Review

Aeromonas Infections in Humans, Antibiotic Resistance and Treatment Options

Noelia Calvo Sánchez , Laura Sancha Domínguez , Ana Cotos Suárez , Juan Luis Muñoz Bellido *

Posted Date: 25 July 2025

doi: 10.20944/preprints202507.2139.v1

Keywords: aeromonas; human infection; antibiotic resistance

 doi:10.20944/preprints202507.2139.v1

Review

Aeromonas Infections in Humans, Antibiotic Resistance and Treatment Options

Noelia Calvo Sánchez [1], Laura Sancha Domínguez [2], Ana Cotos Suárez [2] and Juan Luis Muñoz Bellido [3,*]

[1] Area de Microbiología, Complejo Hospitalario Universitario de Orense (SPAIN)
[2] Servicio de Microbiología, Hospital Universitario de Salamanca (SPAIN); Instituto de Investigación Biomédica de Salamanca (IBSAL). Universidad de Salamanca, SACYL, CSIC
[3] 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)
* 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. General Characteristics of *Aeromonas*

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 (5):

- psychrophilic non motile *Aeromonas*, designated *Aeromonas salmonicida*, with optimal growth temperatures of 22-25°C, that infects reptiles and fish.
- motile mesophilic aeromonads, with an optimal growth temperature of 35-37° C [5,6], which includes most *Aeromonas* commonly isolated as human pathogens [3].

 doi:10.20944/preprints202507.2139.v1

2. *Aeromonas* as a Human Pathogen

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: *Aeromonas caviae*, *Aeromonas veronii* biovar *sobria*, and *Aeromonas hydrophila* [1], recently joined by *Aeromonas 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, such as *Salmonella, Shigella, Campylobacter* and *Escherichia coli* [10] or skin and soft tissue pathogens, such as *Staphylococcus aureus* and *Streptococcus pyogenes* [11], although it is probably an under-diagnosed pathogen, especially when its identification is based on biochemical activity panels [12].

A study conducted in France [13] in 2006 on 78 *Aeromonas* isolates showed that 44% of infections involved wounds, 26% bacteraemia, 19% enteritis, 6% respiratory infections and 5% other infections. Overall, 40% corresponded to *A. veronii*, 35.7% to *A. hydrophila* and 21.4% to *A. caviae*, although *A. hydrophila* predominated in wound infections, *A. caviae* in bacteraemias and *A. veronii* had a more even distribution among the different types of infection.

Studies carried out mainly in Asian and African countries estimate *Aeromonas* isolates in patients with diarrhea at <5% of total diarrheal samples [14–18]. In terms of species and subspecies frequency, *A. caviae* and *A. veronii* rank, as enteric pathogens, well above *A. hydrophila* in virtually all studies [19].

A recent study [20] conducted in Australia also shows a clear predominance of *A. veronii* bv *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. A more recent study also conducted in Australia, but focusing only on faecal isolates, also identifies *A. veronii* as the most frequent species causing gastreoenteritis (52%), followed by *A. caviae* (27%) and *A. hydrophila* (12.5%) [21]. Main prevalence results appear in Table 1. 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 [22]. This behavior is likely to be associated with the higher virulence shown by *A. dhakensis*, compared to other *Aeromonas* species, such as *A. veronii, A. caviae,* and *A. hydrophila*, against fibroblast C2C12 cell line, BALB/c mouse, and *Caenorhabditis elegans* models. [23,24]. Moreover, a type 6 secretion system (T6SS), has been shown in animal models to be associated with an increased ease to produce disseminated infections [25]. On the other hand, exotoxin A has been shown in several studies to be an important virulence factor for *Aeromonas*, showing high virulence in *C. elegans* models [22], and highly virulent to mice [26].

Table 1. *Aeromonas* species prevalence in different studies (%).

Reference	Prevalence	*A. hydrophila*	*A. caviae*	*A. sobria*	*A. veronii*	*A. dhakensis*	Origin of isolates
13	3.1	9	34	26	29	#	Enteric
14	4.25	2.7	1.6	#	#	#	Enteric + extraintestinal
15	4.3	5.7	25.3	#	42.5	#	Enteric and environment

 doi:10.20944/preprints202507.2139.v1

16	*	5.2	41.7	#	31.3	13.9	Enteric + extraintestinal
17	*	1.0	86.7	#	12.2	#	Enteric
18	*	20	14	#	21	39	Enteric + extraintestinal
19	*	17.1	14.5	#	18.4	48.7	Wound
25	*	3.5	68.1	#	15.5	#	Enteric and environment
27	*	26.1	28.7	#	25	18.1	Enteric + extraintestinal

*No overall prevalence specified in the study. #Not studied.

A recent study suggests that the age of the patient may also determine which species are most prevalent. In this study, *A. veronii* would be the most prevalent species at all ages, but would be especially prevalent in young adults, while *A. caviae* would be more frequent in young children and adults over 60 years of age. This higher prevalence in adults over 60 years of age would also occur for A. hydrophila and *A. dakhensis* (27).

Similarly, a recently published study from Iran suggests that *Aeromonas* infection may be more prevalent in immunocompromised individuals. This study, conducted on 130 immunocompromised diarrhoea patients, mostly haematological patients, showed that the prevalence of *Aeromonas* was significantly higher than that of *Clostridioides difficile*, and up to 10 times higher than that of *Campylobacter jejuni* (28).

