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REVIEW

Aeromonas spp. clinical microbiology and disease

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Summary Members of the genus *Aeromonas* inhabit various aquatic environments and are responsible for, and are implicated in, a number of intestinal and extra-intestinal infections in humans as well as other animals. This review focuses on invasive human infection and disease and summarizes available findings regarding the microbiology and detection of *Aeromonas* spp., with emphasis on successful identification and diagnosis, and the control of disease in the population. Antimicrobial resistance and therapy of *Aeromonas* spp. is also discussed.

Introduction

The first time *Aeromonas* was considered as a human pathogen was in 1954 where it was isolated from the blood, lungs, liver, spleen, urine, cerebrospinal fluid (CSF), and necrotic parts of some striated muscles of an immune-compromised woman now known to be suffering from acute fulminating metastatic myositis. The woman died as a result of the infection.[1] Over subsequent years there have been many more confirmed cases of *Aeromonas* infection in humans, with varying severity, the most common being gastroenteritis. This review summarizes available (including very recent) information regarding the microbiology, clinical presentation, detection, and treatment of *Aeromonas* spp. with emphasis on successful identification and diagnosis, and the control of disease in the population.

Microbiology

The 9th edition of Bergey's Manual of determinative Bacteriology classified *Aeromonas* into two main groups; the psychrophilic non motile *Aeromonas*, designated *Aeromonas salmonicida* with optimal growth temperatures of 22–25 °C that infects reptiles and fish, and the much larger group of motile mesophilic aeromonads with an optimal growth temperature of 35–37 °C.[2] The motile mesophilic aeromonads are responsible for and are associated with a range of human diseases. The genera *Aeromonas*, *Oceanimonas*, and *Tolumonas* all belong to the family

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Aeromonadaceae[3,4] of the class of Gamma-proteobacteria. The family known as the *Aeromonadaceae* has now been recognised for over 15 years, where as previously, aeromonads were included in the family *Vibrionaceae*.

Table 4 of a comprehensive review by Janda and Abbott published in 2010[5] lists 21 published *Aeromonas* species and includes both validated and proposed species. Janda and Abbott also noted that *Aeromonas tecta* is the most recently identified and validated *Aeromonas* species that has been linked to human disease, having been isolated from clinical samples.[5,6] Four additional novel *Aeromonas* species have been proposed during 2010; *Aeromonas diversa*,[7] *Aeromonas fluvialis*,[8] *Aeromonas taiwanensis* and *Aeromonas sanarellii*.[9] Of these *A. diversa*, *A. taiwanensis* and *A. sanarellii* are likely to have clinical significance having been isolated from wounds.[7,9] Other species of *Aeromonas* linked to and found to be responsible for human disease include (but are not limited to); *Aeromonas hydrophila*, *Aeromonas media*, *Aeromonas caviae*, *Aeromonas veronii*, *Aeromonas schubertii*, *Aeromonas jandaei*, *Aeromonas trota*, *Aeromonas bestiarum*, and *Aeromonas popoffii*, with the three species *A. hydrophila*, *A. caviae* and *A. veronii* bv sobria (previously called *Aeromonas sobria*) the most frequently isolated and having the most clinical significance.[10] It is important to note that a great deal of importance was once attributed to *A. hydrophila* in terms of human disease, and as a result it is the most referenced species of *Aeromonas*. This importance has now been disputed due to the limitations in the identification of other mesophilic species such as *A. caviae* which previously fell under the umbrella *of A. hydrophila*, but are now known to also play a considerable role in human disease. For further information on the taxonomy, nomenclature and classification of *Aeromonas* we highly recommend the comprehensive reviews of Janda and Abbott,[5,11] Figueras,[12] and Martin-Carnahan and Joseph.[13]

Aeromonas are Gram-negative straight rods with rounded ends which measure 1−3.5 μm across.[13] They are facultative anaerobes which are cytochrome oxidase, catalase and indole positive. They are able to ferment maltose, D-galactose, and trehalose. Negative characteristics for motile *Aeromonas* species include the production of urease, pectinase, ornithine decarboxylase, and tryptophan and phenylalanine deaminases. They are also unable to ferment xylose, sorbose, erythritol, adonitol, dulcitol, or produce H_2S when grown on Kligler iron medium.[2]

