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MINIREVIEW

Bacteriological, Clinical and Virulence Aspects of *Aeromonas*-associated Diseases in Humans

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Abstract

Aeromonads have been isolated from varied environmental sources such as polluted and drinking water, as well as from tissues and body fluids of cold and warm-blooded animals. A phenotypically and genotypically heterogenous bacteria, aeromonads can be successfully identified by ribotyping and/or by analysing gyrB gene sequence, apart from classical biochemical characterization. Aeromonads are known to cause scepticemia in aquatic organisms, gastroenteritis and extraintestinal diseases such as scepticemia, skin, eye, wound and respiratory tract infections in humans. Several virulence and antibiotic resistance genes have been identified and isolated from this group, which if present in their mobile genetic elements, may be horizontally transferred to other naive environmental bacteria posing threat to the society. The extensive and indiscriminate use of antibiotics has given rise to many resistant varieties of bacteria. Multidrug resistance genes, such as NDM1, have been identified in this group of bacteria which is of serious health concern. Therefore, it is important to understand how antibiotic resistance develops and spreads in order to undertake preventive measures. It is also necessary to search and map putative virulence genes of *Aeromonas* for fighting the diseases caused by them. This review encompasses current knowledge of bacteriological, environmental, clinical and virulence aspects of the *Aeromonas* group and related diseases in humans and other animals of human concern.

Key words: Aeromonad, diarrhea, multi-drug, resistance, virulence

Introduction

Aeromonads are recognized not only as an important disease-causing pathogen of fish and other cold-blooded organisms but also as a causative organism in a variety of infectious complications in both immunocompetent and immunocompromised humans. The name *Aeromonas* is derived from Greek noun *aeros* (air, gas) and *monas* (unit). Members of the genus *Aeromonas* can be referred to as aeromonad. Aeromonads (Phylum *Proteobacteria*, Class *Gammaproteobacteria*, Order *Aeromonadales*, Family *Aeromonadaceae*) are Gram-negative, non-spore forming, rod shaped, facultative anaerobic bacteria that occur in natural water bodies of the environment. They are similar in many characters to *Enterobacteriaceae* family.

The DNA-DNA hybridization studies showed the presence of 33 DNA hybridization groups, including 19 genospecies. *Aeromonas hydrophila*, *A. caviae*, *A. sobria*, *A. veronii*, and *A. schubertii* are mesophilic, whereas, *A. salmonicida* are non-motile and psychrophilic. Widely distributed, aeromonads have been isolated from various sources like freshwater fishes, drinking water supply, environmental samples, polluted waters, food items like meat, fish, milk, ready to eat items and oysters (Abeyta *et al*., 1986; Altwegg *et al*., 1990; Manna *et al*., 2013, Figueras *et al*., 2017). *Aeromonas* have been found in the *Aedes aegyptii* and *Culex quinque fasciatus* mosquitoes' midgut, in monkey faeces and bivalve molluscs (Pidiyar *et al.,* 2002), larvae of *Chironomus plumosus* (Rouf and Rigney, 1993).

Over the past few years, researchers have renewed interest in the genus *Aeromonas* as an emergent human pathogen (Janda and Abbott, 1998). Aeromonads have been implicated in septicaemia in variety of aquatic organisms and gastrointestinal/extra-intestinal diseases in humans (Janda and Duffey, 1988; Janda and Abbott, 1996). Several species of genus *Aeromonas* have been implicated in pathogenic cases in human, like cellulitis, surgical wound infections, nosocomial pneumonia, hemolytic-uremic syndrome, sepsis, peritonitis, meningitis, urinary tract infections, and severe muscle degeneration. In all the cases it seems that *Aeromonas*-mediated pathogenesis occurs both in cases of

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immunosuppression and immunocompetence (Wang *et al*., 2003). However, *Aeromonas*-mediated mechanism of pathogenesis in both aquatic organisms and in human subjects remains to be elucidated.

Aeromonas spp. possess multifactorial virulence genes and systems. Several groups have demonstrated the presence of aerolysin (Chakraborty *et al*., 1986), hemolysin (Wang *et al*., 1996), extracellular lipase (Anguita *et al*., 1993), cytolytic enterotoxin (Chopra *et al*., 1993), haemolytic toxin genes (Khan *et al*., 1998), acetylcholinesterase (Nieto *et al*., 1991) and proteases (Leung and Stevenson, 1988). Genome level scans have identified virulence factors in potential open reading frames (ORFs) and few putative genes, like O-antigen and capsule, gene cluster in phage and type III secretion system have been associated with virulent aeromonads. Several genomic islands (GIs) with unusual G-C content, have also been identified that carry mobility-associated genes, such as integrases or transposes and other putative virulence genes (Yu *et al*., 2005). *Aeromonas luxRI* quorum sensing gene homologs and Ribonuclease R (Vac B) have also been implicated in modulation and expression of these virulence genes (Jangid *et al*., 2007; Erova *et al*., 2008). The NDM-1 gene ($bla_{\text{NDM-1}}$) has been found in aeromonads of North India (New Delhi) (Walsh *et al*., 2011).