However, although the presence of specific virulence genes has been demonstrated in the SSU strain, comparative studies of the genomes of different *A. dhakensis* strains show that the presence of these genes is not constant in *A. dakhensis* so that, although there is relevant evidence regarding a higher virulence of *A. dakhensis* [22], the virulence mechanisms remain insufficiently defined.

Although human infections by *Aeromonas* are described preferentially associated with certain risk factors (advanced age, immunosuppression) [27], they can appear in patients with no known risk factors and in any age group [28], 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 [29].

A recent study [30] demonstrates not only that the preferred species are not the same in intestinal infections (*A. veronii*) and extraintestinal infections (*A. caviae, A. hydrophila*), but that genes such as *act*, encoding an enterotoxin, *aexT*, encoding an ADP ribosyltransferase toxin that has recently been identified as involved in the cytotoxicity of *A. salmonicida*, and *asc*F-G, encoding a type III secretion system, are more frequent in intestinal isolates. In contrast, pathogenicity factors such as *alt*, encoding a thermolabile *lip* cytotoxic enterotoxin, *hly*A, encoding a hemolysin, *ela*, encoding an elastase, and, encoding a lipase, were significantly more frequent in isolates obtained from extraintestinal infections.

Transmission occurs primarily through ingestion or contact with aquatic collections that constitute its primary habitat [31], although its eventual resistance to standard potabilization procedures may result in an alternative source of human transmission [32]. 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 [25].

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 [2,33]. In fact, numerous enzymes and toxins have been identified in *Aeromonas* that are susceptible to behave as pathogenicity factors

 doi:10.20944/preprints202507.2139.v1

such as the capsule itself, types 2, 3 and 6 secretion systems, DNAases, proteases, lipases, elastases, adhesins, hemolysins, cytotoxins and enterotoxins [34–40].

3. *Aeromonas*. Antibiotic Resistance

As is the case with other Gram-negative bacilli, *Aeromonas* is a genus 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 [41]. Different species of *Aeromonas* (*A. hydrophila, A. caviae, A. veronii, Aeromonas schubertii*) have shown their ability to produce β-lactamases of classes B, C and D [42]. 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. [43].

A study conducted in France in 2006 on 78 *Aeromonas* isolates [13] showed low levels of susceptibility to amoxicillin, and 1st generation cephalosporins in *A. hydrophila* as well as in *A. veronii* and *A. caviae*. Susceptibility figures were much higher to 3rd and 4th generation cephalosporins, carbapenems, fluoroquinolones and aminoglycosides. (Table 2).

Table 2. Antibiotic susceptibility (% susceptible+%intermediate) of *Aeromonas* in different studies.

Reference	AMP/AMOX	AMOX/CLAV	CIP/LEV	SXT	CRO/CTX	CFP	GEN/AK	IMP/MER
13	5.6	100	94.5	91.7	100	*	100	100
13	14	*	54	60	76	100	100	100
15	14	*	98	99.8	*	*	*	*
16	6.1	87	93.9	94.8	85.2	95.7	94.8	97.4
19	*	*	100	*	97,3	100	100	89.2
24	1.2	6.2	75.8	83.9	97.3	97.6	93.7	76
27	*	*	95.7	*	70.2	89.4	*	95.2

AMP: Ampicillin; AMOX Amoxicillin; AMOX/CLAV: Amoxicillin/clavulanic acid; CIP: Ciprofloxacin; LEV: Levofloxacin; SXT: Trimethoprim+sulphamethoxazole; CRO: ceftriaxone; CTX: Cefotaxime; CFP: Cefpirome; GEN: Gentamicin; AK: Amikacin; IMP: Imipenem; MER: Meropenem. *Not studied.

In recent years, clinical isolates resistant to 3rd generation cephalosporins and carbapenems have been described in numerous countries [44–46]. In studies of the 1990s [47,48], 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 [41,45] and NDM [45,49], began to be described. Data from main antibiotic resistance studies appear in Table 2.

Currently, genes encoding both classical β-lactamases and metallo-β-lactamases and other genes associated to antibiotic resistance are frequently found in most *Aeromonas* species, with no major differences between clinical and environmental isolates [37–39]. This expansion of plasmid-mediated carbapenemases is occurring in clinical settings around the world, and is most likely related to the global increase in carbapenem use as a consequence of the increasing diffusion of ESBL, mainly in enterobacteria.

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 [50], as is the case with other microorganisms such as *Streptococcus pneumoniae*, at least under laboratory conditions.

 doi:10.20944/preprints202507.2139.v1

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.) [51].

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 [52–54]

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% [55].

A very recent study focused only on human *Aeromonas* infections diagnosed over the last 14 years [56], 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%) [57].

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%) [16]

Another interesting fact observed in this study [16] 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 [34] 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 conventional TEM and ESBL beta-lactamases, mainly from the CTX-M group, is of concern, which may pose important challenges from a therapeutic point of view [34].

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 [45]

 doi:10.20944/preprints202507.2139.v1

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%) [58].

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. [59].

A study of *Aeromonas* obtained from hospital wastewater showed that 97% carried *cphA* and 39.4% carried *bla*KPC. In addition, it was shown that *bla*KPC was located in plasmid susceptible to transfer to other species [60], suggesting that in some particularly critical areas, such as the hospital environment, the presence of these resistance mechanisms may be growing rapidly.

