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ARTICLE

Pneumonia caused by *Aeromonas* species in Taiwan, 2004–2011

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Abstract We investigated the clinical characteristics of patients with pneumonia caused by *Aeromonas* species. Patients with pneumonia caused by *Aeromonas* species during the period 2004 to 2011 were identified from a computerized database of a regional hospital in southern Taiwan. The medical records of these patients were retrospectively reviewed. Of the 84 patients with pneumonia due to *Aeromonas* species, possible *Aeromonas* pneumonia was diagnosed in 58 patients, probable *Aeromonas* pneumonia was diagnosed in 18 patients, and pneumonia due to *Aeromonas* was conclusively diagnosed in 8 patients. Most of the cases of *Aeromonas* pneumonia developed in men and in patients of advanced age. *A. hydrophila* (n=50, 59.5 %) was the most common pathogen, followed by *A. caviae* (n=24, 28.6 %), *A. veronii* biovar *sobria* (n=7, 8.3 %), and *A. veronii* biovar *veronii* (n=3, 3.6 %). Cancer (n=37, 44.0 %) was the most common underlying disease, followed by diabetes mellitus (n=27, 32.1 %). Drowning-associated pneumonia developed in 6 (7.1 %) patients. Of 47 patients who were admitted to the intensive care ward, 42 patients developed acute respiratory failure and 24 of those patients died. The overall in-hospital mortality rate was significantly associated with liver cirrhosis, cancer, initial presentation of shock, and usage of mechanical ventilation. In conclusion, *Aeromonas* species should be considered as one of the causative pathogens of severe pneumonia, especially in immunocompromised patients, and should be recognized as a cause of drowning-associated pneumonia. Cirrhosis, cancer, and shock as the initial presenting symptom are associated with poor outcome.

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Introduction

Aeromonas species are frequently isolated from fresh or brackish water, sewage, soil, and tap water in temperate or subtropical countries, such as Taiwan [1–5]. Although the gastrointestinal tract is the most common site of infections caused by *Aeromonas* spp. [1, 2], extra-intestinal diseases such as bacteremia, empyema, arthritis, endocarditis, meningitis, urinary tract infections, biliary tract infections, peritonitis, and skin and soft-tissue infections have also been reported [1, 2, 6–19]. Pneumonia due to *Aeromonas* species, however, has rarely been reported and not much is known about the clinical characteristics of this disease [20–27].

In this study, we investigated the clinical characteristics of pneumonia due to *Aeromonas* species in a regional hospital in southern Taiwan over an 8-year period and assessed the risk factors associated with mortality due to this disease.

Methods

Hospital setting and patient selection

This study was conducted at the Chi Mei Medical Center, a 900-bed hospital located in southern Taiwan. Patients with cultures positive for *Aeromonas* species during the period from September 2004 to December 2011 were identified from the hospital's computerized database. The medical records of all patients with pneumonia due to *Aeromonas* species were retrospectively reviewed and the following information was collected: age, gender, underlying conditions (history of immunosuppressant drug use, diabetes mellitus, liver cirrhosis, end-stage renal disease, and active cancer), laboratory data, microbiological findings, antimicrobial susceptibility test results, and patient outcome.

Bacterial isolates and antimicrobial susceptibilities

Blood culture specimens were inoculated into BACTEC culture bottles using the BACTEC 9240 system (Becton Dickinson, Cockeysville, MD, USA). Sputum culture specimens were processed on blood agar, chocolate agar, and eosin methylene blue agar media (Becton Dickinson). Gram-negative isolates that tested positive for cytochrome oxidase, glucose fermentation, citrate usage, indole production, and ornithine decarboxylase were classified as *Aeromonas* species. All strains were identified to the species level by conventional methods and were further verified by the API-20E System (bioMérieux Vitek Inc., Hazelwood, MO, USA), the ID 32 GN System (bioMérieux Vitek Inc.), or the Vitek 2 ID-GNB identification card (bioMérieux Inc., Durham, NC, USA). The susceptibilities of these isolates to a battery of antimicrobial agents were determined using the disk diffusion method, as described by the Clinical and Laboratory Standards Institute (CLSI) [28].