Aeromonads also produce a number of virulence factors which are the focus of many medical microbiology researchers. These include a number of haemolysins including aerolysin, proteases, adhesins, invasins, enterotoxins, phospholipase and lipase. A recent study identified the presence of two Shiga toxin genes (*stx1* and *stx2*) in *Aeromonas* isolates from clinical samples of patients suffering with extra-intestinal infections and diarrhoea.[14] Shiga toxins when produced in bacteria can cause diarrhoea, and in more rare cases, haemorrhagic colitis and haemolytic uremic syndrome.[15] The toxin genes were first identified by PCR and subsequently analysed by sequencing making this the first study to successfully sequence *stx1* and *stx2* from *Aeromonas*.[14]

Motility of the mesophilic aeromonads requires the expression of a single polar flagellum (Fig. 1). A number of the mesophilic species have been shown to express an entirely distinct lateral flagella system when grown on solid media that is required for swarming motility. Interactions between a number of mesophilic *Aeromonas* species and human cells such as Hep-2 and Caco-2 have been investigated[16] and an example has been given here (Fig. 2). Homologues of genes associated with a type III secretion system (T3SS) have been identified in the aeromonads, including both clinical and environmental isolates.[17,18] The T3SS is commonly associated with pathogenesis and virulence, and is required for the injection of bacterial proteins in to eukaryotic cells. In *A. hydrophila* AH-3 the construction of an insertion mutant of the TTSS gene *ascV* resulted in reduced toxicity and virulence in comparison with the wild-type strain.[17] A functional type VI secretion system (T6SS) has also been identified in a clinical isolate of *A. hydrophila*.[19] The physiological role and mechanism of this secretion system is still relatively poorly understood, however it is known that the components of the T6SS are encoded on a single gene cluster with the primary function of the T6SS thought to be for the extracellular export of virulence factors.[20] Findings in a study on *A. hydrophila* revealed that the virulence-associated secretion genes *vasH* and *vasK* are required for the expression of the T6SS, with deletion of the *vasK* gene preventing secretion of hemolysin coregulated protein (Hcp) into host cells. The *vasH* and *vasK* mutants were also less toxic to murine macrophages and human epithelial HeLa cells, and more efficiently phagocytosed by macrophages. The mutant strain of *A. hydrophila* was less virulent in a septicaemic mouse model of infection compared to the wild-type strain.[19] Taken together this evidence demonstrates aeromonads have a large repertoire of putative pathogenicity determinants.

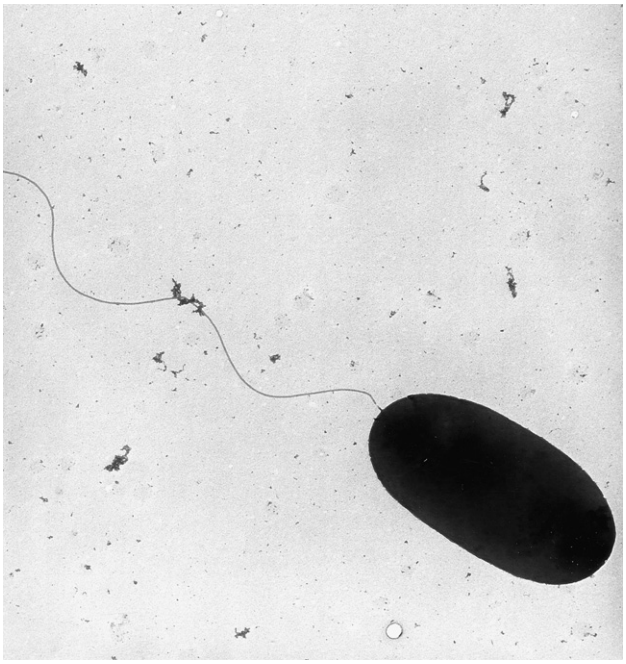

Figure 1 Transmission electron microscopy of the *A. caviae* strain Sch3N (wild-type) grown at 37 °C in BHIB. The single polar flagellum is clearly visible.

