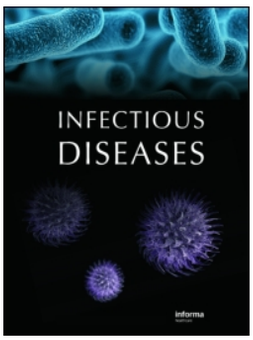

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LETTER TO THE EDITOR

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Resistance trends and epidemiology of *Aeromonas* and *Plesiomonas* infections (RETEPAPI): a 10-year retrospective survey

To the Editor,

A high incidence of resistance among Gram-negative isolates from patients in a Lithuanian cancer centre was recently reported in this journal [1]. Multidrug resistance was observed in 55, 82, 95 and 97% of *Escherichia coli*, *Enterobacter* spp., *Klebsiella pneumoniae* and *Acinetobacter baumannii* isolates, respectively. Herein, we report the resistance data on *Aeromonas* and *Plesiomonas* species at a tertiary-care hospital in Hungary during a 10-year period, a period which to find trends, is divided in a 2008–2012 and a 2013–2017 period. The genera *Aeromonas* and *Plesiomonas* are oxidase-positive, glucose-fermenting Gram-negative rods (they can be phenotypically distinguished, based on the ability of *Aeromonas* to ferment inulin), that are members of the *Enterobacterales* order [2,3]. These bacteria are ubiquitous in marine environments (freshwater, drinking water, wastewater sites, in addition to fish, amphibians and reptilians) and can survive osmotic stress (high salt concentrations), but their isolation from processed food products has also been described [4]. Although *Aeromonas* and *Plesiomonas* may be isolated from asymptomatic individuals, these pathogens have been implicated in a wide range of infectious processes, due to the plethora of virulence factors they possess, such as toxins (incl. enterotoxins), polar flagella, pili, adhesins, lipases, proteases, haemolysin and a Type-VI secretion system [2,4–6]. Among the *Aeromonas* genus, only the motile, mesophilic species are capable of causing diseases in mammals and humans [2,4].

This study was carried out using microbiological data collected between 01 January 2008 and 31 December 2017 at the SZTE Albert Szent-Györgyi Clinical Centre, an academic primary and tertiary-care teaching hospital in Szeged, Hungary, which has a bed capacity of 1820-beds and annually serves more than 400,000 patients in the region. An electronic search of the laboratory information system (LIS) records was conducted. Isolates were considered separate if they occurred >14 days apart or isolates with different antibiotic susceptibilities were detected. Data on affected patients were also collected, which was limited to demographic characteristics (age, sex and inpatient/outpatient status), indication for sample submission and the administered empiric antibiotic therapy.

The processing of samples arriving to our Institute was carried out according to guidelines in routine clinical bacteriology. Relevant culture media plates were incubated at 37 °C for 24–48 h, aerobically. If *Aeromonas* or *Plesiomonas* species presented in significant colony count, the plates were passed on for further processing. Between 2008 and 2012, presumptive phenotypic/biochemical methods and VITEK 2 Gr- ID (bioMérieux, Marcy-l'Étoile, France) were used for bacterial identification, while after 2013, this was complemented by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonik GmbH., Bremen, Germany) [7,8]. Sample preparation and settings for MALDI-TOF MS measurements is described elsewhere.

Routine antimicrobial susceptibility testing in our Institute was performed for ciprofloxacin, ceftriaxone, cefepime, doxycycline, gentamicin, meropenem, sulphamethoxazole/trimethoprim and tigecycline, using disk diffusion. Interpretation of the results was based on CLSI criteria (CLSI guideline M45; https://clsi.org/standards/products/microbiology/documents/m45/). *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains.

Descriptive statistical analysis (including means or medians with ranges and percentages to characterize data) was performed using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA). Statistical analyses were performed with SPSS software version 24 (SPSS, Chicago, IL, USA) (IBM SPSS Statistics for Windows version 24.0, IBM Corp., Armonk, NY), using the χ^2-test, Student's *t*-test and Mann–Whitney U test. The normality of variables was tested using Shapiro–Wilk tests. $p < .05$ were considered statistically significant.