Overall, the comparability of these results is limited, given the number of factors that may influence resistance levels (human or non-human origin, intestinal or extraintestinal origin of the isolates, species involved, etc.). Overall, it appears that the intestinal and extraintestinal isolates correspond mostly to different species, and this probably has an important influence on the resistance figures found. Similarly, the fact that some studies were conducted in immunocompromised patients may mean that the species associated with the extraintestinal cases are different, and thus modify the resistance figures. This without forgetting that, obviously, the greater or lesser use of the different families of antimicrobials, both at the clinical level and in other areas, can have an impact on the overall resistance figures for both Aeromonas and other bacterial genera.

4. Colistin Resistance

A cause of concern in relation to *Aeromonas* and antimicrobial resistance, is colistin resistance. The previously cited meta-analysis [55] 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 [61]. 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 [62–65]. Resistance to colistin in bacteria can arise by different mechanisms, such as capsule formation, overexpression of efflux pumps [64] or loss of LPS through mutations in the *lpx*A, *lpx*C, and *lpx*D genes [63]. 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. [66–68].

Despite colistin has been extensively used in livestock farming, both for therapeutic and prophylactic purposes [69], colistin resistance has remained infrequent until recently [70,71]. It was commonly considered that resistance to colistin was primarily mediated by chromosomal mutations, which limited its capacity for horizontal transfer of resistance [71]. These chromosomal processes involved chromosomal mutations (e.g., *pmrA*/*pmrB*, *phoP*/*phoQ*, and the *mgrB* gene) that trigger the *arn*BCADTEF 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 [71], modifying its charge and reducing its affinity for colistin.

 doi:10.20944/preprints202507.2139.v1

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 [68,72–75].

In 2015, the first plasmid-mediated mobile colistin-resistance gene (*mcr-1*) was discovered in China, in *E. coli* isolated from pigs [76] 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 [77–84].

mcr genes are believed to have originated from intrinsic, chromosomal *mcr*-like genes present on *Moraxella, Aeromonas, Shewanella* and other mostly environmental bacteria [85].

Resistance to colistin in *Aeromonas* has been described in different areas, including aquaculture, although it is not the most widely used antimicrobial in aquaculture, since, according to some authors, its use in this field is much lower than that of other antimicrobials such as tetracyclines, quinolones, amoxicillin, macrolides, sulfonamides and amphenicols [86]. Resistance to colistin seems to be more frequent in the clinical setting [87]. 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* [88].

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* (25isolates), *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. dakhensis*), and of *mcr*-7 in 13% (mainly in *A. veronii*) [89].

The emergence and the worldwide dissemination of *mcr* has endangered colistin efficacy, raising public health concerns [90].

5. 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 -lactamase inhibitors did not substantially improve their efficacy [89]. However, at that time, the use of 3rd generation cephalosporins and carbapenems was still advocated, given the low prevalence of resistance [84].

The study by Sakurai et al. [89] 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 [90], 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 [91] 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 [90]. 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 [89–93], it seems prudent, especially in severe invasive cases, and when there are risk factors suggesting the possibility

 doi:10.20944/preprints202507.2139.v1

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.

However, the resistance data available, especially in extraintestinal infections, make it necessary to consider new alternatives. In this sense, the new β-lactams and the new β-lactam- β-lactamase inhibitor combinations that have appeared in recent years may represent an important contribution, especially in extraintestinal infections, due to their severity and the greater frequency of resistant isolates.

In this sense, the new 5th generation cephalosporins (ceftaroline, ceftobiprole) do not provide significant improvements since, in general, their activity in Gram-negative infections is similar to that of 3rd generation cephalosporins [94]. With regard to new β-lactam/ β-lactamase inhibitor combinations, both avibactam, vaborbactam and relebactam inhibit β-lactamases of class A, including KPC, class C and, in the case of avibactam and relebactam, partially of class D , which allows good coverage of gram-negative bacilli, except for metallo-β lactamase producers.

As regards class B β-lactamase-producing isolates, both the combination of ceftazidime/avibactam with aztreonam and cefiderocol may be an alternative, although experience is scarce. However, it should be taken into account that, in isolates producing this type of carbapenemases, other antimicrobials such as colistin, aminoglycosides and fluroquinolones are frequently active, although frequently associated with less bactericidal activity or more toxicity.

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.

Author Contributions: Conceptualization, JLMB, NCS; references search and review, LSD, ACS; writing, NCS; writing—review and editing, JLMB. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Barger, P.C.; Liles, M.R.; Beck. B.H.; Newton,J.C.. Differential production and secretion of potentially toxigenic extracellular proteins from hypervirulent *Aeromonas hydrophila* under biofilm and planktonic culture. BMC Microbiol **2021**; 21: 8.
2. Fernández-Bravo, A., Figueras, M.J. An Update on the Genus *Aeromonas*: Taxonomy, Epidemiology, and Pathogenicity. Microorganisms **2020**; 8: 129.
3. Gonçalves Pessoa, R.B.; de Oliveira, W.F.;, Marques D.S.C.; Dos Santos Correia, M.T.; de Carvalho, E.V.M.M.; Coelho, L.C.B.B. The genus *Aeromonas*: A general approach. Microb Pathog **2019**; 130: 81-94.
4. Conte, D.; Palmeiro, J.K.; Bavaroski, A.A.; Rodrigues, L.S.; Cardozo, D.; Tomaz, A.P.; Camargo, J.O.; Dalla-Costa, L.M. Antimicrobial resistance in *Aeromonas* species isolated from aquatic environments in Brazil. J Appl Microbiol **2021**; 131: 169-181.
5. Parker,J.L., Shaw, J.G. *Aeromonas* spp. Clinical microbiology and disease J. Infect.,2011; 62: 109-118,

