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Original Article

Polymicrobial bloodstream infection involving *Aeromonas* species: Analysis of 62 cases

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ABSTRACT

Objective: To better understand *Aeromonas*-involved polymicrobial bacteremia (AIPMB).
Materials and Methods: We conducted a retrospective analysis of patients with AIPMB admitted to three large referral hospitals in Taiwan between 2001 and 2008.
Results: Of a total of 62 patients with AIPMB, 22 had healthcare-associated infection and 40 had community-acquired infection. *Enterobacteriaceae* was the most common concurrent pathogen (82%). The leading underlying diseases/conditions in the affected patients were solid cancers (45%), recent gastric acid suppressant therapy (39%) and liver cirrhosis (26%). More than 95% of the *Aeromonas* isolates were susceptible to an aminoglycoside, a third- or fourth-generation cephalosporin, imipenem or ciprofloxacin. Antibiotic susceptibilities did not significantly differ between *Aeromonas* isolates in patients with healthcare-associated AIPMBs and those in patients with community-acquired AIPMBs. Coinfection with *Enterobacteriaceae* occurred more commonly in community-acquired AIPMB (93% vs. 64%; $p = 0.012$).
Conclusions: AIPMB occurred commonly in patients with liver cirrhosis, solid cancers or recent gastric acid suppressant therapy. *Enterobacteriaceae* were the most common concurrent pathogens. Similar antibiotic profiles were found in *Aeromonas* isolates of healthcare-associated and community-acquired AIPMBs.

1. Introduction

The proportion of cases of bacteremia involving more than one species has ranged from 5% to 20% over the past 50 years [1]. Polymicrobial bacteremia is associated with malignancy, surgery and the placement of central venous catheters [1]. The mortality in patients with polymicrobial bacteremia is approximately twice that of patients with monomicrobial bacteremia [2–4].

Aeromonas, a member of the *Aeromonadaceae* family, is associated with a variety of human infections including gastroenteritis, wound infection and septicemia [5–8]. *Aeromonas* infection is mainly acquired from the environment, especially contaminated water. In previous studies, there have been high proportions of polymicrobial infection where *Aeromonas* spp. have been involved in infections of the bloodstream [9–14]. No study has yet delineated the clinical picture of *Aeromonas*-involved polymicrobial bacteremia (AIPMB), possibly because of a lack of sufficient cases in a single healthcare institution. We therefore conducted a retrospective multicenter study of AIPMB.

2. Materials and methods

This is a retrospective study of patients diagnosed with AIPMB admitted to Buddhist Tzu Chi General, Buddhist Dalin Tzu Chi General and Buddhist Taipei Tzu Chi General Hospitals in Taiwan between January 2001 and November 2008. Patient data, clinical and laboratory information were retrieved from the medical charts of the patients included in the study.

An AIPMB was defined as the simultaneous growth of an *Aeromonas* spp. and at least one other microbe from the blood culture of

Conflict of interest: none.

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a patient with sepsis. Death was considered attributable to AIPMB if the patient died of unrelenting sepsis within 7 days after blood was sampled for culture where the culture was positive for *Aeromonas* species and one or more other microbes.

An AIPMB was considered healthcare-associated if the *Aeromonas* isolate was obtained from blood sampled ≥72 hours after admission to the hospital in a patient who had been asymptomatic upon admission, or in a patient who had received antineoplastic chemotherapy within the past 2 weeks, regardless of his or her symptoms at admission [15]. Acute respiratory failure was defined as the ratio of arterial oxygen tension (PaO_2) to fractional inspired oxygen (FiO_2) <200 [16]. The severity of the AIPMB was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score less than 72 hours after the development of sepsis [17].

Gastric acid-suppressant therapy was defined as the use of a proton-pump inhibitor or a histamine H_2 blocker for ≥7 days within 4 weeks before the emergence of an AIPMB.