A total of 193 individual isolates were identified ($n = 193$; 19.3 ± 12.3/year, highest in 2015 and lowest in 2010) from various sample types during the 10-year study period. The number of isolates between 2008 and 2012 was $n = 46$ (9.2 ± 4.2/year, range: 5–16) while for 2013–2017, this number was $n = 147$ (29.4 ± 8.2/year, range: 18–38); the difference in the isolation frequency was statistically significant ($p = .0012$). 51.8% of isolates originated from inpatient departments ($p > .05$). 75.6% of isolates were identified in the period between May and September of the relevant year. Most of the isolates were *Aeromonas* spp. (97.9%; namely: *Aeromonas hydrophila* 45.6%, *Aeromonas caviae* 36.7%, *Aeromonas veronii* 13.2%, *Aeromonas salmonicida* 3.3%, *Aeromonas bestiarum* 1.1% and *Aeromonas ichtiosima* 1.1%), while *Plesiomonas shigelloides* isolates were fewer (2.1%, one isolate in 2008, 2012, 2014 and 2016, respectively). Before 2013, *A. hydrophila* and *A. caviae* were mainly isolated.

The patients affected presented no relevant dominance towards either sex (female-to-male ratio: 0.97; 49.2% female; $p<.05$). The median age of the affected patients was 61 years overall (range: 2–99 years), however, in the second half of the study period, a pronounced shift towards older patients was detected ($\text{median}_{2008–2012} = 46$ years, range: 2–79 *vs.* $\text{median}_{2013–2017} = 71$ years, range: 3–99; $p < .0001$). The age distribution of patients was the following: 11.2% 0–18 years, 7.1% 19–29 years, 8.2% 30–45 years, 10.2% 46–59 years and 63.3% of patients were older than 60 years. Wounds samples (lacerations, punctures and avulsions) were the most common sample type (27.4%), followed by abscesses and surgical samples (18.2%), high vaginal swabs and cervical samples (10.2%), midstream urine and urethral swabs, lower respiratory tract samples (7.9% each), blood cultures and feces (6.8% each), inner ear puncuture (5.7%), bile (4.5%) and sinus aspirates and semen (2.3% each). Indications for sample submission, associated with the isolation of these pathogens included skin ulcers (20.4%), cholecystitis and gall stones (15.1%), septicaemia, solid tumours or hematological malignancy (10.9% each), wound infections (8.3%), vaginitis, diarrhoea (7.3% each), dermatitis, urinary tract infections, cystic fibrosis (5.2% each) and inner ear infections (4.2%). In most cases, the reported empiric therapy was ampicillin (70.9%), followed by piperacillin/tazobactam (19.8%), amoxicillin/clavulanic acid (4.1%), ceftriaxone, ceftazidime (1.6% each) and gentamicin and imipenem (1.0% each).

Table 1. Resistance trends among *Aeromonas* and *Plesiomonas* species (2008–2017).

	CIP R%	CRO R%	FEP R%	DOX R%	GEN R%	MER R%	SUM R%	TIG R%
Overall	13.9%	19.8%	13.0%	5.2%	3.6%	10.9%	17.7%	1.0%
	$n = 15$	$n = 38$	$n = 25$	$n = 10$	$n = 7$	$n = 21$	$n = 34$	$n = 2$
2008–2012	18.8%	29.6%	27.2%	22.7%	9.1%	15.9%	25.0%	4.6%
	$n = 8$	$n = 13$	$n = 13$	$n = 10$	$n = 4$	$n = 7$	$n = 11$	$n = 2$
2013–2017	4.7%	16.9%	8.8%	0%	2.0%	9.5%	15.5%	0%
	$n = 7$	$n = 25$	$n = 12$	$n = 0$	$n = 3$	$n = 14$	$n = 23$	$n = 0$
Statistics	$p>.05$	$p=.036$	$p>.05$	$p=.047$	$p>.05$	$p=.038$	$p=.04$	$p>.05$

CIP: ciprofloxacin; CRO: ceftriaxone; FEP: cefepime; DOX: doxycycline; GEN: gentamicin; MER: meropenem; SUM: sulphamethoxazole/trimethoprim; TIG: tigecycline.