Aeromonads are found to inhabit a variety of niches including soil, aquatic habitats, aquatic animals, terrestrial animals, birds, insects, and human beings (Table I). *A. hydrophila* are found to inhabit a wide range of thermal and pH conditions, except in extremely polluted and saline water and hot water springs. Estuaries are ideal for *Aeromonas,* where they either exist freely or associated with crustaceans (Fiorentini *et al*., 1998). Most of the aeromonads come into human systems through ingestion of water or food contaminated with *Aeromonas*. In India, *Aeromonas* spp. have been detected in 13.4% of animal-origin food samples, the highest being in fish (Kumar *et al*., 2000). Aeomonads mostly infect the gastrointestinal tract, urinary tract and blood of human beings. Three *Aeromonas* species viz., *A. hydrophila*, *A. caviae* and *A. veronii* bv. Sobria are known to infect human beings (Janda and Abbott, 1998). Some other species like *A. jandaei*, *A. veronii* bv. *veronii*, *A. schubertii*, *A. popoffi* are also known to infect human (Janda *et al*., 1994; Hua *et al*., 2004). Hua *et al*. (2004) isolated *A. popoffi* from the urine of a patient with urinary tract infection (Hua *et al*., 2004). *A. salmonicida*, generally known to infect cold blooded animals, has also been isolated from blood sample of a patient in India (Tewari *et al*., 2014). *A. salmonicida* was identified by Vitek 2 compact automated system. Non-culturable *Aeromonas* can be found in drinking water in various concentrations. The first report of *Aeromonas* from drinking water was confirmed by sequencing 16S rRNA (Figueras *et al*., 2005). Different concentrations of *Aeromonas* have been detected in consumable products from markets (Isonhood and Drake, 2002).

Epidemiology

Mesophilic bacteria grow well at higher temperatures and therefore an increase in bacterial load may be attributed to their increase in concentration in both freshwater environments and drinking water sources with the increase of ambient temperature (Moyer, 1987; Edberg *et al*., 2007; Khardori and Fainstein, 1988). The seasonality is also seen in extra-intestinal infections such as septicemia, where 42% to 67% of bacteremic diseases appear during the summer season (Tsai *et al*., 2006). The elevated levels of these bacteria in aquatic environments during the summer season increases the opportunities of human or aquatic organisms of getting exposed to them and thus the risk of getting infected by these bacteria also gets higher. Infections caused by aeromonads seem to be rather more prevalent in developing countries like India, Bangladesh, Brazil, China, Cuba, Egypt, Iran, Libya, Nigeria, Venezuala and Vietnam (Ghenghesh *et al*., 2008). Prevalence of *Aeromonas* related disease is more during rainy seasons when the water salinity is low than at high salinity during dry season (Marcel *et al*., 2002).

Infections and Symptoms

Gastrointestinal tract is the most common site of *Aeromonas* infection. Evidences show that *Aeromonas*-associated diarrhoea or cholera-like disease occurs in some patients, whereas no symptom may appear in cases of low-level infections (Gurwith *et al*., 1977; Holmberg *et al*., 1984). Kelly *et al*. (1993) isolated *Aeromonas* from non-fecal samples from 58 patients, suffering from gangrene, septicemia, osteomyelitis and peritonitis. *Aeromonas*-related diarrhoea may be watery and self-limiting. In other cases, fever, abdominal pain and bloody diarrhea may develop along with dehydration (Ghenghesh *et al*., 1999). Hematologic cancer patients, patients with tumours in their gastrointestinal tract or having alimentary canal diseases are more likely to be infected by *Aeromonas*. In rare cases of segmental colitis *Aeromonas* segmental colitis may occur that seem to be ischemic colitis or Crohn's disease (Bayerdorffer *et al*., 1986). Although any portion of the colon may be affected, it mostly affects the ascending or transverse sections. Iileal ulceration has also been linked to *Aeromonas enteritis* (Yamamoto *et al.,* 2004). It may also cause intra-mural intestinal hemorrhage including small bowel obstruction (Block *et al*., 1994),

Table I
Genomospecies and phenospecies of the genus *Aeromonas*.