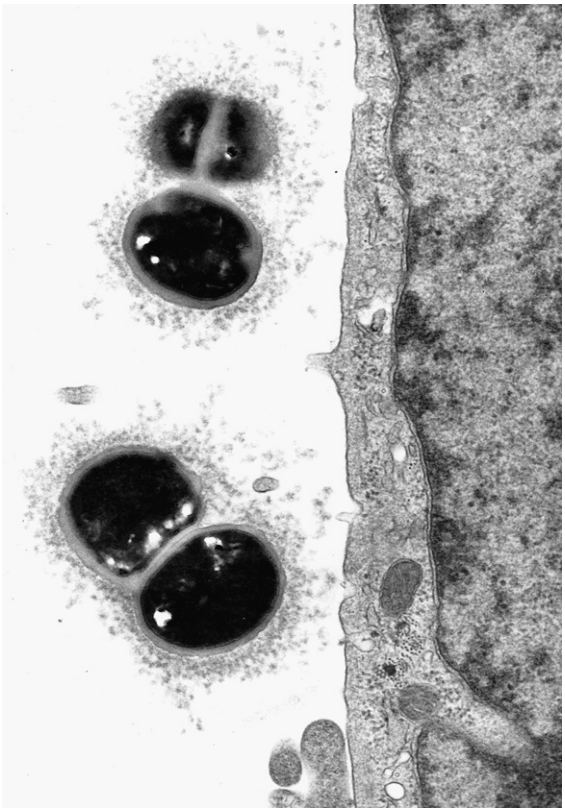

Figure 2 Transmission electron micrograph of a Hep-2 cell monolayer infected by *A. caviae strain* Sch3N (wild-type). Aeromonads are shown adhering to the cell (magnification ×18,500).

Symptoms of infection and disease

Gastroenteritis

Aeromonads have been described as the causative agents of a variety of infections, with gastroenteritis being the disease most commonly associated with aeromonads. In some cases there can be advancement of the infection to cause peritonitis, colitis and cholangitis.[21] The most common species identified are *A. hydrophila*, *A. caviae* and *A. veronii* biovar sobria which cause 85% of *Aeromonas* gastrointestinal infections.[10] *A. veronii* biovar sobria and *A. caviae* are the *Aeromonas* species most commonly associated with traveler's diarrhoea.[22,23] Case studies have shown that *Aeromonas* enteritis caused by *A. veronii* bv sobria and *A. caviae* infection often has the symptom of watery diarrhoea, whereas enteritis caused by *A. hydrophila* and *A. jandaei* tends to result in loose stools.[23] *A. caviae* are particularly prevalent in cases of paediatric diarrhoea.[24] Immunocompetent individuals with no predisposing medical conditions have also been affected by gastroenteritis linked to *Aeromonas* infection. Aeromonad gastroenteritis usually manifests itself in three ways; an acute self-limiting, watery diarrhoea, dysentery-like mucus and bloody diarrhoea, and chronic diarrhoea.[25,26] Intestinal aeromonad infections (including gastroenteritis, colitis, peritonitis and cholangitis) that develop in to extra-intestinal infections can on rare occasions lead to meningitis in immunocompromised individuals.[27] Studies have noted that *Aeromonas* meningitis presents itself as bacterial meningitis with the observation of additional skin lesions potentially aiding diagnosis.[27]

Wound infections

The second most common type of infection associated with *Aeromonas* are wound infections. Aeromonad wound infections usually arise in previously healthy individuals following a penetrating or abrasion injury that occurs in an aquatic environment or in soil, where *Aeromonas* species are present in high numbers.[28,29] *Aeromonas* wound infections are more commonly found in patients whose injury was obtained in fresh water rather than sea water.[30] Such wound infections include cellulitis,[31] myonecrosis,[32] and ecthyma gangrenosum,[33] with *Aeromonas* isolated from patients with metastatic myositis,[34] osteomyelitis,[35] as well as in a number of cases of gangrene.[36,37] Such infections can manifest themselves as pustules,[38] ulcers or abscesses.

Less commonly, *Aeromonas* has been shown to cause infections in burns, often in cases where water was used in the first aid treatment,[39] surgical wounds,[40] compound fractures, crush injuries,[28] and animal bites.[41–44] It has been noted that *Aeromonas* are not typically isolated from infected wounds in pure culture, and are commonly associated with *Enterococcus*, *Clostridia*, *Enteric bacilli* and *Bacteroides*.[28,30,45] Fatalities of previously healthy adults caused by aeromonad wound infections have been reported,[46,47] and can arise from the wound infection leading to septicaemia and bacteraemia in both immunocompromised and immunocompetent individuals. The mortality rate for patients suffering with *Aeromonas* wound infections as a result of trauma, as well as the predisposing condition of liver cirrhosis has been observed at as high as 67%.[48] In a recent review by Janda and Abbott it was estimated that for immunocompetent individuals *Aeromonas* wound infection caused by trauma has a lower mortality rate of approximately 60%, and that this high mortality rate may be more related to the trauma itself rather than the resulting *Aeromonas* infection.[5]

