

Variable	OR	95% CI		p-Value
		Low OR	High OR	
<65 years	1			
65–79 years	1.41	0.56	3.56	0.463
≥80 years	4.37	1.68	11.35	<b>0.002</b>
Previously healthy	1			
Malignancy	3.62	1.32	9.90	<b>0.012</b>
Chronic diseases	2.66	0.92	7.72	0.07
Miscellaneous	1.75	0.40	7.59	0.45
Appropriate antimicrobial	2	0.96	4.16	0.064
ICU stay	6.59	2.17	19.99	<b>0.001</b>

east Asia and among westerners [9, 11, 20, 21, 36, 40, 41]. These epidemiological differences could be a consequence of variations in the ecology of *Aeromonas* and with differences in the fecal carriage rate of *Aeromonas* spp. in certain parts of south-east Asia that can be as high as 30%, whereas it is only 3% in Europe [42]. One-third of our cases, however, were healthy, and, among these, there was a predominance of very elderly patients. It has been suggested that contaminated lines, such as catheters, can also serve as a portal of entry to seed blood-borne infection [41]. In our series, only in one patient was *Aeromonas* bacteremia catheter-related.

The antibiotic susceptibility patterns of the clinical isolates in this study were similar to those reported previously [4, 43, 44]. Most of the isolates were not susceptible to ampicillin or co-amoxiclav, in agreement with what should be expected because this is a phenotypic characteristic of the genus *Aeromonas*, where only one species, *A. trota*, shows susceptibility and occasionally some other strains [43, 45]. More than 90% of the *Aeromonas* isolates demonstrated a high level of susceptibility to third- or fourth-generation cephalosporins, aminoglycosides, aztreonam, and tigecycline, indicating that these antibiotics would be the first choice for the empiric treatment of infections by *Aeromonas*. A quarter of strains were found to be resistant to imipenem, ciprofloxacin, and piperacillin + tazobactam, antibiotics widely used in the treatment of severe infections by Gram-negative bacteria. Multidrug-resistant isolates of *Aeromonas* spp. are of major concern. Recently, a study of different human and environmental sources indicated that *Aeromonas* is developing a high level of resistance to aminoglycosides, carbapenems, and third-generation cephalosporins [46].

Fatality rates range from 25 to 46% in cases of bacteremia and are higher than 50% among patients with pneumonia [2–4, 9, 13, 20–22, 31, 36, 47]. All of the patients with pneumonia died during hospitalization despite having been treated

with appropriate antibiotics and 50% patients were admitted to the ICU. The high mortality may be a consequence of the development of acute respiratory distress syndrome (ARDS). A case of ARDS related to *Aeromonas* pneumonia successfully treated with antibiotics and extracorporeal membrane oxygenation (ECMO) has been recently reported [48]. Although about 30% of patients with *Aeromonas* peritonitis required treatment in the ICU, the in-hospital mortality for this condition was 20%. This relatively favorable outcome may be due to the fact that most of the patients received immediate drainage in addition to appropriate antibiotic therapy. The low mortality among patients with wound and skin and soft tissue infections was due to the absence of cases with fulminant cellulitis and necrotizing fasciitis [14, 49].

Multivariate analysis revealed three independent factors influencing mortality in patients with *Aeromonas* spp. infection. Age older than 80 years, ICU admission, and neoplastic disease were independent risk factors predicting unfavorable outcomes in patients with *Aeromonas* infection. Half of the patients over 80 years old died during the follow-up period after the isolation of *Aeromonas* due to conditions that were non-related to infection. Contaminated food is one of the transmission routes of *Aeromonas* spp. and the elderly are particularly susceptible to foodborne illness compared with healthy adults, many of whom are affected by chronic illness or advanced cancer [50].

The present study has some limitations. Firstly, all the isolates were obtained from a medical center and, therefore, the interpretation of our results may not be generalized to other areas. Secondly, this is a retrospective work based on phenotypic methods, which are less accurate than genotypic methods for precise *Aeromonas* identification. During the study period, there have been several shifts in the taxonomy of the genus *Aeromonas*, in particular, the *A. hydrophila* subspecies *dhakensis* [51, 52]. Nowadays, only molecular characterization using the sequences of housekeeping genes like *rpoD* or *gyrB* enable the proper identification of the *Aeromonas* spp. Another limitation is that the pathogenicity of *Aeromonas* in some cases might be debated because analyses of toxin production were not performed. Nevertheless, the main strength of this study is that the cohort was generated from the database of a large teaching referral center in a defined time period. Our study highlights that the isolation of *Aeromonas* spp. from clinical samples in humans is a marker of poor prognosis among those patients aged >80 years, with severe underlying disease, in particular with advanced malignancy, and acute illness requiring ICU admission.

**Acknowledgements** The authors wish to thank Marta Gas, Secretary of the Intensive Care Unit, for her help with the database design, and Sergi Mojal, IMIM statistician, for his advice and support with the statistical analysis.

### Compliance with ethical standards

**Conflict of interest** None declared.

**Ethics statement** The study was approved by the Institutional Review Board of Parc de Salut Mar in Barcelona, Spain.

**Consent statement** Not applicable given the non-interventional nature of the study, since data were retrospectively collected.

**Consent to publish statement** Not applicable.

**Accession number to microarray data** Not applicable.

**Clinical trial registration number and date** Not applicable.

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