DNA Hybridization group	Type Strain/ Reference	Genospecies	Phenospecies	Remarks	Reference
1	ATCC 7966	*A. hydrophila*	*A. hydrophila*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
1	BCCM/LMG 19562	*A. hydrophila* subsp. *dhakensis*	*A. hydrophila* subsp. *dhakensis*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
1	BCCM/LMG 19707	*A. hydrophila* subsp. *ranae*	*A. hydrophila* subsp. *ranae*	Pathogenic for frogs	Martin-Carnahan and Joseph, 2005
2	ATCC 14715	*A.bestiarum*	*A. hydrophila- like*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
3	ATCC 33658	*A. salmonicida*	*A. salmonicida* subsp. *Salmonicida*	Nonmotile fish pathogen	Martin-Carnahan and Joseph, 2005
3	ATCC 33659	*A. salmonicida*	*A. salmonicida* subsp. *Achromogenes*	Nonmotile fish pathogen	Martin-Carnahan and Joseph, 2005
3	ATCC 27013	*A. salmonicida*	*A. salmonicida* subsp. *Masoucida*	Nonmotile fish pathogen	Martin-Carnahan and Joseph, 2005
3	ATCC 49393	*A. salmonicida*	*A. salmonicida* subsp. *Smithia*	Nonmotile fish pathogen	Martin-Carnahan and Joseph, 2005
3	CDC 0434-84, Popoff C316	Unnamed	*A. hydrophila*- like	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
4	ATCC 15468	*A. caviae*	*A. caviae*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
5A	CDC 0862-83	*A. media*	*A. caviae*-like	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
5B	CDC 0435-84	*A. media*	*A. media*	–	Martin-Carnahan and Joseph, 2005
6	ATCC 23309	*A. eucrenophila*	*A. eucrenophila*	–	Martin-Carnahan and Joseph, 2005
7	CIP 7433, NCMB 12065	*A. sobria*	*A. sobria*	–	Martin-Carnahan and Joseph, 2005
8X	CDC 0437-84	*A. veronii*	*A. sobria*	–	Martin-Carnahan and Joseph, 2005
8Y	ATCC 9071	*A. veronii*	*A. veronii* biovar sobria	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
9	ATCC 49568	*A. jandaei*	*A. jandaei*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
10	ATCC 35624	*A. veronii* biovar *veronii*	*A. veronii* biovar *veronii*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
11	ATCC 35941	Unnamed	*Aeromonas* spp. (ornithine Positive	–	Martin-Carnahan and Joseph, 2005
12	ATCC 43700	*A. schubertii*	*A. schubertii*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
13	ATCC 43946	*Aeromonas* Group 501	*A. schubertii*-like	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
14	ATCC 49657	*A. trota*	*A. trota*	Isolated from clinical specimens	Martin-Carnahan and Joseph, 2005
15	ATCC 51208, CECT 4199	*A. allosaccharophila*	*A. allosaccharophila*	–	Martin-Carnahan and Joseph, 2005
16	ATCC 51020	*A. encheleia*	*A. encheleia*	Pathogenic for eels	Martin-Carnahan and Joseph, 2005
17	BCCM/LMG 1754	*A. popoffii*	*A. popoffii*	–	Martin-Carnahan and Joseph, 2005
UA	MTCC 3249, NCIM 5147	*A. culicicola*	*A. culicicola*	Isolated from mosquitoes	Martin-Carnahan and Joseph, 2005

Table I. Continued.

DNA Hybridization group	Type Strain/ Reference	Genospecies	Phenospecies	Remarks	Reference
UA	–	*A. eucrenophila*	*A. tecta*	Isolated from clinical and environmental sources	Demarta *et al.*, 2008
UA	–	*A. trota*	*A. aquariorum*	Isolated from monkey faeces	Harf-Monteil *et al.*, 2004
UA	–	*A. popoffii*	*A. bivalvium*	Isolated from aquaria of ornamental fish	Martinez-Murcia *et al.*, 2008
UA	–	Unnamed	*A. sharmana*	Isolated from bivalve molluscs	Minana-Galbis *et al.*, 2004
UA	868E^T (=CECT 7113^T =LMG 23376^T)	*A. bivalvium* sp. nov.	–	Isolated from bivalve molluscs	Minana-Galbis *et al.*, 2007
UA	–	*A. schubertii*	*A. simiae*	Isolated from midgut of Mosquitoes	Pidiyar *et al.*, 2002
UA	–	*A. sharmana* sp. nov.	*A. sobria*	Isolated from a warm spring	Saha and Chakrabarti, 2006
UA	266^T (5CECT 8023^T 5LMG 26707^T)	*Aeromonas australiensis* sp. nov.	*Aeromonas fluvialis*, *Aeromonas veronii* and *Aeromonas allosaccharophila*	Isolated from irrigation water system	Aravena-Roman *et al.*, 2013
UA	A.11/6T (=DSMZ 24095T, =CECT 7828T)	*Aeromonas lusitana* sp. nov.	–	Isolated frm untreated water and vegetables (lettuce/celery)	Martinez-Murcia *et al.*, 2016
UA	ATCC 49803	*Aeromonas enteropelogenes*	*Aeromonas trota*	Isolated from human stool	Schubert *et al.*, 1990
UA	CECT 4254T	*Aeromonas diversa*	*Aeromonas schubertii*	Isolated from leg wound of a patient	Farfan *et al.*, 2013
UA	717^T (=CECT 7401^T =LMG 24681^T)	*Aeromonas fluvialis*	*Aeromonas veronii*	Isolated from river water	Alperi *et al.*, 2010b
UA	848T^T (=CECT 5864^T =LMG 22214^T)	*Aeromonas molluscorum* sp. nov.	–	Isolated from Wedge-shells	Minana-Galbis *et al.*, 2004
UA	WB4.1-19^T (CECT 7518^T DSM 22539^T MDC 2511^T)	*Aeromonas rivuli* sp. nov.	–	Isolated from a karst hard water creek	Figueras *et al.*, 2011
UA	S1.2^T (=CECT 7443^T =LMG 24783^T)	*Aeromonas piscicola* sp. nov.	–	Isolated from wild diseased Salmon	Beaz-Hidalgo *et al.*, 2009
UA	A2-50^T (=CECT 7403^T =LMG 24683^T)	*Aeromonas taiwanensis* sp. nov.	–	Isolated from wound infection of a patient	Alperi *et al.*, 2010a
UA	A2-67^T (=CECT 7402^T =LMG 24682^T)	*Aeromonas sanarellii* sp. nov.	–	Isolated from a wound culture from a patient	Alperi and Figueras, 2010
UA		*A. hydrophila*	–	Isolated from wild birds	Glunder and Seigmann, 1989