2.1. Species identification and antimicrobial susceptibility

Detection of bacterial growth from blood specimens was performed using the BACTEC 9240 blood culture system (BD Diagnostic Instrument Systems, Spark, MD, USA). *Aeromonas* species (Gram-negative bacilli) were identified by a positive oxidase test, growth on MacConkey agar, no growth on thiosulfate-citrate-bile-sucrose agar, and resistance to 150 μg vibriostatic compound O/129 [5,18]. Isolates were further confirmed with use of the Vitek II system (BioMérieux, Lyon, France), BD-Phoenix system (BD Diagnostic Instrument Systems, Spark, MD, USA) or API-20NE system (BioMérieux Marcy-l'Etoile, France). Additional tests, such as esculin hydrolysis, gas production from glucose, Voges-Proskauer reaction, ornithine decarboxylase and arginine dihydrolase production, were performed for the identification of bacterial species as necessary [5,18].

In vitro antimicrobial susceptibilities of *Aeromonas* isolates were tested using the Kirby-Bauer disk-diffusion method or automated methods (Vitek II system or the BD-Phoenix system). All of the methods tested for gentamicin, amikacin, cefazolin, ceftriaxone, ciprofloxacin, piperacillin/tazobactam and imipenem. The BD-Phoenix system also ran tests including aztreonem. In the disk-diffusion method, antibiotics selected for testing also included cefmetazole, cefuroxime, ceftazidime, cefpirome and aztreonam. There were, however, some differences in the antibiotics selected for different *Aeromonas* isolates tested using the disk-diffusion method. The susceptibility breakpoints in the disk diffusion method were in accordance with those of the National Committee for Clinical Laboratory Standards for *Enterobacteriaceae* [19], while the susceptibility breakpoints in the automated methods were in accordance with those recommended by the Clinical and Laboratory Standards Institute M45-A [20].

2.2. Statistical analyses

The Chi-square test or Fisher's exact test was used to compare nominal data using the SPSS software package, version 11.0 (SPSS Inc, Chicago, IL, USA). A two-tailed p value of ≤0.05 was considered statistically significant.

3. Results

Of a total of 62 patients [mean age 62 years (range: 24–90 years); males: 33/62] with AIPMB, 22 had healthcare-associated infection and 40 had community-acquired infection. Four patients presented with necrotizing fasciitis, one with acute cholangitis and the others with primary bacteremia. Fifty-one patients (82%) had *Enterobacteriaceae* coinfection. Solid cancer (45%) was the most common underlying disease/condition, followed by gastric acid suppressant therapy (39%) and liver cirrhosis (26%). Forty-five patients (73%) presented with fever, 31 (50%) with thrombocytopenia and only 23 (37%) with leukocytosis. Eighteen (29%) patients had very severe disease (APACHE II score ≥20) and the overall mortality rate of AIPMB was 31% (19/62). The clinical characteristics of healthcare-associated and community-acquired AIPMBs are detailed in Table 1. The ratios of male gender and *Enterobacteriaceae* coinfection were significantly higher in community-acquired AIPMB than in healthcare-associated APIMB.

The concurrent pathogens for healthcare-associated and community-acquired AIPMBs are listed in Table 2. In community-acquired infection, *Escherichia coli* (23/40, 58%) was most commonly found, followed by *Klebsiella* spp. (9/40, 23%) and *Enterobacter* spp. (5/40, 13%). In healthcare-associated infection, *Klebsiella* spp. (5/22, 23%) were most frequently found, followed by *Enterobacter* spp. (5/22, 23%) and *Acinetobacter* spp. (5/22, 23%).

The *in vitro* antimicrobial susceptibilities of *Aeromonas* isolates are listed in Table 3. There were 44 *Aeromonas* isolates tested by the disk-diffusion method, 12 by the Vitek II system and six by the BD-Phoenix system. The majority of *Aeromonas* isolates were susceptible to amikacin, gentamicin, ceftriaxone, ceftazidime, cefpirome, aztreonam, piperacillin/tazobactam, imipenem and ciprofloxacin. Thirty-nine out of 49 (80%) isolates tested were susceptible to cefuroxime, 15 of 62 (24%) were susceptible to cefazolin, and 23 of 41 (56%) were susceptible to cefmetazole. Antibiotic susceptibilities were not statistically different between community-acquired and healthcare-associated *Aeromonas* isolates.