 doi:10.20944/preprints202507.2139.v1

6. Tewari, R.; Dudeja, M.; Nandy, S.; Das, A.K. Isolation of *Aeromonas salmonicida* from Human Blood Sample: A Case Report. J Clin Diagn Res **2014**; 8:139-40.
7. Chen, P.L.; Lamy, B.; Ko, W.C. *Aeromonas dhakensis*, an increasingly recognized human pathogen. Front Microbiol **2016**; 27: 793.
8. Caselitz, F.H. How the *Aeromonas* story started in medical microbiology. Med Microbiol Lett **1996**; 5: 46-54.
9. Parker, J.L.; Shaw, J.G. *Aeromonas* spp. clinical microbiology and disease. J Infect **2011**; 62: 109-118.
10. Fleckenstein, J.M.; Matthew Kuhlmann, F.; Sheikh, A. Acute Bacterial Gastroenteritis. Gastroenterol Clin North Am **2021**; 50: 283-304.
11. Clebak, K.T.; Malone, MA. Skin Infections. Prim Care **2018**; 45: 433-454.
12. Lamy, B.; Laurent, F.; Verdier, I.; Decousser, J.W.; Lecaillon, E.; Marchandin, H.; Roger, F.; Tigaud, S.; de Montclos, H; colBVH Study Group; Kodjo, A. Accuracy of 6 commercial systems for identifying clinical *Aeromonas* isolates. Diagn Microbiol Infect Dis **2010**; 67: 9-14.
13. Lamy B, Kodjo A; colBVH Study Group; Laurent F. Prospective nationwide study of Aeromonas infections in France. J Clin Microbiol. 2009 Apr;47(4):1234-7.
14. Soltan Dallal MM, Mazaheri Nezhad Fard R, Kavan Talkhabi M, Aghaiyan L, Salehipour Z. Prevalence, virulence and antimicrobial resistance patterns of Aeromonas spp. isolated from children with diarrhea. Germs 2016; 6: 91-6.
15. Mohan, B.; Sethuraman, N.; Verma, R.; Taneja, N. Speciation, clinical profile & antibiotic resistance in *Aeromonas* species isolated from cholera-like illnesses in a tertiary care hospital in north India. Indian J Med Res. **2017**; 146 (Supplement): S53-S58.
16. Mbuthia, O.W.; Mathenge, S.G.; Oyaro, M.O.; Ng'ayo, M.O. Etiology and pathogenicity of bacterial isolates: a cross sectional study among diarrheal children below five years in central regions of Kenya. Pan Afr Med J **2018**; 31 :88.
17. Li, F.; Wang, W.; Zhu, Z.; Chen, A.; Du, P.; Wang, R.; Chen, H.; Hu, Y.; Li, J.; Kan, B.; Wang, D. Distribution, virulence-associated genes and antimicrobial resistance of Aeromonas isolates from diarrheal patients and water, China. J Infect. **2015**; 70: 600-608.
18. Zhou, Y.; Yu, L.; Nan, Z.; Zhang, P.; Kan, B.; Yan, D.; Su, J. Taxonomy, virulence genes and antimicrobial resistance of *Aeromonas* isolated from extra-intestinal and intestinal infections. BMC Infect Dis **2019**; 19: 158.
19. Elorza, A.; Rodríguez-Lago, I.; Martínez, P.; Hidalgo, A.; Aguirre. U.; Cabriada J.L. Gastrointestinal infection with *Aeromonas*: incidence and relationship to inflammatory bowel disease. Gastroenterol Hepatol **2020**; 43: 614-619.
20. Sinclair, H.A.; Heney, C.; Sidjabat, H.E.; George, N.M.; Bergh, H.; Anuj, S.N.; Nimmo, G.R.; Paterson, D.L. Genotypic and phenotypic identification of *Aeromonas* species and CphA-mediated carbapenem resistance in Queensland, Australia. Diagn Microbiol Infect Dis **2016**; 85: 98-101
21. Yuwono C, Wehrhahn MC, Liu F, Riordan SM, Zhang L. The Isolation of *Aeromonas* Species and Other Common Enteric Bacterial Pathogens from Patients with Gastroenteritis in an Australian Population. Microorganisms. 2021; 9:1440.
22. Chen, P.L.; Wu, C.J.; Chen, C.S.; Tsai, P.J.; Tang, H.J.; Ko, W.C. A comparative study of clinical *Aeromonas dhakensis* and *Aeromonas hydrophila* isolates in southern Taiwan: *A. dhakensis* is more predominant and virulent. Clin Microbiol Infect **2014**; 20: 428-434.
23. Chen PL, Wu CJ, Tsai PJ, Tang HJ, Chuang YC, Lee NY, Lee CC, Li CW, Li MC, Chen CC, Tsai HW, Ou CC, Chen CS, Ko WC. Virulence diversity among bacteremic Aeromonas isolates: ex vivo, animal, and clinical evidences. PLoS One. 2014; 9: e111213.
24. Mosser T, Talagrand-Reboul E, Colston SM, Graf J, Figueras MJ, Jumas-Bilak E, Lamy B. Exposure to pairs of Aeromonas strains enhances virulence in the Caenorhabditis elegans infection model. Front Microbiol. 2015;;6: 1218.
25. Suarez G, Sierra JC, Sha J, Wang S, Erova TE, Fadl AA, Foltz SM, Horneman AJ, Chopra AK. Molecular characterization of a functional type VI secretion system from a clinical isolate of Aeromonas hydrophila. Microb Pathog. 2008; 44: 344-361.