Septicaemia

Septicaemia caused by *Aeromonas* is mainly associated with immunocompromised patients with predisposing medical conditions, such as impaired hepatobiliary function and malignancy.[49–51] On rare occasions it can occur in apparently healthy adults, usually arising from severe aeromonad wound infections.[52–54] The main symptoms include diarrhoea, fever, chills and abdominal pain.[55] Septicaemia that develops in patients suffering from a severe wound infection has a mortality rate of over 90%.[52,56] The mortality rate of infected adults with underlying medical conditions such as cancer and diabetes is 25–50%.[50,57] A case of septic shock arising from a wound infection in a patient suffering with cirrhosis of the liver has been previously reported.[58]

Respiratory infections

Aeromonas species are not normally considered to be respiratory pathogens, however, there have been a small number of cases where respiratory infections have been linked to or directly caused by *Aeromonas* in both healthy individuals and those with underlying medical conditions. Cases of pneumonia in previously healthy individuals caused by *Aeromonas* infection have been previously reported.[59,60] Such respiratory infections are often caused by near-drowning experiences or inhalation of water whilst swimming.[61–63] However, such cases are extremely rare with *Aeromonas* linked pneumonia and lung abscesses usually as a result of an underlying medical condition such as cardiovascular disease or alcohol abuse.[64]

Other infections

Liver abscesses caused by *Aeromonas* infection are usually always as a result of underlying conditions in immunocompromised individuals usually suffering from conditions such as liver disease, cancer, alcoholism, or blocked biliary tracts.[65] Infections such as these can progress to suppurative cholangitis and empyema.[66] It has also been noted that haemolytic uremic syndrome can be a rare complication of *A. hydrophila* associated infection, as certain strains have been shown to carry the Shiga-like toxin.[67,68] Urinary tract infections as a result of *Aeromonas* have been recorded, again usually in patients with underlying health conditions.[69,70] One particular observation has shown that patients suffering from cirrhosis of the liver are more likely to contract a urinary tract infection linked to *Aeromonas* than individuals without the condition.[71]

Relatively mild infections of the eye linked to *Aeromonas* have also been reported, and on rare occasions more serious infections such as corneal ulcers and endophthalmitis caused by *Aeromonas* have been observed.[72–74] It is important to be aware that in a number of cases of *Aeromonas* eye infections, no prior injury was obtained before initiation of the infection.[73,75]

Epidemiology

Aeromonas are ubiquitous to water, with the ability to form biofilms in and subsequently colonise water systems.[76] The heterotrophic plate count (HPC) calculated that *Aeromonas* can make up 1–27% of total bacteria in samples of finished drinking water, implicating drinking water as a possible source of infection.[77] The number of cases of *Aeromonas*-associated gastroenteritis increases during the summer months correlating with increased numbers of *Aeromonas* in the water systems.[78] As well as aquatic habitats, *Aeromonas* species have been isolated from soil, fish, foods, domesticated pets, invertebrates, and birds,[5] although it is important to note that in many of these cases their isolation has not been linked with transmission to humans and subsequent disease. A recent study analysed the presence of 11 virulence factors in over 200 isolates of *Aeromonas* from water and clinical stool samples. Three sets of water and clinical isolates were found to have the same virulence signature identifying a subset of *Aeromonas* species that are prevalent in water with the ability to cause human disease. These findings provide evidence of successful colonization and subsequent infection of a number of *Aeromonas* species after transmission from water to humans.[79]

Aeromonas can lead to infection in both immunocompetent and immunocompromised individuals. Current thinking is that there is a subset of aeromonad strains that are pathogenic. A risk assessment of the opportunistic bacterial pathogens *Aeromonas*, *Pseudomonas*, *Acinetobacter*, *Moraxella*, *Xanthomonas*, *Mycobacterium*, and *Legionella* in drinking water has been previously undertaken.[77] Findings show that the oral infectious dose required for *A. hydrophila* is >10 colony forming units in both human and animal test subjects. The infectious dose for an opportunistic pathogen is lower for immunocompromised individuals or those already on antibiotic treatment. The risk characterisation of the study showed that the risk of infection from oral ingestion of low exposures of *Aeromonas* to be low at 7.3/billion, however the health risks for individuals with multiple exposures to opportunistic pathogens is yet to be determined.[77]