UA-Unassigned; – Un Named

and refractory inflammatory bowel disease (Doman *et al.*, 1989). Gastrointestinal tract infection symptoms may mimic cholera (Mohan *et al.*, 2017).

The second most common area of *Aeromonas*-related infection in our body is the skin and the soft tissues underlying the skin. Aeromonads may cause several types of skin and soft tissue infections, ranging from mild problems like pustular lesions to dangerous conditions that can cause morbidity in infected person. Some of these conditions include cellulitis, necrotizing fasciitis, myonecrosis, septic arthritis and septic shock (Lai *et al.*, 2007). Some medical treatment procedures like medicinal leech therapy, appendectomies, colectomy, cholecystectomy and elective surgery enhance

the chances of *Aeromonas*-associated wound infections (Moawad and Zelderman, 2002; Tena *et al*., 2009). *A. hydrophila* and *A. caviae* were isolated from five burn patients admitted in Royal Brisbane hospital, where the patients had been immersed in water immediately after getting burnt, putatively contaminated with *Aeromonas* (Kienzle *et al*., 2000).

A. hydroplila sensu stricto, *A. caviae* and *A. veronii* bv. Sobria have been implicated in blood borne infections. Less frequently, three other species namely, *A. jandaei, A. veronii* bv. *veronii* and *A. schubertii* are known to cause sepsis (Janda *et al*., 1994). *Aeromonas*-septicemia is more prevalent in immunocompromised conditions viz. myeloproliferative disorders, chronic liver disease, neoplasia, biliary disease, AML, myeloplastic syndromes, non-Hodgkin's lymphoma and acute lymphocytic leukemia (Ko *et al.,* 2000; Tsai *et al*., 2006). *Aeromonas* septicemia is also related to diseases like diabetes mellitus, renal and cardiac problems, thallasemia, multiple myeloma, aplastic anemia and Waldenstrom's macroglobulinemia (Janda and Abbott, 1996; Padmaja *et al*., 2013). Aeromonad-contaminated catheters and dialysis chambers may serve as points of entry into human blood. *Aeromonas* cause peritonitis and cholangitis as intra-abdominal disease. *Aeromonas*-associated cholangitis may result in pancreatic carcinoma, cholangiocarcinoma, cholelithiasis patients or patients with non-malignant biliary disease by the invasion of the bacteria from the gastrointestinal tract to the biliary tract via surgery or endoscopy (Chan *et al*., 2000). *A. hydrophila*, *A. veronii* bv. Sobria, *A. popoffi* and *A. caviae* infections have been implicated in UTI, aspiration pneumonia, keratitis, endophthalmitis, corneal ulceration and blood stream infections through biofilm formation (Ender *et al*., 1996; Hsueh *et al*., 1998; Miyake *et al*., 2000; Hua *et al*., 2004; Pinna *et al*., 2004; Hondur *et al*., 2008; Tang *et al*., 2014). First case of neonatal meningitis in a premature baby has been reported recently caused by *A. hydrophila* (Kali *et al*., 2016).

Aeromonas affects both cold and warm-blooded non-human animals. Mass deaths in fishes occur every year due to *Aeromonas*-associated diseases resulting in huge economic loss to the fish industry (Monette *et al*., 2006). Furunculosis in the salmonids, caused by *A. salmonicida sensu stricto* is characterized by symptoms like heamorrhages at fin bases, muscles and internal organs; loss of appetite, disordered melanin production, loss of energy and exopthalmia (Austin, 1997). Secondly, septicemia in carps, tilapia, catfishes, salmons, cods, bass and freshwater prawns is caused by *A. hydrophila* and *A. veronii* (Joseph and Carnahan, 1994). *A. hydrophila* has been detected in tissues like kidney, liver and blood of carps in farms (Mohanty *et al*., 2008). Incidences of *A. hydrophila* seem to be more prevalent than *A. caviae* and *A. sobria*, which indicates that *A. hydrophila*, is more virulent than the other (Daood, 2012). In a very recent study it was shown that *A. caviae* infection causes thrombocytopenia which contributes to elongation of clotting time which leads to hamorrhages in internal organs, muscles and bases of fins (Baldissera *et al*., 2018). Diseases in other ectothermic animals include ulcers (Lizards and snakes), "red leg" disease (frogs), septicemia (dogs), septic arthritis (calves), vesiculitis (bulls) (Gosling, 1996).

