

Review

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Noelia Calvo Sánchez , [Laura Sancha Domínguez](#) , [Ana Cotos Suárez](#) , [Juan Luis Muñoz Bellido](#) *

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Review

Aeromonas Infections in Humans. Antibiotic Resistance and Treatment Options

Noelia Calvo Sánchez ¹, Laura Sancha Domínguez ², Ana Cotos Suárez ³ and Juan Luis Muñoz Bellido ^{4,*}

¹ Area de Microbiología, Complejo Hospitalario Universitario de Orense (SPAIN); noefar@hotmail.com

² Servicio de Microbiología, Hospital Universitario de Salamanca (SPAIN); Instituto de Investigación Biomédica de Salamanca (IBSAL). Universidad de Salamanca, SACYL, CSIC.; lsancha@saludcastillayleon.es

³ Servicio de Microbiología, Hospital Universitario de Salamanca (SPAIN); Instituto de Investigación Biomédica de Salamanca (IBSAL). Universidad de Salamanca, SACYL, CSIC; acotos@saludcastillayleon.es

⁴ Servicio de Microbiología, Hospital Universitario de Salamanca; Departamento de Ciencias Biomédicas y del Diagnóstico, Universidad de Salamanca; Instituto de Investigación Biomédica de Salamanca (IBSAL). Universidad de Salamanca, SACYL, CSIC. (SPAIN), jlmubel@usal.es

* Correspondence: jlmubel@usal.es; Tel.: +34923291100-Ext. 56642.

Abstract: The genus *Aeromonas* is widely distributed in aquatic environments. It is frequent as a fish pathogen, but has also been described associated to human infections. Most human cases are caused by *A. caviae*, *A. veronii* biovar *sobria*, and *A. hydrophila*, though *A. dhakensis* is becoming increasingly important. Transmission happens primarily by ingestion or contact with aquatic collections, or by consumption of contaminated food, especially of aquatic origin. Increasing resistance has been described in *Aeromonas* to penicillins, including their combinations with classical β -lactamase inhibitors, cephalosporins and carbapenems. Among the β -lactam antibiotics, only the 4th generation cephalosporins remain almost uniformly active. In addition, the simultaneous presence of resistance genes to 3rd generation cephalosporins and carbapenems in the same isolates is increasing. Recently, the presence of mobile genes linked to colistin resistance has also been described, in some cases with resistance percentages higher than 30%. Most likely, this evolution of colistin resistance is linked to its use in aquaculture, and, together with the evolution of β -lactam resistance, may be turning this genus into a reservoir of resistance genes that may affect other species much more frequently linked to human infections, such as *Enterobacterales*.

Keywords: *Aeromonas*; human infection; antibiotic resistance

1. Genus *Aeromonas*. General characteristics.

The genus *Aeromonas*, included in the family *Aeromonadaceae*, consists of a group of Gram-negative bacilli widely distributed in numerous ecosystems, such as plants and soils, although they are more commonly found in aquatic environments [1]. It comprises more than 30 species and behaves primarily as a fish pathogen [2]. However, *Aeromonas* has also been described associated to many other animals (insects, reptiles, amphibians, birds [3], as well as to human infections, in which it has progressively gained importance, especially linked to resistance to some antimicrobials such as colistin [4].

From the point of view of its physiology, *Aeromonas* is classified into two main groups:

- Psychrophilic species (grow well between 22°C and 28°C). The most representative species in this group is *A. salmonicida*, a primarily fish pathogen, although it has occasionally been described as a human pathogen [5,6].

- Mesophilic species (grow well at temperatures over 35°C (usually between 35 °C and 37°C). Includes most *Aeromonas* commonly isolated as human pathogens [3].

Nineteen of the more than 30 species described so far in this genus, are considered as emerging human pathogens. Recent studies suggest that more than 95% of cases described in humans are caused by 3 species: *A. caviae*, *A. veronii* biovar *sobria*, and *A. hydrophila* [1], recently joined by *A. dhakensis*, linked mainly to wound infections [7].

Its first description in human disease did not occur until 1954 [8]. Human infections with *Aeromonas* are mainly associated with gastroenteritis, although its etiological role is often unclear. It is also associated with wound infections, skin and soft tissue infections and eventually bacteraemia and sepsis [9].