Definitions

Pneumonia due to *Aeromonas* was diagnosed in patients with purulent sputum sample cultures positive for *Aeromonas* species, associated symptoms such as fever, chills, cough, chest pain, or dyspnea, and the presence of newly developed lung infiltrates. Probable pneumonia (monomicrobial infection) due to *Aeromonas* species was diagnosed in patients whose purulent sputum specimens grew *Aeromonas* species in the absence of potential pathogenic respiratory microorganisms (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus* species, Enterobacteriaceae, *Pseudomonas aeruginosa*, *Stenotrophomonas* species, and *Acinetobacter* species), but whose blood cultures were negative for *Aeromonas* species. Possible pneumonia (polymicrobial infection) caused by *Aeromonas* species was diagnosed in patients with pneumonia whose purulent sputum specimens grew *Aeromonas* species along with one or more pathogenic respiratory microorganisms. Definitive pneumonia was diagnosed in patients whose blood cultures or pleural effusion cultures were positive for the same *Aeromonas* species, with identical antibiograms. Shock was diagnosed in patients with a systolic blood pressure<90 mmHg or in patients who required inotropic agents to maintain blood pressure. In-hospital mortality was defined as death due to any cause during hospitalization. Immunocompromised status was diagnosed in patients with liver cirrhosis, diabetes mellitus, end-stage renal disease, or active cancer, as well as in patients receiving immunosuppressant agents. Pneumonia was classified as healthcare-associated infections in patients who acquired the disease during the course of treatment for other conditions within a healthcare setting. Otherwise, pneumonia was classified as community acquired.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation. These variables were compared using the Wilcoxon rank-sum test or the Student's independent *t*-test, as appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test. Patient outcome was analyzed using the Chi-square test. A p-value<0.05 was considered to represent statistical significance. All statistical analyses were conducted using the statistical package SPSS for Windows (version 11.0, SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

The clinical characteristics of the 84 patients with pneumonia caused by *Aeromonas* species are summarized in Table 1. Of these patients, possible *Aeromonas* pneumonia was diagnosed in 58 (69.0 %), probable pneumonia was diagnosed in 18 (21.4 %), and definitive pneumonia was diagnosed in 8 (9.5 %) patients, including seven patients with concomitant *Aeromonas* bacteremia and one patient with empyema thoracis caused by *A. hydrophila*. The patients ranged in age from 18 to 93 years (mean, 72.1 years) and most were men or of advanced age. *A. hydrophila* (n=50, 59.5 %) was the most common pathogen, followed by *A. caviae* (n=24, 28.6 %), *A. veronii* biovar *sobria* (n=7, 8.3 %), and *A. veronii* biovar *veronii* (n=3, 3.6 %) (Fig. 1). Cancer (n=37,

Table 1 Clinical characteristics of the 84 patients with pneumonia caused by *Aeromonas* species