 doi:10.20944/preprints202507.2139.v1

26. Masuyer G, Taverner A, MacKay J, Lima Marques AR, Wang Y, Hunter T, Liu K, Mrsny RJ. Discovery of mono-ADP ribosylating toxins with high structural homology to Pseudomonas exotoxin A. Commun Biol. 2025; 8: 413.
27. Singh A, Liu F, Yuwono C, Wehrhahn MC, Slavich E, Young AM, Chong SKT, Tay ACY, Riordan SM, Zhang L. Age-Dependent Variations in the Distribution of *Aeromonas* Species in Human Enteric Infections. Pathogens 2025; 14: 120.
28. Heydari H, Iranikhah A, Ghasemi A, Mohammadbeigi A, Sadat-Mirei SA, Shams S, Kermani S. Evaluation of the prevalence of Aeromonas spp., Campylobacter spp., and Clostridioides difficile in immunocompromised children with diarrhea. BMC Infect Dis. 2024 May 22;24(1):512.
29. Llovo J, Fusté MC, Bofill-Mas S. Virulence Factors of *Aeromonas spp*.: A Brief Review. Front Microbiol 2020; 11: 590050.
30. Ponnusamy D, Kozlova EV, Sha J, Erova TE, Azar SR, Fitts EC, Kirtley ML, Tiner BL, Andersson JA, Grim CJ, Isom RP, Hasan NA, Colwell RR, Chopra AK. Cross-talk among flesh-eating Aeromonas hydrophila strains in mixed infection leading to necrotizing fasciitis. Proc Natl Acad Sci U S A. 2016; 113: 722-727.
31. Nolla-Salas, J.; Codina-Calero, J.; Vallés-Angulo, S.; Sitges-Serra, A.; Zapatero-Ferrándiz, A.; Climent, M.C.; Gómez, J.; Masclans, J.R. Clinical significance and outcome of *Aeromonas* spp. infections among 204 adult patients. Eur J Clin Microbiol Infect Dis **2017**; 36: 1393-1403.
32. Silva, L.C.A.D.; Leal-Balbino, T.C.; Melo, B.S.T.; Mendes-Marques, C.L.; Rezende, A.M.; Almeida, A.M.P.; Leal, N.C. Genetic diversity and virulence potential of clinical and environmental *Aeromonas* spp. isolates from a diarrhea outbreak. BMC Microbiol **2017**; 17: 179.
33. Hoel, S.; Vadstein, O.; Jakobsen, A.N. Species Distribution and Prevalence of Putative Virulence Factors in Mesophilic *Aeromonas* spp. Isolated from Fresh Retail Sushi. Front Microbiol **2017**; 8: 931.
34. Zhang, D.; Li, W.; Hu, X.; Huang, H.; Zhang, X. Requiring Reconsideration of Differences of *Aeromonas* Infections Between Extra-Intestinal and Intestinal in Hospitalized Patients. Infect Drug Resist **2023**; 16: 487-497.
35. Harnisz, M.; Korzeniewska, E. The prevalence of multidrug-resistant *Aeromonas* spp. in the municipal wastewater system and their dissemination in the environment. Sci Total Environ **2018**; 626: 377-383.
36. Janda, J..;, Abbott, S.L. The genus *Aeromonas*: taxonomy, pathogenicity, and infection. Clin Microbiol Rev **2010**; 23: 35-73.
37. Pattanayak, S.; Priyadarsini, S.; Paul, A.; Kumar, P.R.; Sahoo, P.K. Diversity of virulence-associated genes in pathogenic *Aeromonas hydrophila* isolates and their *in vivo* modulation at varied water temperatures. Microb Pathog **2020**; 147: 104424.
38. Agarwal, R.K.; Kapoor, K.N.; Kumar, A. Virulence factors of aeromonads--an emerging food borne pathogen problem. J Commun Dis **1998**; 30: 71-78.
39. Cascón, A.; Yugueros, J.; Temprano, A.; Sánchez, M.; Hernanz, C.; Luengo, J.M.; Naharro, G. A major secreted elastase is essential for pathogenicity of *Aeromonas hydrophila*. Infect Immun. **2000**; 68: 3233-3241.
40. Rabaan, A.A.; Gryllos, I.; Tomás, J.M.; Shaw, J.G. Motility and the polar flagellum are required for *Aeromonas caviae* adherence to HEp-2 cells. Infect Immun **2001**; 69: 4257-4267.
41. Libisch, B.; Giske, C.G.; Kovács, B.; Tóth, T.G.; Füzi, M. Identification of the first VIM metallo-beta-lactamase-producing multiresistant *Aeromonas hydrophila* strain. J Clin Microbiol **2008**; 46: 1878-1880.
42. Rossolini GM, Walsh T, Amicosante G. The Aeromonas metallo-beta-lactamases: genetics, enzymology, and contribution to drug resistance. Microb Drug Resist. 1996; 2: 245-52.
43. Marchandin, H.; Godreuil, S.; Darbas, H.; Jean-Pierre, H.; Jumas-Bilak, E.; Chanal, C.; Bonnet, R. Extended-spectrum beta-lactamase TEM-24 in an *Aeromonas* clinical strain: acquisition from the prevalent *Enterobacter aerogenes* clone in France. Antimicrob Agents Chemother **2003**; 47: 3994-3995.
44. Nwaiwu, O.; Aduba, C.C. An *in silico* analysis of acquired antimicrobial resistance genes in *Aeromonas* plasmids. AIMS Microbiol **2020**; 6: 75-91.
45. Pourmohsen, M.; Shakib, P.; Zolfaghari, M.R. The Prevalence of *bla* VIM, *bla* KPC, *bla* NDM, *bla* IMP, *bla* SHV, *bla* TEM, *bla* CTX-M, and class I and II integrons Genes in *Aeromonas hydrophila* Isolated from Clinical Specimens of Qom, Iran. Clin Lab **2023**; 69 (1).