Classically, it has been considered a much less frequent pathogen than the main digestive pathogens (*Salmonella*, *Shigella*, *Campylobacter*, *E. coli*...) [10] or skin and soft tissue pathogens [*S. aureus*, *S. pyogenes*...] [11], although it is probably an under-diagnosed pathogen, especially when its identification is based on biochemical activity panels [12].

Studies carried out in Asian and African countries estimate *Aeromonas* isolates in patients with diarrhea at <5% of total diarrheal samples [13–17]. In terms of species and subspecies frequency, *A. caviae* and *A. veronii* rank, as enteric pathogens, well above *A. hydrophila* in virtually all studies [17].

A recent study [18] conducted in Australia also shows a clear predominance of *A. veronii* by *sobria* in fecal samples (66.7% of *Aeromonas* fecal isolates), while in wound samples *A. dhakensis* clearly predominates, followed by *A. hydrophila*, and in blood cultures the most frequent species are *A. dhakensis* and *A. caviae*, which, in whole, account for more than 63% of blood cultures positive for *Aeromonas* spp. However, this species differentiation may be biased both by geographical factors and by the fact that the identification was carried out by MALDI-TOF MS and sequencing of the *rpoB* and *gyrB* genes, methods that allow reliable identification of species such as *A. dhakensis*, whose identification by classical biochemical methods is much more complex and less reliable. Similar results in purulent infections, with a clear predominance of *A. dhakensis*, have also been published by other authors [19].

Although human infections by *Aeromonas* are described preferentially associated with certain risk factors (advanced age, immunosuppression) [20], they can appear in patients with no known risk factors and in any age group [21], due to their capacity to overcome the immune mechanisms of the host, which allows them to infect both immunosuppressed and immunocompetent patients. [8].

Its pathogenesis is multifactorial and is associated with a wide number of enzymes and toxins it can produce, such as proteases, lipases, hemolysins, cytotoxins and enterotoxins [22].

Transmission occurs primarily through ingestion or contact with aquatic collections that constitute its primary habitat [23], although its eventual resistance to standard potabilization procedures may result in an alternative source of human transmission [24]. Another source of transmission is the consumption of contaminated food of plant or animal origin, especially of aquatic origin and in preparations that do not involve cooking of the product [22].

One factor that may be important in modulating the pathogenicity of *Aeromonas* is the temperature of the aquatic habitat, which may have significance under current global warming conditions. It has been shown in several *Aeromonas* species that warming of their habitat above usual temperatures increases the expression of different virulence factors [2,25].

In fact, numerous enzymes and toxins have been identified in *Aeromonas* that are susceptible to behave as pathogenicity factors such as the capsule itself, types 2, 3 and 6 secretion systems, DNAases, proteases, lipases, elastases, adhesins, hemolysins, cytotoxins and enterotoxins [26–28].

2. *Aeromonas*. Antibiotic Resistance. Carbapenems Resistance

As with other Gram-negative bacilli, it is a group of microorganisms capable of developing resistance to numerous antibiotics [4].

Most *Aeromonas* species can show resistance to antimicrobials, regardless of the origin of the isolates. In *Aeromonas* the production of inducible cephalosporinases is frequent, and already in the early 2000s the presence of plasmid-mediated carbapenemases was described [29]. Different species of *Aeromonas* (*A. hydrophila*, *A. caviae*, *A. veronii*, *A. schubertii*) have shown their ability to produce β -lactamases of classes B, C and D [29]. Occasionally even the presence of ESBL of the TEM group has been described, specifically a TEM-24, probably acquired from a clone of *Enterobacter aerogenes* highly prevalent in France, as a clinical isolate, at that time. [30].

In recent years, clinical isolates resistant to 3rd generation cephalosporins and carbapenems have been described in numerous countries [31–33]. In studies of the 1990s [34,35], CphA was the most common carbapenemase in *Aeromonas*. It is an inducible chromosomal metallo- β -lactamase, present in numerous *Aeromonas* species. However, since 2008, the presence of typically plasmid-encoded carbapenemases, such as VIM, IMP [29] and NDM [36], began to be described.

Currently, genes encoding both classical β -lactamases and metallo- β -lactamases are frequently found in most *Aeromonas* species, with no major differences between clinical and environmental isolates [31–33].