	No. (%) of all patients (n=84)	No. (%) of patients with possible pneumonia (n=58)	No. (%) of patients with probable pneumonia (n=18)	No. (%) of patients with definitive pneumonia (n=8)
Age, years (mean ± SD)	72.1±14.2	73.3±13.3[a]	76.3±7.8[b]	54.0±19.3[a, b]
Age ≥65 years, no. (%)	67 (79.8)	49 (84.5)[a]	17 (94.4)[a]	1 (12.5)[a, b]
Female, no. (%)	11 (13.1)	7 (12.1)	4 (22.2)	0 (0.0)
Healthcare-associated infections, no. (%)	26 (31.0)	17 (29.3)[a]	3 (16.7) [b]	6 (75.0)[a, b]
Aeromonas species				
A. hydrophila	50 (59.5)	38 (65.5)	8 (44.4)	4 (50.0)
A. caviae	24 (28.6)	14 (24.1)	8 (44.4)	2 (25.0)
A. veronii biovar *sobria*	7 (8.3)	4 (6.9)	1 (5.6)	2 (25.0)
A. veronii biovar *veronii*	3 (3.6)	2 (3.4)	1 (5.6)	0 (0.0)
Underlying condition, no. (%)				
Diabetes mellitus	27 (32.1)	19 (32.8)	5 (27.8)	3 (37.5)
Active cancer	37 (44.0)	24 (41.4)	8 (44.4)	5 (62.5)
Liver cirrhosis	14 (16.7)	10 (17.2)	1 (5.6)	3 (37.5)
End-stage renal disease	10 (11.9)	7 (12.1)	3 (16.7)	0 (0.0)
HIV infection	1 (1.2)	0 (0.0)	0 (0.0)	1 (12.5)
Receiving immunosuppressant drugs	14 (16.7)	7 (12.1)	4 (22.2)	3 (37.5)
Immunocompromised status, no. (%)	61 (72.6)	41 (70.7)	12 (66.7)	8 (100.0)
Drowning-associated pneumonia, no. (%)	6 (7.1)	4 (6.9)	1 (5.6)	1 (12.5)
Initial presentation, no. (%)				
Fever	31 (36.9)	21 (36.2)	5 (27.8)	5 (62.5)
Shock	24 (28.6)	18 (31.0)	3 (16.7)	3 (37.5)
Laboratory findings (mean ± SD)				
White blood cell count (cells/μL)	10,222.6±5,606.0	10,041.4±5,163.0	9,850.0±4,486.6	12,375.0±10,038.6
Aspartate transaminase (IU/L)	38.8±37.4	42.9±42.1	29.0±23.1	33.0±21.0
Albumin (g/dL)	2.7±0.5	2.6±0.5	2.8±0.4	2.6±0.8
Urea nitrogen (mg/dL)	29.8±28.6	31.0±31.1	26.0±22.6	28.7±17.0
Serum creatinine (mg/dL)	1.5±2.1	1.6±2.5	1.3±0.6	1.5±0.6
C-reactive protein (mg/L)	59.2±49.5	56.1±37.4	65.8±69.3	61.7±67.7
Radiologic findings, no. (%)				
Presence of pleural effusion	36 (42.9)	22 (37.9)	8 (44.4)	6 (75.0)
Cavity	1 (1.2)	1 (1.7)	0 (0.0)	0 (0.0)
Bacteremia, no. (%)	7 (8.3)	0 (0.0)	0 (0.0)	7 (87.5)
Outcome, no. (%)				
Intensive care unit admission	47 (56.0)	35 (60.3)	7 (38.9)	5 (62.5)
Mechanical ventilation	42 (50.0)	32 (55.2)	7 (38.9)	3 (37.5)
In-hospital mortality	24 (28.6)	18 (31.0)	2 (11.1)	4 (50.0)

[a] Significant difference between possible and definitive infection

[b] Significant difference between probable and definitive infection

42.9 %) was the most common underlying disease, with lung cancer (n=8) and hepatocellular carcinoma (n=6) being the most common types of cancer. Diabetes mellitus (n=27, 32.1 %) was the second most common underlying disease. Shock was the initial presentation in 24 (28.6 %) patients and 6 (7.1 %) of the 84 patients developed drowning-associated pneumonia. Radiographic evidence of pleural effusion was noted in 36 (42.9 %) patients. Of the patients who had possible pneumonia, *Klebsiella pneumoniae* was the most common co-pathogen (n=19), followed by *Acinetobacter* spp. (n=14), *Pseudomonas aeruginosa* (n=13), *Enterobacter* species (n=10), *Stenotrophomonas maltophilia* (n=7), *E. coli* (n=6),