 doi:10.20944/preprints202507.2139.v1

46. Hilt, E.E.; Fitzwater, S.P.; Ward, K.; de St Maurice, A.; Chandrasekaran, S.; Garner, O.B.; Yang, S. Carbapenem Resistant *Aeromonas hydrophila* Carrying *bla cph*A7 Isolated From Two Solid Organ Transplant Patients. Front Cell Infect Microbiol **2020**; 10: 563482.
47. Rossolini, G.M.; Zanchi, A.; Chiesurin, A.; Amicosante, G.; Satta, G.; Guglielmetti, P. Distribution of *cph*A or related carbapenemase-encoding genes and production of carbapenemase activity in members of the genus *Aeromonas*. Antimicrob Agents Chemother **1995**; 39: 346-349.
48. Walsh, T.R.; Stunt, R.A.; Nabi, J.A.; MacGowan, A.P.; Bennett, P.M. Distribution and expression of beta-lactamase genes among *Aeromonas* spp. J Antimicrob Chemother **1997**; 40: 171-178.
49. Walsh, T.R.; Weeks, J.; Livermore, D.M.; Toleman, M.A. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect Dis. **2011**; 11: 355-362.
50. Bello-López, J.M.; Cabrero-Martínez, O.A.; Ibáñez-Cervantes, G.; Hernández-Cortez, C.; Pelcastre-Rodríguez, L.I.; Gonzalez-Avila, L.U.; Castro-Escarpulli, G. Horizontal Gene Transfer and Its Association with Antibiotic Resistance in the Genus *Aeromonas* spp. Microorganisms **2019**; 7:363.
51. Fluit, A.C.; Schmitz, F.J. Class 1 integrons, gene cassettes, mobility, and epidemiology. Eur J Clin Microbiol Infect Dis **1999**;18: 761-770.
52. Rhodes, G.; Huys, G.; Swings, J.; McGann, P.; Hiney, M.; Smith, P.; Pickup, R.W. Distribution of oxytetracycline resistance plasmids between aeromonads in hospital and aquaculture environments: implication of Tn1721 in dissemination of the tetracycline resistance determinant *tet*A. Appl Environ Microbiol **2000**; 66: 3883-3890.
53. Dubey, S,; Ager-Wiick, E.; Peng, B.; DePaola, A.; Sørum, H.; Munang'andu, H.M. The mobile gene cassette carrying tetracycline resistance genes in *Aeromonas veronii* strain Ah5S-24 isolated from catfish pond sediments shows similarity with a cassette found in other environmental and foodborne bacteria. Front Microbiol **2023**; 14: 1112941.
54. Drk, S.; Puljko, A.; Dželalija, M.; Udiković-Kolić, N. Characterization of Third Generation Cephalosporin- and Carbapenem-Resistant *Aeromonas* Isolates from Municipal and Hospital Wastewater. Antibiotics (Basel) **2023**;12: 513.
55. Jones, D.C.; LaMartina, E.L.; Lewis, J.R.; Dahl, A.J.; Nadig, N.; Szabo, A.; Newton, R.J.; Skwor, T.A. One Health and Global Health View of Antimicrobial Susceptibility through the "Eye" of *Aeromonas*: Systematic Review and Meta-Analysis..Int J Antimicrob Agents **2023**; 62: 106848.
56. Pineda-Reyes, R.; Neil, B.H.; Orndorff, J.; Williams-Bouyer, N.; Netherland, M. Jr; Hasan, N.A.; Tahashilder, M.I.; Sha, J.; Chopra, A.K.; Reynoso, D. Clinical presentation, antimicrobial resistance, and treatment outcomes of *Aeromonas* human infections: A 14-year retrospective study and comparative genomics of two isolates from fatal cases. Clin Infect Dis **2024**: ciae272.
57. Esteve, C.; Alcaide, E.; Giménez, M.J. Multidrug-resistant (MDR) *Aeromonas* recovered from the metropolitan area of Valencia (Spain): Diseases spectrum and prevalence in the environment. Eur. J. Clin. Microbiol **2015**; 34: 137–145.
58. Xu, C.; Lin, Q.; Zhao, Y.; Zhu, G.; Jiang, E.; Li, S.; Mi, Y.; Zheng, Y.; Zhang, F.; Zhu, X.; Xiao, Z.; Han, M.; Wang, J.; Feng, S. Clinical characteristics and risk factors of *Aeromonas* bloodstream infections in patients with hematological diseases. BMC Infect Dis **2022**; 22: 303.
59. Puah, S.M.; Khor, W.C.; Aung, K.T.; Lau, T.T.V.; Puthucheary, S.D.; Chua, K.H. *Aeromonas dhakensis*: Clinical Isolates with High Carbapenem Resistance. Pathogens.**2022**; 11: 833.
60. Zhang, Q.; Zhang, S.; Xu, B.; Dong, L.; Zhao, Z.; Li. B. Molecular Epidemiological Characteristics of Carbapenem Resistant *Aeromonas* from Hospital Wastewater. Infect Drug Resist **2024**; 17: 2439-2448.
61. Bialvaei, A.Z.; Samadi Kafil, H. Colistin, mechanisms and prevalence of resistance. Curr Med Res Opin **2015**; 31: 707-721.
62. Falagas, M.E.; Rafailidis, P.I.; Ioannidou, E.; Alexiou, V.G.; Matthaiou, D.K.; Karageorgopoulos, D.E.; Kapaskelis, A.; Nikita, D.; Michalopoulos, A. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. Int J Antimicrob Agents **2010**; 35: 194-199.