Studies of isolates of environmental origin suggest the presence of high levels of resistance in non-human ecosystems. This suggests a possible environmental reservoir of resistance genes, which poses a clear danger for a possible transfer of these multidrug-resistant (MDR) profiles to microorganisms of this or other genus, linked to human infections.

Previous studies have demonstrated the ability of *Aeromonas* to acquire and donate DNA by transformation [37], as is the case with other microorganisms such as *Streptococcus pneumoniae*, at least under laboratory conditions.

Regardless of their ability to acquire DNA from other microorganisms, even belonging to other genera, through transformation, a probably determining element in the spread of antimicrobial resistance in *Aeromonas* is the acquisition of resistance genes through mobile genetic elements. In this regard, the existence of integrons has been demonstrated in numerous *Aeromonas* species, including some of the most frequent species as human pathogens and, associated with them, different cassette genes associated with resistance to different families of antimicrobials (trimethoprim, chloramphenicol, β -lactams, aminoglycosides, etc.) [38].

Several studies have demonstrated the possibility of transferring different genetic elements associated with antimicrobial resistance between human digestive pathogens and environmental *Aeromonas*, which can thus acquire these elements of resistance, and behave at the same time as a source of these elements for species that may eventually behave as pathogens [39–41].

A recent meta-analysis shows how the levels of resistance to *Aeromonas* in clinical isolates are generally not alarming when compared to current levels of other Gram-negatives, such as enterobacteria, *Pseudomonas* or *Acinetobacter*. Thus, the levels of resistance to gentamicin are 10.8%, the levels of resistance to 3rd and 4th generation cephalosporins are between 7.7 and 12.6%, and the levels of resistance to ciprofloxacin and levofloxacin are 7–8% [42].

A very recent study focused only on human *Aeromonas* infections diagnosed over the last 14 years [43], covering 112 isolates, also shows acceptable levels of sensitivity to aminoglycosides, 3rd generation cephalosporins, aztreonam and fluoroquinolones, with resistance rates of less than 7.1% in all cases. However, resistance percentages to carbapenems are in the 40–60% range, which leads us to suspect an important diffusion of either CphA or carbapenemases described in *Aeromonas* in the first decade of the 2000s.

These results also coincide with what was published in Spain in 2015, with imipenem resistance figures, in clinical isolates, of 34.5%, much higher than those found in environmental sources (8.8%) and in fish fauna (18.8%) [44].

However, a study conducted in China and published in 2019, on isolates obtained between 2015 and 2017, shows discreetly higher resistance percentages in some 3rd generation cephalosporins (ceftriaxone, 14.8%), but still shows percentages below 10% in 4th generation cephalosporins (cefepime, 4.3%), aminoglycosides (gentamicin, 5.2%) and fluoroquinolones (ciprofloxacin, 6.1%). Surprisingly, and in contrast to what was already recorded at that time in other studies, the percentages of carbapenem resistance are also below this figure (imipenem, 2.6%) [45].

Another interesting fact observed in this study [45] is the clear difference in the levels of resistance observed in isolates obtained from intestinal (imipenem, 2%; ceftriaxone, 5.1%; cefepime, 1%; gentamicin, 2%; ciprofloxacin, 1%) and extraintestinal infections (imipenem, 25.9%; ceftriaxone, 70.6%; cefepime, 23.5%; gentamicin, 23.5%; ciprofloxacin, 35.3%).

Another study [46] conducted in China and published in 2023, on 188 intestinal and extraintestinal isolates of *Aeromonas* obtained between 2013 and 2020, also shows significantly higher levels of resistance in extraintestinal isolates in cases of ceftazidime (22.8% vs 6.7%), ceftriaxone (34.8 vs 6.7%), imipenem (23.3% vs 3.2%) and ciprofloxacin (20.2 vs 3.3%). It is true that these differences may also have to do with the different species distribution since, in this study, more than 50% of the intestinal isolates corresponded to *A. veronii*, while *A. caviae* and *A. hydrophila* predominated in the extraintestinal isolates.

The study on resistance mechanisms of these strains shows that CphA remains the most frequent carbapenemase. However, the co-presence, in some isolates, of different types of carbapenemases

with TEM, conventional and ESBL beta-lactamases, mainly from the CTX-M group, is of concern, which may pose important challenges from a therapeutic point of view [46].