4. Discussion

In agreement with previous reports [9–14], the majority of AIPMBs were of primary bacteremia.

Table 1
Comparisons of clinical characteristics between healthcare-associated and community-acquired *Aeromonas*-involved polymicrobial bacteremias.

Variable	Polymicrobial *Aeromonas* bacteremia		p
	Healthcare-associated $N=22$	Community-acquired $N=40$	
Age ≥65 y, *n* (%)	7 (32)	24 (60)	0.063
Male, *n* (%)	17 (77)	16 (40)	0.011
Enterobacteriaceae coinfection[a], *n* (%)	14 (64)	37 (93)	0.012
Underlying disease/condition			
ESRD, *n* (%)	0 (0)	2 (5)	0.535
Recent intra-abdominal surgery, *n* (%)	4 (18)	8 (20)	1.000
Solid cancer, *n* (%)	13 (59)	15 (38)	0.171
Diabetes mellitus, *n* (%)	5 (23)	8 (20)	1.000
Liver cirrhosis, *n* (%)	6 (27)	10 (25)	1.000
Neutropenia, *n* (%)	2 (9)	1 (3)	0.285
Gastric acid suppressant therapy, *n* (%)	10 (45)	14 (35)	0.592
Laboratory and clinical features			
Thrombocytopenia, *n* (%)	11 (50)	20 (50)	1.000
Leukocytosis, *n* (%)	8 (36)	15 (38)	1.000
Fever, *n* (%)	17 (77)	28 (70)	0.751
Diarrhea, *n* (%)	2 (9)	1 (3)	0.285
Shock, *n* (%)	11 (50)	16 (40)	0.623
Abdominal pain, *n* (%)	5 (23)	12 (30)	0.751
Acute renal failure, *n* (%)	8 (36)	7 (18)	0.177
Acute respiratory failure, *n* (%)	4 (18)	7 (18)	1.000
APACHE II score ≥20, *n* (%)	7 (32)	11 (28)	0.947
Death due to sepsis, *n* (%)	7 (32)	12 (30)	1.000

Abbreviations: APACHE = acute physiology and chronic health evaluation, ESRD = end-stage renal disease.
[a] See Table 2 for details.

Table 2
Concurrent pathogens in patients with *Aeromonas*-involved polymicrobial bacteremias.

Concurrent pathogen	Healthcare-associated infection ($N = 22$), (%)	Community-acquired infection ($N = 40$), (%)
Escherichia coli	3 (14)	23 (58)
Klebsiella spp.	6 (27)	9 (23)
Enterobacter spp.	5 (23)	5 (13)
Proteus spp.	1 (5)	—
Serratia spp.	—	1 (3)
Morganella morganii	—	1 (3)
Citrobacter spp.	1 (5)	2 (5)
Pantoea agglomerans	1 (5)	—
Bacteroides spp.	1 (5)	1 (3)
Prevotella oralis	1 (5)	—
Coagulase-negative *Staphylococcus*	1 (5)	—
Streptococci spp.	3 (14)	3 (8)
Enterococcus spp.	3 (14)	2 (5)
Acinetobacter spp.	5 (23)	4 (10)
Stenotrophomonas maltophilia	1 (5)	—
Pseudomonas aeruginosa	2 (9)	—

Aeromonas spp. exist in the environment, especially in fresh water. They are not considered as commensal organisms in the human gastrointestinal tract but can be isolated from feces in asymptomatic people [21]. Of all *Aeromonas* species, *A hydrophila*, *A sobria* and *A caviae* are the most common in human infection. In a mouse model, these three *Aeromonas* species were found to have higher colonization rates in colon tissue compared with other *Aeromonas* species [22]. Low-pH stomach acid has been reported to be effective in killing *Aeromonas* [23]. The high proportion of patients with AIPMB with prior gastric acid-suppressant therapy in this study therefore suggests that a higher pH milieu in the stomach enhances chances of *Aeromonas* intestinal colonization. The findings that *Enterobacteriaceae* are the most common concurrent pathogens for AIPMB in other reports and ours further support the gastrointestinal tract as the most likely portal of entry for *Aeromonas* leading to bacteremia [12–14].