Pathogenicity

The identified virulence factors in *Aeromonas* are haemolysins, cytotoxins, enterotoxins, proteases [serine protease (AspA), elastase (AhpB)], lipases (Pla and Plc, Sat), DNAses, adhesins [type IV pili, polar flagella (FlaA and FlaB)] (Agarwal *et al*., 1998; Cascon *et al*., 2000; Rabaan *et al*., 2001), capsule and T3SS (Grim *et al*., 2013). Genome sequencing and annotation can be used to detect these virulence factors in *Aeromonas* (Grim *et al*., 2013). Enterotoxins, Act and Ast (Sha *et al*., 2002), elastase (Cascon *et al*., 2000), flagellin (Rabaan *et al*., 2001), and Stx1 and Stx2 (Alperi and Figueras, 2010) are directly involved in the pathogenesis. In a study *Aeromonas* isolates from well, tap and bottled water samples were found to have *aer* and *ast* genes, which poses a serious health concern for the human society (Didugu *et al*., 2015).

Aeromonas inections are mostly polymicrobial (Figueras and Beaz-Hidalgo, 2015), in which there is competition and cooperation between the bacterial cells (Armbruster *et al*., 2016). Virulence when checked in *C. elegans* was found to be higher in paired *Aeromonas* infections than in single strain (Mosser *et al*., 2015). The dual strain *A. hydrophila* infection showed synergistic effect by local tissue damage and antagonistic effect by elimination (Ponnusamy *et al*., 2016). The pathogenic potential of *A. veronii* isolates from clinical samples when tested were found to be like the drinking water and environmental isolates (Lye, 2011). The protein secretion systems of *Aeromonas* play important roles in pathogenesis caused by them. The type II secretion system is associated with the extracellular release of proteases, amylases, DNases and aerolysin (Pang *et al*., 2015). Type III secretion system, which is found in greater frequency in clinical isolates than environmental ones (Pang *et al*., 2015) functions by inserting effective toxins inside the host cells (Sierra *et al*., 2010). The type VI secretion system allows insertion of virulence factors into host cells through valine-glycine repeat protein and hemolysin-coregulated proteins. These proteins when secreted show antimicrobial pore-forming properties or remain as structural proteins (Bingle *et al*., 2008).

Gastroenteritis. Aeromonads enter the human gut via oral cavity, escape the effects of gastric acidity and produce bacteriocin-like compounds, which facilitate colonization of the intestine. They attach themselves to gastrointestinal epithelium, form biofilm, colonize and elaborate virulence factors to cause infection. Bacterial flagella and pili play important roles in gastric pathogenicity (Kirov *et al*., 2000).

Wound infections. Virulence caused by *Aeromonas* and the virulence factors possessed by them are similar to those of Gram-negative *P. aeruginosa*. The first step is settlement of the bacteria in wound site with the help of adhesion factors such as OmpA protein (Namba *et al*., 2008). The second step involves production of proteases (metalloproteases, serine proteases and aminopeptidases) and the breakdown of proteinaceous material of the host cells to gain energy, for multiplication of bacilli (Janda, 2001). The third step includes the entry of aeromonads into deeper tissues via chemotactic motility (Janda, 1985).

Septicemia. Most cases of primary *Aeromonas* septicaemia apparently arise through transfer of bacteria from the gastrointestinal tract into the blood circulatory system. They may also travel to the bloodstream from infected wounds, peritonitis, or biliary disease. Most of the *Aeromonas* septicemias are caused by a small number of species. Specific strains having certain markers are only responsible for most of the blood-borne diseases. Aeromonads of sergroups O:11, O:16, O:18, and O:34 are responsible for most cases of septicemia, which shows that lipo-polysaccharide (LPS) antigens are important in causing systemic diseases. The presence of LPS or the S layers makes most *Aeromonas* isolates resistant to the lytic effects of the host's classical complement pathway (Janda *et al.,* 1994).