In this regard, it should be noted that a recently published article on clinical isolates obtained in Iran between 2018 and 2020 already puts the presence of ESBLs at 60%, with a clear predominance of CTX-M, and the presence of VIM, KPC, NDM and IMP-type carbapenemases at 50%, regardless of the predictably high presence of CphA, which is not collected in the study [32].

However, a study conducted in China specifically on invasive *Aeromonas* infections in haematological patients does not confirm these high levels of resistance in invasive infections, except in the case of carbapenems. In general, the percentages of resistance to the most common antibiotics remain below 10% (ceftazidime, 6.1%; ceftriaxone, 8.2%; cefepime, 0%; aztreonam, 8.2%; levofloxacin, 2.1%; gentamicin, 4.1%), and only carbapenems show significantly higher figures (imipenem, 70.8%; meropenem, 71.4%) [47].

Recent studies focused on *A. dhakensis*, a species whose clinical importance has grown rapidly, also show similar data for 3rd and 4th generation cephalosporins, aztreonam, and aminoglycosides, with relatively low resistance figures, and high resistance figures for carbapenems, ranging from 41.9% for meropenem to 76.9% for imipenem. [48].

A study of *Aeromonas* obtained from hospital wastewater showed that 97% carried *cphA* and 39.4% carried *blaKPC*. In addition, it was shown that *blaKPC* was located in plasmid susceptible to transfer to other species [49], suggesting that in some particularly critical areas, such as the hospital environment, the presence of these resistance mechanisms may be growing rapidly.

3. Colistin Resistance

A cause of concern in relation to *Aeromonas* and antimicrobial resistance, is colistin resistance. The previously cited meta-analysis [42] shows an overall colistin resistance of 21.2%, which rises to 30.7% in clinical strains.

Colistin is a cationic peptide antibiotic mainly used in severe infections caused by multidrug-resistant gram-negative bacteria. Colistin was obtained from *Bacillus polymyxa* in 1947 and licensed for therapeutic usage in the 1950s as an intravenous preparation [50]. Due to its considerable toxicity and side effects, colistin has always been a restricted use antimicrobial, which has probably contributed, over the years, to its high levels of susceptibility.

The main target for colistin is the outer cell membrane of Gram-negative bacteria. Moreover, cationic colistin binds to the anionic lipid A, an essential component of LPS of Gram-negative bacteria. The interaction between lipid A and colistin causes a displacement of Ca²⁺ and Mg²⁺ ions from LPS. This results in disruption of the permeability barrier of the outer membrane, which in turn increases uptake of the polymyxin, leading to loss of cellular contents and finally bacterial killing [51–54]. Resistance to colistin in bacteria can arise by different mechanisms, such as capsule formation, overexpression of efflux pumps [53] or loss of LPS through mutations in the *lpxA*, *lpxC*, and *lpxD* genes [52]. However, resistance to colistin occurs mainly because of the introduction of a series of modifications in the structure of LPS, resulting in a reduction of its negative charge which decreases its affinity for colistin. [55–57].

Despite colistin has been extensively used in livestock farming, both for therapeutic and prophylactic purposes [58], colistin resistance has remained infrequent until recently [59,60]. It was commonly considered that resistance to colistin was primarily mediated by chromosomal mutations, which limited its capacity for horizontal transfer of resistance [60]. These chromosomal processes involved chromosomal mutations (e.g., *pmrA/pmrB*, *phoP/phoQ*, and the *mgrB* gene) that trigger the *arnBCADTEF* operon, as well as the phosphoethanolamine (pEtN) transferase gene *pmrC* (also known as *eptA*), which facilitates the synthesis and transfer of aminoarabinose (L-Ara4N) and pEtN to lipid A [61], modifying its charge and reducing its affinity for colistin.

A decisive factor in the dissemination of colistin resistance among Gram-negative bacteria has been the horizontal transfer of plasmid-borne genes, such as mobile colistin resistance (*mcr*). MCR belongs to the pEtN enzyme family, thus its expression results in the incorporation of pEtN into lipid A, lipid A charge modification and colistin affinity decrease [57,62–64].