 doi:10.20944/preprints202507.2139.v1

63. Beceiro, A.; Moreno, A.; Fernández, N.; Vallejo, J.A.; Aranda, J.; Adler, B.; Harper, M.; Boyce, J.D.; Bou, G. Biological cost of different mechanisms of colistin resistance and their impact on virulence in *Acinetobacter baumannii*. Antimicrob Agents Chemother **2014**; 58: 518-526.
64. Baron, S.; Hadjadj, L.; Rolain, J.M.; Olaitan, A.O. Molecular mechanisms of polymyxin resistance: knowns and unknowns. Int J Antimicrob Agents **2016**; 48: 583-591.
65. El-Sayed Ahmed, M.A.E.; Zhong, L.L.; Shen, C.; Yang, Y.; Doi, Y.; Tian, G.B. Colistin and its role in the era of antibiotic resistance: an extended review (2000-2019). Emerg Microbes Infect **2020**; 9: 868-885.
66. Chew, K.L.; La, M.V.; Lin, R.T.P.; Teo, J.W.P. Colistin and Polymyxin B Susceptibility Testing for Carbapenem-Resistant and mcr-Positive *Enterobacteriaceae*: Comparison of Sensititre, MicroScan, Vitek 2, and Etest with Broth Microdilution. J Clin Microbiol **2017**; 55: 2609-2616.
67. Poirel, L.; Jayol, A.; Nordmann, P. Polymyxins: Antibacterial Activity, Susceptibility Testing, and Resistance Mechanisms Encoded by Plasmids or Chromosomes. Clin Microbiol Rev **2017**; 30: 557-596.
68. Mlynarcik, P.; Kolar, M. Molecular mechanisms of polymyxin resistance and detection of *mcr* genes. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub **2019**;163: 28-38.
69. Kempf, I.; Jouy, E.; Chauvin, C. Colistin use and colistin resistance in bacteria from animals. Int J Antimicrob Agent. **2016**; 48: 598-606.
70. Kempf, I.; Fleury, M.A.; Drider, D.; Bruneau, M.; Sanders, P.; Chauvin, C.; Madec, J.Y.; Jouy, E. What do we know about resistance to colistin in *Enterobacteriaceae* in avian and pig production in Europe? Int J Antimicrob Agents **2013**; 42: 379-383.
71. Olaitan, A.O.; Morand, S.; Rolain, J.M. Mechanisms of polymyxin resistance: acquired and intrinsic resistance in bacteria. Front Microbiol **2014**; 5: 643.
72. Liu. J.H.; Liu, Y.Y.; Shen, Y.B.; Yang. J.; Walsh, T.R.; Wang, Y.; Shen, J Plasmid-mediated colistin-resistance genes: *mcr*.Trends Microbiol **2024**; 32: 365-378.
73. Caniaux, I.; van Belkum, A.; Zambardi, G.; Poirel, L.; Gros, M.F. MCR: modern colistin resistance. Eur J Clin Microbiol Infect Dis **2017**; 36: 415-420.
74. Elbediwi, M.; Li, Y.; Paudyal. N.; Pan, H.; Li, X.; Xie, S.; Rajkovic, A.; Feng, Y.; Fang, W.; Rankin, S.C.; Yue, M. Global Burden of Colistin-Resistant Bacteria: Mobilized Colistin Resistance Genes Study (1980-2018). Microorganisms **2019**; 16: 461.
75. Gharaibeh, M.H.; Shatnawi, S.Q. An overview of colistin resistance, mobilized colistin resistance genes dissemination, global responses, and the alternatives to colistin: A review. Vet World **2019**; 12: 1735-1746.
76. Liu, Y.Y.; Wang, Y.; Walsh, T.R.; Yi, L.X.; Zhang, R.; Spencer, J.; Doi, Y.; Tian, G.; Dong, B.; Huang, X.; Yu, L.F.; Gu, D.; Ren, H.; Chen, X.; Lv, L.; He, D.; Zhou, H.; Liang, Z.; Liu, J.H.; Shen, J. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis. **2016**; 16: 161-168.
77. Xavier, B.B.; Lammens, C.; Ruhal, R.; Kumar-Singh, S.; Butaye, P.; Goossens, H.; Malhotra-Kumar, S. Identification of a novel plasmid-mediated colistin-resistance gene, *mcr*2, in *Escherichia coli*, Belgium, June 2016. Euro Surveill. **2016**; 21: 30280.
78. AbuOun, M.; Stubberfield, E.J.; Duggett, N.A.; Kirchner, M.; Dormer, L.; Nuñez-Garcia, J.; Randall, L.P.; Lemma, F.; Crook, D.W.; Teale, C.; Smith, R.P.; Anjum, M.F. *mcr*-1 and *mcr*-2 variant genes identified in *Moraxella* species isolated from pigs in Great Britain from 2014 to 2015. J Antimicrob Chemother **2017**; 72: 2745-2749.
79. Borowiak, M,; Fischer, J.; Hammerl, J.A.; Hendriksen, R.S.; Szabo, I.; Malorny, B. Identification of a novel transposon-associated phosphoethanolamine transferase gene, *mcr*-5, conferring colistin resistance in d-tartrate fermenting *Salmonella enterica* subsp. *enterica* serovar Paratyphi B. J Antimicrob Chemother **2017**; 72: 3317-3324.
80. Carattoli, A.; Villa, L.; Feudi, C.; Curcio, L.; Orsini, S.; Luppi, A.; Pezzotti, G.; Magistrali, C.F. Novel plasmid-mediated colistin resistance *mcr*-4 gene in *Salmonella* and *Escherichia coli*, Italy 2013, Spain and Belgium, 2015 to 2016. Euro Surveill. **2017**; 22: 30589.
81. Yin, W.; Li, H.; Shen, Y.; Liu, Z.; Wang, S.; Shen, Z.; Zhang, R.; Walsh, T.R.; Shen, J.; Wang, Y. Novel Plasmid-Mediated Colistin Resistance Gene *mcr*-3 in *Escherichia coli*. mBio **2017**; 8: e00543-17.