Genes involved in virulence

Cytotoxic enterotoxin (*act*), haemolysin (*hlyA*)/ aerolysin (*aerA*). The *act* gene of *A. hydrophila* encodes cytotoxic enterotoxin, which has many functions viz., cytotoxic, haemolytic and enterotoxic activities (Chopra and Houston, 1999). Other aeromonads have haemolytic activities due to the presence of other genes, namely *hlyA* and *aerA*, and these strains may have one or more of these genes (Heuzenroeder *et al*., 1999). The mature aerolysin binds to host cells, aggregates there and forms holes in their cell membrane destroying the permeability barrier of the membrane, which ultimately leads to osmotic lysis of the cells (Howard and Buckley, 1982). The haemolysin induces accumulation of fluids in intestinal loops (Asao *et al*., 1986), release of certain inflammation promoting factors from the granulocytes (Scheffer *et al*., 1988) and apoptosis of the host cells (Nelson *et al*., 1999). A study showed that about 50% of the marine fish samples were positive for the haemolysin gene *hyl* in India (Reshma *et al*., 2015). In another study, both environmental and clinical isolates from Kolkata (erstwhile Calcutta) in India were found to be positive for *act* and the enteropathogenic potential of these isolates were found to be comparable to *V. cholerae* (Bhowmik *et al*., 2009).

Cytotonic enterotoxins (*ast*, *alt*). The cytotonic enterotoxins do not degenerate the small intestine. The clones of *E. coli* having cytotonic enterotoxin genes have been showed to cause elongation of Chinese hamster ovary (CHO) cells, which also produces cyclic AMP, and these are enterotoxic responses. The Alt enterotoxin is heat labile, whereas Ast is heat stable at 56°C (Chopra and Houston, 1999). These genes have strong roles in causing diarrhoea (Sha *et al*., 2002).

Elastase (*ahpB*). The knocking out of the *ahpB* gene in *A. hydrophila* causes a high rise in the LD_{50} value of *A. hydrophila* in fishes, which indicates that elastase, a zinc metalloprotease, is an important virulence factor to cause disease in organisms (Cascon *et al*., 2000). The *ahpB* gene in *A. hydrophila* encodes protease with both elastolytic and caseinolytic activities (Cascon *et al*., 2000).

Flagella. Most of the *Aeromonas* species and all of the species responsible for human pathogenesis are motile having polar flagella. The polar flagellum has five flagellin subunits *Fla A*, *Fla B*, *Fla G*, *Fla H* and *Fla J*. The *flaA* and *flaB* genes have been cloned and sequenced from *A. salmonicida* (Umelo and Trust, 1997). All the five genes (*flaA*, *flaB*, *flaG*, *flaH* and *flaJ*) were identified in polar flagellin locus of *A. caviae.* Motility is known as an important virulence factor in the aeromonads. Mutation in either *flaA* or *flaB* did not affect development of flagellum but did reduce adherence and motility by approximately 50%. Mutations in *flaH*, *flaJ* or both cause complete loss of motility, development of flagellum and ability to get attached to HEp-2 cells. Thus, the ability to get attached to Hep-2 cells depends on motility and presence of flagella of aeromonads (Rabaan *et al*., 2001).

Lipase. Lipases change the plasma membrane of the host, increasing the severity of disease (Nawaz *et al.,* 2010). Lipase gene has been recovered from multidrug-resistant virulent aeromonads capable of forming biofilms isolated from cattle feaces (Igbinosa *et al*., 2015).

Shiga toxins (*Stx1 and Stx2*). Shiga toxins are protein toxins, which have two parts A and B. One part has enzymatic property and the other binds to the surface of the host cells. These toxins inhibit protein synthesis of the host cells (Sandvig, 2001) and also induce apoptosis (Jones *et al*., 2000).

Enolase. Enolase is a glycolytic enzyme expressed in cell surfaces, which binds to human plasminogen

leading to the production of plasmin which degrade plasma proteins. Enolase is also a heat-shock protein, which regulated transcription and is also necessary for cell viability (Sha *et al*., 2009).

Others. Other virulence factors include adhesins (Huang *et al*., 2015), nucleases (Ji *et al*., 2015), pore forming toxins (Saurez *et al*., 2012) and catalysts.

Antimicrobial Susceptibility

All species of *Aeromonas* show similar antibiotic susceptibility profiles, which are also independent of the origin of the isolates (Kampfer *et al*., 1999). Most of the aeromonads have inducible chromosomal lactamases, which are their main resistance mechanisms. Among these, metallo-β-lactamases, which work against carbapenems, are of major concern (Janda, 2001; Zhiyong *et al.*, 2002). The Clinical and Laboratory Standards Institute (CLSI) have published consensus guideline for testing *Aeromonas* (Jorgensen and Hindler, 2007). The susceptibility status of *Aeromonas* isolates for therapeutically active drugs also seem to be species independent with one exception of *Aeromonas trota*, which is susceptible to ampicillin (Carnahan *et al*., 1991). In a study antibiotic resistance status of *Aeromonas* isolates from diseased fishes were found to be similar to those isolated from the freshwater fish farm (Daood, 2012). In another study *Aeromonas* strains resistant to mercury and arsenite were found and these got transferred to *E. coli* when conjugation experiments were performed (Huddleston *et al.*, 2006).