Of all bacteremia cases, a higher proportion of polymicrobial bacteremia is reported in cancer patients compared with their non-cancer counterparts [24,25]. Of note, one study found polymicrobial bloodstream infection in 14% of 2340 patients with an underlying malignancy and an episode of nosocomial bloodstream infection [1]. Neutropenia and disruption of the digestive mucosal barrier caused by antineoplastic therapy, surgery or hypoxia in cancer patients enables the invasion of various bacteria, especially from the gut and oropharynx [1,26]. In agreement with these findings, 12 of the 28 cancer patients in the present study had abdominal surgery, eight had received antineoplastic therapy, two had received radiotherapy and six had septicemia shortly before AIPMB occurred.

Cirrhosis plays an important role in the pathogenesis of AIPMB as it leads to many alterations in the immune system, including decreased reticuloendothelial phagocytic activity, deficient ascetic fluid opsonic activity and qualitative neutrophil dysfunction [27–30]. Cirrhosis-associated portal hypertension could alter intestinal permeability as a result of intestinal congestion, edema and local hypoxia [31–36].

In this study, >85% of *Aeromonas* isolates in both community-acquired and healthcare-associated AIPMB were susceptible to gentamicin, amikacin, ceftriaxone, ceftazidime, cefpirome, aztreonam, piperacillin/tazobactam, imipenem and ciprofloxacin. The similarity in antibiotic susceptibility suggests that the bloodstream-invasive *Aeromonas* in healthcare-associated infections existed in the gastrointestinal tracts of affected patients before hospitalization and were not acquired from the institutional environment [8]. The difference in concurrent pathogens in AIPMB between healthcare-associated and community-acquired patients might result from the alteration of microbes that inhabit the patients' bowel after hospitalization [37] and which then invade the bloodstream leading to the development of bacteremia. Non-*Enterobacteriaceae* from hospital environments, such as non-fermentative Gram-negative bacilli or Gram-positive bacteria, can colonize patients' gastrointestinal tracts while they are hospitalized.

One limitation of this study was that the *Aeromonas* isolates could not be identified to species level, as neither automated system (i.e., the API-20NE, Vitek II system and BD-Phoenix system) nor conventional biochemical reactions were ideal for this task.

Table 3
In vitro antibiotic susceptibilities of the *Aeromonas* isolates.

Antimicrobial agents	Susceptible isolates		*p*
	Healthcare-associated infection *n*/*N* (%)	Community-acquired infection *n*/*N* (%)	
Gentamicin	20/22 (91)	35/40 (88)	1.000
Amikacin	21/21 (100)	38/40 (95)	0.541
Cefazolin	7/22 (32)	8/40 (20)	0.298
Cefuroxime	16/20 (80)	23/29 (79)	1.000
Cefmetazole	8/15 (53)	15/26 (58)	0.956
Ceftriaxone	20/22 (91)	35/44 (88)	1.000
Ceftazidime	12/13 (92)	18/19 (95)	1.000
Cefpirome	16/16 (100)	26/26 (100)	1.000
Aztreonam	15/15 (100)	23/24 (96)	1.000
Piperacillin/tazobactam	11/12 (92)	27/28 (96)	1.000
Imipenem	21/22 (95)	38/40 (95)	1.000
Ciprofloxacin	20/20 (100)	35/37 (95)	0.536

Abbreviation: *n*/*N* = Number of *Aeromonas* isolates susceptible to the antibiotic/number of *Aeromonas* isolates available for susceptibility testing.

5. Conclusions

The most common underlying diseases/conditions in patients with AIPMB were solid tumors, liver cirrhosis and gastric acid suppressant therapy. Although *Enterobacteriaceae* were the most common concurrent pathogens for AIPMB, no significant difference in antibiotic susceptibility was found between *Aeromonas* isolates in healthcare-associated and community-acquired AIPMBs.

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