The study of *Aeromonas* infection has been made more complicated by the fact that there is not a good animal model in which to carry out infection studies.[80,81] A number of aeromonads have been isolated from medicinal leeches used in hirudotherapy,[82] and have been shown to be prominent in the resident flora of the leech surface and mouth. *A. veronii* shows the ability to colonise leeches as part of an endosymbiotic relationship in order to aid the digestion of blood meal. This has led to clinical complications, linking the use of medicinal leeches for surgical skin-flaps and reconstructive surgery to *Aeromonas* infection,[83–91] with misidentified *A. hydrophila*[92] and *A. veronii* bv sobria[93] identified as the causative species. A recent study carried out a ciprofloxacin feeding experiment to successfully reduce the number of leech-associated aeromonads.[94]

A number of nationwide and local epidemiology studies have been carried out in both developed and developing nations. These allow for the determination of the extent of the challenge posed by *Aeromonas* infections, the most notable of which will be discussed here.

In 1988 the first population-based study of the epidemiology of *Aeromonas* infections was carried out in the US state of California.[95] Two hundred and eighty individuals were reported during over the course of the year (10.6 cases per one million of the population), 219 of which underwent case investigations. *Aeromonas* was found to be most commonly isolated in the gastrointestinal tract (81%), followed by wound infections (9%). Five (2%) of the 219 patients died; all five had serious underlying medical conditions (apart from *Aeromonas* infection), rendering them immunocompromised. The 219 individual cases were isolated and no common-source enteric outbreaks were reported. The investigators of the study deduced that in developed regions such as California *Aeromonas* infections are not an important public health problem but are however largely nonpreventable.[95]

A prospective multicentre nationwide study involving 17 hospitals has been conducted in France. Over a six month period (May to October 2006), 78 cases of *Aeromonas* infection underwent case investigation, with 84 *Aeromonas* isolates recovered.[96] The disease distribution, patient

characteristics and risk factors were summarized in the study with the most prevalent type of infections identified being wound and skin soft-tissue infections (SSTI) with 34 cases. Of the patients with wound infections, 88% occurred in previously healthy patients (predominantly young men) with no known underlying conditions. Of these cases, 15 arose from injuries with exposure to fresh water, and a further 15 resulted from injuries with soil exposure from penetrating wounds or road accidents. Interestingly no cases were associated with medicinal leech therapy. One limitation of this study is that the hospitals that participated do not perform reconstructive surgery to a great extent (if at all) and therefore such cases may therefore be underrepresented. Surgery or antimicrobial treatment was required for 68% of wound infections and 85% of SSTI, with initial antibiotic treatment inappropriate for 62% of the cases. Also in the French study in cases of bacteraemia, 30% of the 20 patients had no underlying health conditions but such cases were predominantly in the very elderly (nine patients $>$ 80 years of age). In seven of the 20 bacteraemia cases the infection proved fatal. None of the cases of bacteraemia were related to or caused by wound infections or SSTI, with the gastrointestinal tract being the suspected source in all cases. After wound infections, SSTI and bacteraemia, a further 15 cases of gastroenteritis were recorded, five cases of respiratory tract infection (three from patients who suffered near-drowning), and a further four infections which included an ocular infection, hepatobiliary infection, urinary tract infection, and peritonitis.[96]

In some nations, studies have focused on particular common-source enteric outbreaks sometimes following natural disasters, or groups of patients treated at the same medical centre. The significance of aeromonads as human pathogens following natural disasters was evident following the tsunami that struck Thailand in December 2004. Three hundred and five survivors of the tsunami that developed skin or soft tissue infections during the devastation were examined. The results showed that *Aeromonas* species were the single most common bacterial species identified, accounting for over 20% of all those identified.[97] In the USA, during the month that followed Hurricane Katrina in New Orleans, Louisiana in August 2005, an assessment of pathogens and toxicants present in the floodwater was undertaken with high numbers of *Aeromonas* species found in the samples.[98]