In 2015, the first plasmid-mediated mobile colistin-resistance gene (*mcr-1*) was discovered in China, in *E. coli* isolated from pigs [65] and thereafter Enterobacterales carrying *mcr-1* have been

detected all over the world. Additional *mcr* determinants, including *mcr-2* to *mcr-10*, along with several variants have been reported [66–73].

mcr genes are believed to have originated from intrinsic, chromosomal *mcr*-like genes present on *Moraxella*, *Aeromonas*, *Shewanella* and other mostly environmental bacteria [74].

Resistance to colistin in *Aeromonas* has been described in different areas, probably linked to its extensive use in aquaculture, but it seems to be more frequent in the clinical setting [75]. In 2016–2017, a study conducted on 6497 bacterial isolates obtained from 13 provinces in China demonstrates the presence of *mcr-3* in 49 of them, of which eight corresponded to different species of the genus *Aeromonas* [76].

In a recent study of 144 clinical isolates of *Aeromonas* in six tertiary hospitals in Japan, conducted in 2022, *A. caviae* [87 isolates], *A. hydrophila* (25 isolates), *A. veronii* (20 isolates), and *A. dhakensis* (9 isolates) were the most frequent species. This study shows the presence of *mcr-3* genes in 28% of the isolates (mainly in *A. hydrophila* and *A. dhakensis*), and of *mcr-7* in 13% (mainly in *A. veronii*) [77].

The emergence and the worldwide dissemination of *mcr* has endangered colistin efficacy, raising public health concerns [78].

4. Treatment Alternatives

As early as 1995, it was suggested that some of the most empirically used antimicrobials in systemic infections, such as penicillins and their combinations with classic β -lactamase inhibitors (amoxicillin/clavulanic acid, piperacillin/tazobactam) were not considered adequate options for the treatment of *Aeromonas* infections, since the activity of these penicillins was irregular and β -lactamase inhibitors did not substantially improve their efficacy [80]. However, at that time, the use of 3rd generation cephalosporins and carbapenems was still advocated, given the low prevalence of resistance [79].

However, the study by Sakurai et al. [77] shows high levels of resistance in piperacillin/tazobactam (30%), 3rd generation cephalosporins (34% for cefotaxime) and carbapenems (24.3% for imipenem). This sensitivity profile means that failure of conventional empirical treatments cannot be ruled out. In fact, the analysis of the 105 patients with *Aeromonas* hepatobiliary infection included in this study, shows that only 46% received appropriate antimicrobial therapy within 48 hours of diagnosis.

A study published in Korea in 2016 [80], on 242 cases of *Aeromonas* bacteraemia registered between 2000 and 2013, referred to lower resistance percentages, around 15% for piperacillin/tazobactam, 10–15% for 3rd generation cephalosporins and 10% for carbapenems, despite which the percentage of initial empirical treatment that was considered inadequate was over 40%.

A recently published study in Saudi Arabia [81] on 24 cases of human *Aeromonas* infections recorded between 2015 and 2022, shows a resistance rate of 58.3% for piperacillin/tazobactam, 75% resistance to ceftriaxone, 83.3% to ceftazidime and 62.5% to meropenem, which is even significantly higher than previous studies [77]. However, 4th generation cephalosporins (cefepime), fluoroquinolones and aminoglycosides, which show no resistance among the isolates tested, continue to perform very well.

It is difficult to have an overview regarding the treatment of human *Aeromonas* infections, since the described cases in which treatment is specified are scarce, and most of them are descriptions of individual cases. However, given the sensitivity data reported in recent studies [77–81], it seems prudent, especially in severe invasive cases, and when there are risk factors suggesting the possibility of *Aeromonas* infection, to avoid the use of penicillins, including the combination of penicillins with classical β -lactamase inhibitors, 3rd generation cephalosporins and carbapenems, preferably resorting to 4th generation cephalosporins, aminoglycosides, and fluoroquinolones.

In any case, the rapid spread of resistance to β -lactam antibiotics, including carbapenems, together with the spread of plasmid-mediated resistance to colistin, poses a risk both from the point of view that human infections with *Aeromonas* will have increasingly complex treatments, and from the perspective that *Aeromonas* may become a reservoir of resistance genes, leading eventually to increases in resistance to antimicrobials that are not yet a massive problem, such as colistin. To prevent this from happening, we need both a prudent use of antimicrobials in human therapeutics, as well as a thorough control of their use in other areas such as animal nutrition, aquaculture, etc.

In few cases will the importance of the "One Health" concept be as evident as in this one.

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