Resistance Mechanisms. Three major classes of β-lactamases are present in *Aeromonas* species, viz, C cephalosporinase, D penicillinase, and a class B metallo-β-lactamase (MBL) (Libisch *et al*., 2008). Fosse *et al.* (2003) classified strains expressing these β-lactamases into five groups as *A. hydrophila*: class B, C, and D β-lactamases, *A. caviae*: class C and D β-lactamases, *A. veronii*: class B and D lactamases, *A. schubertii*: class D lactamases and *A. trota:* class C β-lactamases. Many *A. veronii* bv. Sobria isolates also express a class C cephalosporinase. In few cases, infecting *Aeromonas* strains expressed a class A β-lactamase of the TEM family of ESBLs (Extended Spectrum β-Lactamases), a character similar to the *Enterobacteriaceae* (Marchandin *et al*., 2003). The β-lactamases are involved in detoxification of antibiotics, changes in the drug binding site of the target and inhibiting the entry of the drug into the bacterial cells by causing changes in structure and function of the cytoplasmic and cell membranes (Benveniste and Davies, 1973). Each strain can produce a maximum of three β-lactamases, which work in a coordinated manner (Walsh *et al.*, 1997). Class C cephalosporinases of the AmpC family are resistant to cephamycins, extended spectrum cephalosporins and β-lactamase inhibitor compounds, like clavulanic acid, tazobactam, and sulbactam, which hydrolyse the CO-NH bond in the lactum ring of cephalosporin to inactivate it (Fosse *et al.*, 2003).

"CphA", is the most common MBL produced by *Aeromonas* species, which is largely found in *A. hydrophila* and *A. veronii* isolates (Walsh *et al.,* 1997). Two other MBLs (VIM and IMP) are also found in *A. hydrophila* and *A. caviae* strains, which encode an integron and a plasmid, respectively (Libisch *et al*., 2008). These MBL-producing strains are resistant to ceftazidime, cefepime, imipenem, and piperacillin-tazobactam; both strains are found to be susceptible to aztreonam *in vitro*. MBLs work in a two-step process: firstly, the C-N bond of the beta-lactam antibiotic is cleaved and then the binding nitrogen is protonated (Crowder *et al*., 2006).

Recently, NDM-1 ($bla_{\text{NDM-1}}$) gene has been detected in this group of bacteria (Walsh *et al.*, 2011). The spread of mobile NDM-1, also known as carbapenemase, is of great concern, not only because these enzymes confer resistance to carbapenems and other β-lactam antibiotics, but also because such pathogens typically are resistant to multiple antibiotic classes, making treatment difficult. Plasmids having the sequence encoding this carbapenemase can have up to 14 other antibiotic-resistance determinants and can make other bacteria also resistant, resulting in multi-drug resistant or extreme drug-resistant phenotypes. Resistance of this scale could have serious public health implications because modern medicine is dependent on the ability to treat infection (Livermore, 2009).

Quinolone resistance in *Aeromonas* strains isolated from two European rivers is a matter of rising concern because quinolone was previously known to be effective in combating *Aeromonas* infections (Goni-Urriza *et al*., 2000). Several *A. caviae* strains showed resistance to nalidixic acid, ciprofloxacin, and norfloxacin (Sinha *et al.*, 2004). Aeromonads pathogenic to fish are found to be resistant to amoxicillin, ampicillin-sulbactum and streptomycin (Abu-Elala *et al*., 2015). These antibiotic resistant bacteria come into the environment through improper septic systems, agriculture and wastewater treatment plants (Rosenblatt-Farrell, 2009). River sediments adsorb antibiotics (Zhou *et al*., 2011) some of which may remain there for months (Lai *et al*., 2011). These impart antibiotic resistance to bacterial populations at that location. Biofilm formation increases resistance to antimicrobial substances (Acker *et al*., 2014), disinfectants (Jahid and Ha, 2014). Biofilm formation in *Aeromonas* is affected differently in different strains under several food related stresses. However, low temperature and pH conditions were found to facilitate biofilm formation in a recent study, which is the first study of this kind regarding *Aeromonas* (Nagar *et al*., 2017).

Role of plamids, integron systems and transposons in disease transmission

In *Aeromonas*, gene transfer mainly occurs through conjugation and transformation, in which type IV pili play a vital role (Huddleston *et al*., 2013). In a study, seven ESBL and two AmpCBL-producing *Aeromonas* strains were able to transfer their antibiotic resistance genes to *E. coli* (Bhaskar *et al*., 2015). Bacterial conjugative plasmids, transposable elements and integron systems are the panoply on which bacteria depend for their resistance to anti-bacterial compounds. Plasmids in particular serve as a platform on which useful resistance genes are assembled and subsequently disseminated (Bennett, 2008). Plasmid profiling and molecular characterization of aeromonad plasmids were undertaken by several research groups to address to the problems of generation and transmission of antibiotic resistance genes (Toranzo *et al*., 1983; Rhodes *et al*., 2000). Studies in eastern India focussed on the characterization of *Aeromonas* spp. isolated from cyprinid and silurid fishes affected with ulcerative disease (EUS) and the involvement of a low molecular weight plasmid has been implicated in the etiology of this disease in fishes (Pradhan and Pal, 1990; Majumdar *et al*., 2006; Majumdar *et al*., 2007). Subsequent investigations have also proved that, the degree of antibiotic resistance in these bacterial isolates is gradually increasing through the years (Pradhan and Pal, 1993; Saha and Pal, 2002; Das *et al*., 2009; Pal and Bhattacharjee, 2011).