 doi:10.20944/preprints202507.2139.v1

82. Yang, Y.Q.; Li, Y.X.; Lei, C.W.; Zhang, A.Y.; Wang. H.N. Novel plasmid-mediated colistin resistance gene *mcr*-7.1 in *Klebsiella pneumoniae*. J Antimicrob Chemother **2018**; 73: 1791-1795.
83. Wang, X.; Wang, Y.; Zhou, Y.; Li, J.; Yin, W.; Wang, S.; Zhang, S.; Shen, J.; Shen, Z.; Wan, Y. Emergence of a novel mobile colistin resistance gene, *mcr*-8, in NDM-producing *Klebsiella pneumoniae*. Emerg Microbes Infect **2018**; 7: 122.
84. Carroll, L.M. Gaballa, A.; Guldimann, C.; Sullivan, G.; Henderson, L.O.; Wiedmann, M. Identification of Novel Mobilized Colistin Resistance Gene *mcr*-9 in a Multidrug-Resistant, Colistin-Susceptible *Salmonella enterica* Serotype Typhimurium Isolate. mBio **2019**; 10: e00853-19.
85. Hussein, N.H.; Al-Kadmy, I.M.S.; Taha, B.M.; Hussein, J.D. Mobilized colistin resistance (*mcr*) genes from 1 to 10: a comprehensive review. Mol Biol Rep **2021**; 48: 2897-2907.
86. Bondad-Reantaso, M.G., MacKinnon, B., Karunasagar, I., Fridman, S., Alday-Sanz, V., Brun, E., Le Groumellec, M., Li, A., Surachetpong, W., Karunasagar, I., Bin H., Dall'Occo, A., Urbani, R., Caputo, A.nReview of alternatives to antibiotic use in aquaculture. Rev Aquac 2023; 15: 1421-1451.
87. Gonzalez-Avila, L.U.; Loyola-Cruz, M.A.; Hernández-Cortez, C.; Bello-López, J.M.; Castro-Escarpulli, G. Colistin Resistance in *Aeromonas* spp. Int J Mol Sci **2021**; 22: 5974.
88. Xu, Y.; Zhong, L.L.; Srinivas, S.; Sun, J.; Huang, M.; Paterson, D.L.; Lei, S.; Lin, J.; Li, X.; Tang, Z.; Feng, S.; Shen, C.; Tian, G.B.; Feng, Y. Spread of MCR-3 Colistin Resistance in China: An Epidemiological, Genomic and Mechanistic Study. EBioMedicine **2018**; 34:139-157.
89. Sakurai, A.; Suzuki, M.; Ohkushi, D.; Harada, S.; Hosokawa, N.; Ishikawa, K.; Sakurai, T.; Ishihara, T.; Sasazawa, H.; Yamamoto, T.; Takehana, K.; Koyano, S.; Doi, Y. Clinical Features, Genome Epidemiology, and Antimicrobial Resistance Profiles of *Aeromonas* spp. Causing Human Infections: A Multicenter Prospective Cohort Study. Open Forum Infect Dis **2023**; 10: ofad587.
90. Rhee, J.Y.; Jung, D.S.; Peck, K.R. Clinical and Therapeutic Implications of *Aeromonas* Bacteremia: 14 Years Nation-Wide Experiences in Korea. Infect Chemother **2016**; 48: 274-284.
91. Hassan, I.Z.; Qekwana, D.N.; Naidoo, V. Prevalence of colistin resistance and antibacterial resistance in commensal *Escherichia coli* from chickens: An assessment of the impact of regulatory intervention in South Africa. Vet Med Sci **2024**; 10: e1315.
92. Jones, B.L.; Wilcox, M.H. *Aeromonas* infections and their treatment. J Antimicrob Chemother **1995**; 35: 453-461.
93. Kaki, R. A retrospective study of *Aeromonas hydrophila* infections at a university tertiary hospital in Saudi Arabia. BMC Infect Dis **2023**; 23: 671.
94. Soriano, A. Ceftaroline. Rev Esp Quimioter 2021; 34 (Suppl1):29-31.