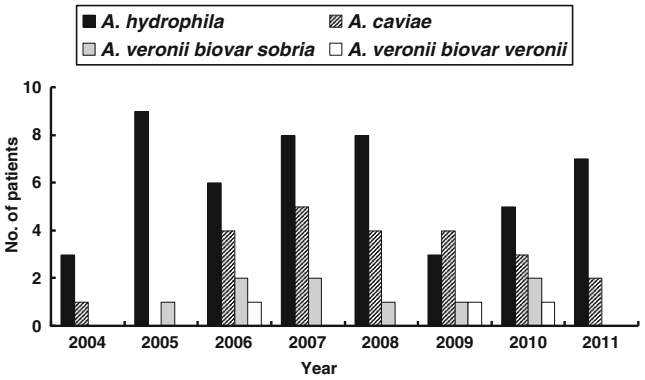

Fig. 1 Distribution of *Aeromonas* species causing pneumonia at a regional hospital in southern Taiwan from 2004 to 2011

Haemophilus species (n=4), *Proteus* spp. (n=2), *Citrobacter freundii* (n=1), and *Morganella morganii* (n=1). The results of the laboratory studies revealed that 31 (36.9 %) patients had leukocytosis and 42 (50.0 %) patients had hypoalbuminemia. In addition, C-reactive protein (CRP) levels were elevated in 47 (94 %) of the 50 patients who underwent testing for that inflammatory biomarker. Furthermore, patients with definitive pneumonia were significantly younger than patients with possible or probable pneumonia, and the majority of those patients acquired the infection in the hospital.

Outcome analysis

Clinical outcomes, including intensive care unit (ICU) admission, acute respiratory failure, and mortality, were similar among patients with possible, probable, and definitive pneumonia. Of the 47 patients who were admitted to the intensive care ward, 42 patients developed acute respiratory failure and 24 of them died. Death was significantly associated with liver cirrhosis, cancer, shock as the initial presentation, the requirement of ICU admission, and usage of mechanical ventilation (Table 2). In contrast, the overall mortality was not associated with age, gender, or other underlying conditions, such as diabetes mellitus, end-stage renal disease, receipt of immunosuppressant drugs, or initial inappropriate antibiotic therapy.

Antimicrobial susceptibilities

The results of in vitro susceptibility testing to various antimicrobial agents against *Aeromonas* species are shown in Table 3. More than 98 % of clinical isolates were susceptible to amikacin and imipenem. In contrast, more than 90 % of the isolates were not susceptible to ampicillin or cefazolin.

Discussion

This study is the largest-scale study on 84 patients with *Aeromonas* pneumonia, including possible, probable, and definitive cases, at a hospital in southern Taiwan during an 8-year period. In contrast to a recent prospective nationwide study of 78 *Aeromonas* infections in France [29], only 5 (%) cases of respiratory tract infection were identified during 6 months. This variation may be due to the geographical difference in that southern Taiwan is endemic for *Aeromonas* [1–5]. A previous report indicated that the documentation of *Aeromonas* spp. as a pathogen causing pneumonia is complicated, because it can be a transient colonization and may often be isolated with other pathogens in the respiratory tract secretions [30]. However, all of the patients enrolled in this study had compatible symptoms

Table 2 Outcome analysis of 84 patients with pneumonia caused by *Aeromonas* species

	No. (%) of survivors (n=56)	No. (%) of non-survivors (n=24)	p-Value
Age ≥65 years, no. (%)	50 (83.3)	17 (70.8)	0.3331
Female, no. (%)	9 (15.1)	2 (8.3)	0.6418
Healthcare-associated infection, no. (%)	15 (25.0)	11 (45.8)	0.1150
Underlying condition			
Liver cirrhosis	6 (10.0)	8 (33.3)	0.0265
Diabetes mellitus	15 (25.0)	12 (50.0)	0.0539
Active cancer	22 (11.7)	15 (62.5)	<0.0001
End-stage renal disease	7 (11.7)	3 (12.5)	0.7833
Receiving immunosuppressant drugs	9 (15.0)	5 (20.8)	0.7565
Initial shock	12 (20.0)	12 (50.0)	0.0146
Leukocytosis	21 (35.0)	10 (41.7)	0.7519
Aeromonas bacteremia	3 (5.0)	4 (16.7)	0.2000
Initial inappropriate antibiotic	10 (17.9)	6 (25.0 %)	0.4693
Intensive care unit admission	28 (46.7)	19 (79.2)	0.0147
Acute respiratory failure	25 (41.7)	17 (70.8)	0.0322