Our laboratory tested antibiotic resistance status in few environmental *Aeromonas* isolates and the results showed an increase in antibiotic resistance in case of some antibiotics, while decrease in resistance in others (Dey Bhowmick and Bhattacharjee, 2017). Since antibiotic resistance is increasing in *Aeromonas,* aquaculture should resort to alternate means such as probiotics, essential oils and phage therapy to combat this problem.

In contrast to bacterial conjugative plasmids, which tend to be larger, mobilizable resistance plasmids tend to be relatively smaller (~10 to 20 kb) and encode only a handful of genes including the resistance gene(s) (Bennet, 2008). Therefore, resistance to multi-drugs and presence of small-sized plasmids in environmental isolates of this medically important bacteria group may indicate potential threat to human and culture fisheries (Pal and Bhattacharjee, 2011). Through horizontal gene transfer R-plasmids are spread between different species of *Aeromonas*, which spread multi-drug resistance (Indra *et al*., 2015). Transfer of antibiotic resistance genes from *Aeromonas* to other environmental and clinical bacteria makes treatment of both fish and humans difficult. Presence of multidrug resistance genes on mobile genetic elements is therefore a serious threat to society (Piotrowska and Popowska, 2015).

Conclusion

Phenotypically and genotypically a heterogenous group, aeromonads have been detected, isolated and characterized from varied sources such as brackish, fresh, estuarine, marine waters, chlorinated and unchlorinated water supplies, heavily polluted waters, cold and warm-blooded animals and humans alike. In contrast to the traditional morphological and biochemical differentiation, identification of aeromonads from clinical and environmental sources are presently based on PCR-based genotyping approach such as ribotyping and analysis of gyrB.

In the post World War II period, extensive use (or abuse) of antibiotics have given rise to drug-resistant varieties of bacteria, owing to the success and speed of bacterial adaptation. Bacteria apply many mechanisms to show antibiotic resistance. These resistance genes get accumulated in plasmids and are thought to spread among other bacteria through them. In order to find solution to this problem many researchers have undertaken plasmid profiling and molecular characterization of aeromonad plasmids (Toranzo *et al.,* 1983). Therefore, assessment of anti-microbial drug resistance and possible involvement of bacterial plasmids in this resistance, in the locally isolated clinically and agriculturally important aeromonads, may be rewarding. To understand fully the virulence potential of any pathogen, it is imperative to understand pathogenic factors and/or mechanisms that are involved in their virulence. This is crucial since the expression of different virulence genes could contribute to infection depending upon the anatomical niche where the pathogenic organisms colonize and the microenvironment that dictates the differential expression of genes.

So far, many virulence factors have been discovered and characterized from *Aeromonas* group, especially from *A. hydrophila*, the causative organism of septicemia, wound infections and diarrhoea in humans and in animals. Novel putative virulence factors and/or virulence transfer systems, such as the NDM-1 gene, are being discovered on a regular basis in this diverse and ubiquitous group of bacteria. Although its emergence and distribution is controversial, the detection of NDM-1 gene in this clinically and agriculturally important bacteria group calls for a detailed surveillance of antibiotic resistance and also mode of transferability of NDM-1 gene in this bacteria group.

Plasmid-mediated horizontal gene transfer and acquisitions are thought to be one of the many adaptive ways by which bacteria acquire genes that may be useful periodically in combating environmental stresses, *e.g.*, confronting potentially hazardous anti-bacterial agents, such as antibiotics (Bennett, 2008). Useful genes are thought to be selected and persist that ultimately confer

better adaptability to microorganisms. Plasmid profiling in pathogenic isolates of *A. hydrophila* from fishes with ulcers, had been done to investigate plasmid-mediated virulence potential of the bacterium. Plasmid profiling, plasmid-mediated antibiotic resistance and pathogenesis in aeromonads have been investigated by several groups but further works are necessary to investigate the mode of transmission of virulence and drug-resistance genes in this bacterial group. This is imperative in heavily populated tropical countries like India, especially where sanitary requirements are not upto the standard.

Moreover, knowledge on how antibiotic resistance develops and is spread by mobile genetic elements is necessary for designing and developing prevention strategies intended to minimize the threat of bacterial infections. Considering the great adaptive ability of these bacteria vis-a-vis the environmental stresses and increasing use of anti-bacterial agents in combating *Aeromonas*-associated pathogenesis, newer virulence genes may be acquired by these organisms. Therefore, a search and mapping for putative virulence genes of *Aeromonas* should be undertaken.

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