A. sobria was found to be the cause of an outbreak of acute diarrhoea in Benghazi, Libya which occurred over a one month period in 1997. Of 28 patients that were admitted with acute gastroenteritis all tested positive for "*A. sobria*" later thought to be *A. hydrophila*. The source of the infection was unable to be traced.[99] Far more recently a study carried out in the Limpopop province of South Africa involved the isolation of *A. hydrophila* strains from water-storage containers.[100] In this study 32 strains of *Aeromonas* were isolated from HIV/AIDS patients suffering with gastroenteritis. Their household water-storage containers were subsequently analysed, revealing genetic relatedness of *A. hydrophila* isolates from household drinking water and clinical sources in South Africa indicating that more emphasis should be placed on the monitoring and evaluation of infection control measures, as well as an improvement in hygiene for the prevention of cross-contamination.[100]

The clinical presentation and prognostic factors of cases of monomicrobial *Aeromonas* bacteraemia were analysed in a medical centre in southern Taiwan between 1989 and 1998.[101] One hundred and four cases of monomicrobial *Aeromonas* bacteraemia accounting for 74% of all aeromonad-associated infections bacteraemia were studied. Fifty four percent of the cases occurred in patients suffering with hepatic cirrhosis, and 21% in patients with malignancy. Seventy four percent of the infections were community-acquired and of these, they were much more likely to have already been suffering with cirrhosis. Associated infections such as peritonitis, cellulitis, or necrotizing fasciitis, biliary tract, or burn infections were present in 43% of cases. Thirty percent of patients died within two weeks from the onset of infection, with concomitant infections, cirrhosis and malignancy a strong indication of a poor prognosis.[101]

In many countries such as Brazil, stool samples from gastroenteritis patients are not routinely screened for the presence of *Aeromonas*. In a recent study in southern Brazil, 680 stool samples from patients suffering with watery diarrhoea and 300 from healthy controls were tested for the presence of *Aeromonas* spp. and *Plesiomonas*.[102] *Aeromonas* strains were isolated from 18 of the 680 patients ($\sim$2.6%) suffering with diarrhoea with patients ranging from 1 to 82 years of age. In the control group, *Aeromonas* was also isolated from one of the healthy samples ($\sim$0.33%).[102] From the 19 strains identified, *A. caviae* was the most commonly isolated species (12 of 19). These findings indicate the involvement of *Aeromonas* in the diarrhoea causing infection. The authors also noted that the prevalence of *Aeromonas* in this study is similar to those observed in other studies for other enteric pathogens such as *Escherichia coli*, *Shigella* and *Camplyobacter*.[103,104]

Clinical microbiology and detection

Aeromonas spp. grow well on common laboratory media, including Luria Bertani, MacConkey's, Heckteon enteric agar, nutrient, and blood agar. *Aeromonas* grown on blood agar form circular colonies of 1–3 mm in diameter. The colonies start off greyish in colour as a result of β-haemolysis and after three days growth the colonies turn dark green.[37] By Gram stain, aeromonads appear singly or in pairs and on occasions in short chains.[105] Most aeromonads can grow at a range of temperatures (4–42 °C), with most clinical isolates showing the ability to grow up to 42 °C.[106] The maximal growth temperature for most strains is between 37 and 44 °C.[107] Tolerance to pH and salt concentration varies between species[108] with the optimum concentration of NaCl ranging between 0.3 and 5%.[107] *Aeromonas* species are facultative anaerobes which are both oxidase and catalase positive. In the laboratory, they can be easily differentiated from *E. coli* using a simple oxidase assay on blood agar.[25]

It has been noted previously that clinical cases of *Aeromonas* infection may be underestimated due to the improper handling and/or culture methods of clinical samples.[99] Transport of specimens from patients to the laboratory can be undertaken at room temperature using a variety of media, including buffered glycerol in saline, Stuart's medium, Amies, or Cary-Blair.[5,13] Successfully