The resistance trends of relevant species during the study period is presented in Table 1. The highest resistance levels overall were observed for ceftriaxone (∼20%), sulphamethoxazole/trimethoprim (∼18%), ciprofloxacin (∼14%) and cefepime (13.0%). Meropenem resistance was also above 10%, while resistance rates agaist doxycycline, tigecycline and gentamicin were around or lower, than 5%. There was a significant increase in the number of resistant isolates corresponding to ceftriaxone, sulphamethoxazole/trimethoprim and meropenem, while a drop was noted in case of doxycycline. No statistical tendency was observed for ciprofloxacin, cefepime and tigecycline. Relevant differences in the susceptibility trends of *A. hydrophila* and *A. caviae* (the two most numberus species) were not detected ($p>.05$).

Aeromonas and *Plesiomonas* species are emerging pathogens in the twenty-first century, especially since laboratory technology (MALDI-TOF MS, polymerase chain reaction and whole-genome sequencing) is available to identify them swifly and reliably [2,4]. These bacteria mainly act as pathogens in pathologies affecting the skin and gastrointestinal tract, which was verified by our local results; however, uncommon presentations, such as genitourinary infections, cholecystitis, invasive infections and bacteremia were also noted locally. The temporal nature of their isolation (both regarding the age of affected patients and their isolation frequency in warmer months) was also verified, while the male dominance in our settings was not present. Skin infections are more

common in regions affected by natural disasters (floods and tsunamis) and in individuals working near aquatic environments or with fish/animals, especially if an underlying disease/trauma is present [2,4,5]. Based on retrospective analyses, *Aeromonas* species were causative agents of traveller's diarrhoea in 2–5% of cases [4]. These cases are usually self-limiting, and the addition of antibiotic therapy to complement rehydration is only necessary if the symptoms do not cease after a reasonable period of time [2,4,5]. However, enterocolitis with haemolytic uremic syndrome (HUS) has also been described [9]. While uncommon in Western countries, bacteraemia and severe *Aeromonas* wound infections were associated with the medicinal use of leeches [10]. Septicaemia and severe manifestations have been associated with advanced age, malignant diseases and politraumatization in the literature [2,4,5,9,10].

As there are no strict guidelines for the therapy of *Aeromonas/Plesiomonas* infections, therapeutic decisions are mainly based on monitoring clinical response. Education of clinicians is a must, as we observed that more than two-thirds of patients were treated with ampicillin empirically, which is not a viable therapeutic option in these infections [2,4,5]. Based on Infectious Diseases Society of America (IDSA) guidelines, empiric therapy is not recommended, if local susceptibility levels are lower, than 90%; therefore, the use of several tested drugs (ceftriaxone, sulphamethoxazole/trimethoprim, ciprofloxacin and cefepime) empirically is not wise. Our results are especially daunting in regards to β-lactam antibiotics (coupled with the instrinsic resistance already present in these bacteria), as in several vulnerable patient groups (e.g. children and pregnant women) there are the first-choice therapeutic alternatives [2,4]. Due to the emergence of antimicrobial resistance, the submission of samples suspected of infection and the adjusting of therapy based on the final antibiogram is of utmost importance.

In conclusion, a total of 193 individual isolates were identified (*A. hydrophila*, *A. caviae* and *A. veronii* in highest numbers). Wounds samples (lacerations, punctures and avulsions) were the most common sample type, followed by abscesses and surgical samples. The median age of the affected patients was 61 years overall. The highest resistance levels overall were observed for ceftriaxone, sulphamethoxazole/trimethoprim, ciprofloxacin and cefepime, while 70.9% of cases, the reported empiric therapy was inappropriate (ampicillin). Although these bacteria thought to be infrequent pathogens, their clinical relevance and prevalence is increasing in the era of complex surgeries, severely immunosuppressed patients (mainly due to malignant diseases and organ transplantation) and current diagnostic technologies. Due to the emergence of antimicrobial resistance, the submission of samples suspected of infection and the adjusting of therapy based on the final antibiogram is of utmost importance.

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Ethical approval

This study was deemed exempt from ethics review by the Institutional Review Board and informed consent was not required as data anonymity was maintained.

Disclosure statement

The author declares no conflict of interest, monetary or otherwise.

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