Table 3 Rates of non-susceptibility of 84 isolates of *Aeromonas* species to 11 antimicrobial agents as determined by the disk diffusion method

	No. (%) of isolates not susceptible to:				
	A. hydrophila (*n*=50)	*A. caviae* (*n*=24)	*A. veronii* biovar *sobria* (*n*=7)	*A. veronii* biovar *veronii* (*n*=3)	All isolates (*n*=84)
Ampicillin	48 (96.0)	24 (100.0)	6 (85.7)	3 (100.0)	81 (96.4)
Ampicillin–sulbactam	35 (70.0)	16 (67.7)	5 (71.4)	3 (100.0)	59 (70.2)
Cefazolin	46 (92.0)	23 (95.8)	4 (57.1)	3 (100.0)	76 (90.4)
Cefuroxime	24 (48.0)	12 (50.0)	3 (42.9)	1 (33.3)	40 (47.6)
Ceftazidime	15 (30.0)	6 (25.5)	1 (14.3)	1 (33.3)	23 (27.4)
Cefepime	10 (20.0)	3 (12.5)	0 (0.0)	0 (0.0)	13 (15.5)
Piperacillin–tazobactam	9 (18.0)	3 (12.5)	0 (0.0)	0 (0.0)	12 (14.3)
Imipenem	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Ciprofloxacin	8 (16.0)	6 (25.0)	0 (0.0)	0 (0.0)	14 (16.7)
Gentamicin	8 (16.0)	5 (20.8)	0 (0.0)	0 (0.0)	13 (15.5)
Amikacin	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

and signs of pneumonia in addition to positive cultures of *Aeromonas* species in the purulent sputum specimens. The clinical condition should be more than colonization. Moreover, we divided all the study subjects into three subgroups, possible, probable, and definite pneumonia, for comparison. It would be helpful for clinicians to understand better the real clinical manifestations of *Aeromonas* pneumonia and further emphasizes that clinicians should remain alert in regards to *Aeromonas* pneumonia in tropical or subtropical areas, such as Taiwan.

In this study, we found that approximately 85 % of the patients with *Aeromonas* pneumonia were older than 65 years of age and that most of them had various underlying diseases, such as cancer and diabetes mellitus. Moreover, more than 70 % of the cases of *Aeromonas* pneumonia developed in patients with immunocompromised conditions. Similar findings have been reported in a number of case reports [21, 22, 25]. For example, Nagata et al. described a case of *A. hydrophila* pneumonia in a 75-year-old woman with colon cancer who died of the disease [21], Ye et al. reported on a patient with severe pneumonia due to drug-resistant *A. caviae* [25], and Murata et al. reported on a case of fulminant *A. hydrophila* pneumonia in a patient with chronic renal failure and liver cirrhosis [22]. Therefore, physicians should be aware that immunocompromised patients of advanced age are at risk of developing *Aeromonas* pneumonia.

In the present work, 26 (31 %) cases were classified as healthcare-associated infections. Except for one patient who was immunocompetent, all of the other patients had underlying immunocompromised conditions, including cancer (*n*=18, 69.2 %), diabetes mellitus (*n*=8, 30.8 %), and liver cirrhosis (*n*=7, 15.4 %). Among them, nine (34.6 %) acquired infection during ICU admission, and seven (26.9 %) cases were classified as ventilator-associated pneumonia. The overall *Aeromonas* healthcare-associated infection-related in-hospital mortality was 42.3 %. Although healthcare-associated infection is unusual for *Aeromonas* species, clinicians should consider that *Aeromonas* species can be one of the possible pathogens causing healthcare-associated pneumonia, especially in immunocompromised patients. Importantly, the mortality was higher than in community-acquired *Aeromonas* pneumonia.