determining how many aeromonads are in involved in a bout of diarrhoeal disease requires the use of an appropriate selective medium. For the isolation from human faeces ampicillin-blood agar (ABA) and cefsulodin-Irgasan-novobiocin agar (CIN) have previously been recommended,[109,110] however the emergence and increase of ampicillin resistance in other members of the *Enterobacteriaceae* as well the inability to identify ampicillin susceptible aeromonads such as *A. trota* makes this selection more difficult and therefore ABA and CIN have become less suitable selection media for this purpose.[111] Recent findings suggest that *Aeromonas* agar (AA; Lab M) is more effective for the isolation of aeromonads. AA contains the selective agents brilliant green and Irgasan and enables the growth of aeromonads susceptible to ampicillin. Results of a two year study showed that AA had a number of advantages over a number of media typically used in a clinical laboratory. The study found that AA allowed the frequency of isolation of aeromonads to double and that *Aeromonas* colonies grown on AA could undergo an oxidase test directly as on ABA without the issue of neglecting to isolate ampicillin susceptible aeromonads.[111] It has however been noted that pseudomonads are indistinguishable in terms of colony appearance and oxidase activity from aeromonads on AA but can be separated by their oxidative metabolism.[5] Misidentification of *Aeromonas* strains as a member of the genus *Vibrio* has also previously been shown to be a problem.[112] An important feature that differentiates *Aeromonas* species from the *Vibrionaceae* is that they are resistant to the vibriostatic agent 2,4-diamino-6,7-diisopropylpteridine (O/129).[2] The separation and isolation of aeromonads from *Vibrio* and *Plesiomonas* as well as the isolation of specific species of *Aeromonas* has been comprehensively reviewed by Janda and Abbott 2010.[5] Isolation of *Aeromonas* from *E. coli*, *Klebsiella*, and *Enterococcus faecalis* using a variety of media has also been attempted, resulting in the recommendation that a medium should be used that inhibits the growth of non-aeromonad bacteria as much as possible.[113] A recent study tested 87 clinical isolates and compared the accuracy of six commercial systems manufactured for the identification of *Aeromonas* species.[114] The study found the accuracy of identification of infrequent clinical *Aeromonas* spp., and their corresponding type strains to be poor due to limitations caused by outdated and incomplete databases and inaccurate algorithms. It was also noted that the convenience of additional tests needs improvement and particular focus should be paid on the misidentification of *Aeromonas* with the genus *Vibrio*.[114]

The importance of developing methods for accurate biotyping, molecular fingerprinting, and virulence factor analysis for the successful differentiation and comparison of clinical samples has previously been highlighted.[79,115] Currently, one limitation of such techniques is that many of the DNA probes developed for *Aeromonas* have a very narrow spectrum, not allowing the identification of more than one species of *Aeromonas*.[116] *Aeromonas* species-specific probes have been developed for *A. hydrophila*, *A. trota*, *A. schubertii*, and *A. jandaei*.[5,116] However, two probes, one that detects glycerophospholipid-cholesterol acyltransferase and other that detects an outer membrane protein have been shown to detect all members of the genus.[117,118] At present, neither probe is available commercially.

16S rRNA gene sequencing is the most commonly used technique for bacterial genus and species identification. The use of this straightforward and largely reliable technique for the identification of *Aeromonas* species has been comprehensively reviewed.[119] Some difficulties can arise when using this technique for the identification of aeromonads due to high sequence divergence between 16S rRNA genes in the same strain, which can be up to 1.5%.[120] It has been documented that caution should be applied when attempting to identify aeromonads using this technique.[5,120] Amplified fragment length polymorphism (AFLP) analysis has been shown as a reproducible and accurate method for the identification, classification and subtyping of aeromonads[121–123] and more recently, multilocus sequence analysis of the housekeeping genes *rpoD* and *gyrB* has also been used successfully.[124] In another study, the method of random amplified polymorphic DNA PCR (RAPD) was used to determine the genetic relatedness of *A. hydrophila* strains isolated from stool specimens collected from HIV/AIDS patients suffering from gastroenteritis and their household drinking water from different geographical areas in South Africa. The method proved reproducible and may be a valuable way of monitoring and evaluating outbreaks of *Aeromonas* infection.[100]

Treatment

Very few studies have been undertaken that focus on the susceptibility of *Aeromonas* species to antimicrobial agents. Those that have been undertaken will be discussed in this section.

Fluoroquinolones such as ciprofloxacin have been shown to be active against clinical isolates of *A. hydrophila*,[125] *A. caviae* and *A. veronii* bv sobria.[23,126] In both *in vitro* studies and in mouse models, MICs of the fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin) were calculated at less than 1 μg/ml for 90% of the clinical isolates tested.[125] The results of the study also suggested that with cefotaxime-susceptable strains, ciprofloxacin was as effective cefotaxime-minocyline against *A. hydrophila* infections.[125] Susceptibility of *Aeromonas* species to cefotaxime and ciprofloxacin, as well as nalidixic acid and trimethoprim was also reported in a separate study from the same year.[23] The findings of Vila et al., 2003 also indicated that all *Aeromonas* species isolated from 863 patients with Traveler's diarrhoea showed variable resistance to chloramphenicol, tetracycline and cotrimoxazole.[23] More recently, 16 quinolone-resistant isolates of the species *A. hydrophila*, *A. caviae*, and *A. veronii* bv sobria were recovered from non-hospitalized humans.[127] Quinolone-resistant *A. hydrophila* peritonitis has also been reported recently in a patient on continuous ambulatory peritoneal dialysis. Susceptibility testing revealed that the strain was susceptible to ceftazidime, but resistant to ciprofloxacin and the patient was treated successfully with ceftazidime (intravenous for 2 days followed by intraperitoneal ceftazidime for 12 days).[128]

Many *Aeromonas* species show full resistance to ampicillin via chromosomally-mediated inducible β-lactamases which have both been extensively studied.[129,130] In susceptibility studies using clinical isolates, resistance to ampicillin has also been observed.[23,102,126,131–134] In one recent study,

16 of 19 *Aeromonas* strains isolated from stool samples from patients with diarrhoea were also found to be resistant to cefoxitin, and 15 of the 19 resistant to cefazolin.[102] Just recently, a strain of *A. caviae* with resistance to all β-lactams but imipenem was isolated and believed to be the cause of a case of severe pneumonia in a cancer patient.[135] Expression of metallo-β-lactamases that are active against carbapenems has been identified[136] and are of growing concern with regards to *Aeromonas* infection.[137–139]

In summary, with regards to the data described in this section and with the concerns regarding chromosomally-mediated β-lactam resistance, the use of fluoroquinolones such as ciprofloxacin and cefotaxime are in the main the most successful treatment for *Aeromonas* infection. Studies have indicated their activity both *in vivo* in infected patients and *in vitro* with clinical isolates, in addition to this the identification of fluoroquinolone-resistant strains is still rare. In cases where patients are infected with multiple opportunistic pathogens, successful treatments are more complicated, however a recent study found that clinical isolates of Shigella were also susceptible to the fluoroquinolones ciprofloxacin and ceftriaxone.[140]

Conclusions

It has become clear from a number of studies that *Aeromonas* is an emerging player in infectious disease, particularly in developing nations and in immunocompromised individuals suffering with conditions such as malignancy, liver cirrhosis, and diabetes. The ubiquitous nature of *Aeromonas* in aquatic environments indicates that their interactions with humans are continual and unavoidable enabling their opportunistic pathogenicity, with aeromonads confirmed as an undisputed cause of wound infections. It is likely that clinical cases of *Aeromonas* infection have been significantly underestimated and in order to fully determine and pinpoint the risk factors associated with *Aeromonas* infection and disease there is a need for more detailed and unbiased epidemiology studies, paying particular attention to the health risks found for individuals with multiple exposures to opportunistic pathogens. Although, no fully described outbreaks of *Aeromonas*-associated diarrhoea have been reported, it is clear from the evidence that a small subset of *Aeromonas* species encompassing a minority of strains, that possess the correct collection of virulence factors are able to cause diarrhoeal disease in humans.

Aeromonads are both genetically amenable and fast growing, which in turn has allowed them to become the focus of a number of research groups. Much research is currently being undertaken, focusing on virulence factors, motility, adhesion, and quorum sensing. The recent developments in genomics and high throughput full genome sequencing should allow the discrepancies and controversy regarding taxonomy issues, as well as outstanding nomenclature problems to be addressed. In return this will allow researchers to focus on the studying of *Aeromonas* infection outbreaks, as well as its physiology, genetics and biochemistry. Of the mesophilic aeromonads, only *A. hydrophila* ATCC 7966^T has had its 4.7-Mb genome fully sequenced, with the identification of 5, 195 predicted genes.[141] The genome sequence revealed *A. hydrophila* ATCC 7966^T to have broad metabolic capabilities and a large array of virulence genes. This is indicative of considerable virulence potential, with the ability to infect a wide range of host organisms.[141] The availability of the full genome sequences of many other *Aeromonas* species are likely to be available in the near future providing a further insight in to this fascinating and medically important genera of bacteria.

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