Studies have shown that *Aeromonas* species should be considered as a possible causative agent of drowning-associated pneumonia [26, 28]. In this study, 6 of the 84 cases of pneumonia caused by *Aeromonas* species were associated with drowning. Of those six patients, three had alcoholic liver cirrhosis and three were immunocompetent. In addition, drowning-associated pneumonia was due to *A. hydrophila* in four patients and due to *A. veronii* biovar *sobria* in two patients. All of the patients with drowning-associated pneumonia required ICU admission and the use of mechanical ventilation, and all three of the patients with underlying liver cirrhosis died. Thus, drowning-associated pneumonia due to *Aeromonas* species is associated with high morbidity and mortality rates, especially among patients with underlying liver cirrhosis.

The morbidity and mortality rates associated with *Aeromonas* pneumonia were relatively high. Of the 84 patients who developed pneumonia due to *Aeromonas* species during the study period, more than half required ICU admission and the use of mechanical ventilation. Furthermore, more than 25 % of the patients died. These findings are consistent with those reported in previous studies [21–27]. Moreover, we found that liver cirrhosis, active cancer, and shock as the initial presentation were independent risk factors for death due to *Aeromonas* pneumonia. Among patients with *Aeromonas* pneumonia, only 36.9 % had

leukocytosis, but 94 % of them had elevated values of CRP. Leukocytosis was not associated with poor outcome. In addition, the need for ICU admission and the use of mechanical ventilation among patients with *Aeromonas* pneumonia were found to be predictors of mortality. Finally, we also noted that the patients with "possible pneumonia" had a higher frequency of ICU admission, acute respiratory failure, and higher mortality than patients with "probable pneumonia". The subgroup with "possible pneumonia" had polymicrobial infection, and other pathogens could participate in the infectious process, therefore, it may contribute to the unfavorable outcomes.

In this study, *A. hydrophila* was the most common *Aeromonas* species, followed by *A. caviae*. We found similar findings in our previous studies on biliary tract infections, urinary tract infections, and bacteremia due to *Aeromonas* [10, 11]. In contrast, Wu et al. found that *A. sobria* (55 %) and *A. hydrophila* (45 %) were the most common *Aeromonas* species among 31 patients with spontaneous bacterial peritonitis [12], and Lamy et al. found that *A. caviae* and *A. veronii* were the most common *Aeromonas* species causing bacteremia and gastroenteritis [29]. Therefore, more epidemiological studies are needed in order to establish the bacteriology of different types of *Aeromonas* infections in different regions.

The antibiotic susceptibility patterns of the clinical isolates in this study were similar to those reported previously [2]. Although most of the isolates were not susceptible to ampicillin or first-generation cephalosporins, more than 80 % of the clinical isolates were susceptible to third- or fourth-generation cephalosporins, aminoglycosides, fluoroquinolones, and imipenem. Therefore, third- or fourth-generation cephalosporins as well as fluoroquinolones should be considered as the antibiotic treatments of choice for patients with severe *Aeromonas* pneumonia.

There are two main limitations of this study. Firstly, this is a retrospective work based on phenotypic methods, which are less accurate than genotypic methods for *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* has been renamed as *A. aquariorum* [31]. Furthermore, resistance to antibacterial agents may be species dependent [32]. Secondly, a large number (n=58) of 84 pneumonia cases were "possible *Aeromonas* pneumonia" cases, and, as defined, the sputa from these patients also contained other known pathogens.

In conclusion, *Aeromonas* species can cause severe pneumonia, especially in immunocompromised patients, and can cause drowning-associated pneumonia. Liver cirrhosis and shock as the initial presentation are significant risk factors for mortality.

Conflict of interest The authors declare that they have no conflict of interest.

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