Evoking Concepts Regarding the Genus *Aeromonas*: An Expanding Panorama of Species, Disease Presentations, and Unanswered Questions

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It has been almost 10 years since a major review on the association of *Aeromonas* with human disease has been published. During that period the number of valid species in the genus has grown to 14, with a new family (Aeromonadaceae) established to house this genus. Despite this explosion in the number of new genomospecies, only five (*Aeromonas hydrophila*, *A. caviae*, *A. veronii*, *A. jandaei*, and *A. schuberti*) are currently recognized as human pathogens. New syndromes attributed to this genus include hemolytic uremic syndrome, burn-associated sepsis, and a variety of respiratory tract infections, including epiglottitis. Convincing evidence suggests that some aeromonads do cause gastroenteritis, but it is presently unclear whether many of the strains isolated from feces are involved in diarrheal disease. Many questions regarding this genus remain unanswered.

The genus *Aeromonas* is one of several medically significant genera that have become an increasingly troublesome group to physicians and microbiologists alike by virtue of their changing phylogenetic relationships, evolving taxonomy, and controversial role in certain human diseases. The turbulent changes in *Aeromonas* taxonomy witnessed over the past 10 years, referred to as a “sea of change” by Carnahan [1], have led many microbiologists to give up attempting to identify aeromonads to the species level in the laboratory when they are recovered from clinical specimens. To compound this problem, new species, taxa, and biogroups continue to be described, further complicating the identification process. In fact, there is such phylogenetic depth within the genus itself that a proposal to create a family to house *Aeromonas* has been made [2].

Although aeromonads were discovered >100 years ago, only during the past 3 decades has their role in a variety of human illnesses been unquestionably proven (table 1). The role of *Aeromonas* species in some syndromes, such as bacterial gastroenteritis, is still speculative and the subject of much debate, with proponents and opponents of their role in diarrheal disease often equally divided. Even less is known regarding the possible role newly described species play in human disease.

The major highlights of the history of aeromonads in relation to human disease are chronicled in table 1. The genus *Aeromonas* has taxonomically resided in the family Vibrionaceae since 1965 with two other genera that are pathogenic for humans (*Vibrio* and *Plesiomonas*). This systematic classification scheme was convenient, if not genetically sound, as all three genera shared similar phenotypic features, ecosystems (water, fish, reptiles, and amphibia), and disease spectrums (gastroenteritis and septicemia). Recently, sophisticated molecular techniques, including 16S rRNA sequencing, have indicated that these three genera are not closely related to each other on an evolutionary basis; plesiomonads are more closely related to the Enterobacteriaceae, and aeromonads are represented by a family of their own [2, 10–12].

Although a number of excellent reviews on various aspects of the microbiology, virulence characteristics, and infectious disease syndromes associated with the genus *Aeromonas* have been published since 1990 [13–19], the increasing number of taxonomic changes in this genus, coupled with case reports and clinical series of various illnesses, dictates a reevaluation of the role of aeromonads as etiologic agents of human disease.

**Taxonomy**

Since the advent of polyphasic molecular approaches in the study of bacterial systematics [20, 21], taxa in the genus *Aeromonas* have undergone a number of significant nomenclature changes in the phylogenetic evolution of this genus [22]. In the mid to late 1970s, most aeromonads were viewed as belonging to one of two major groups. Those strains that grew at 35°C to 37°C (mesophiles) and were responsible for a variety of human infections were commonly referred to as *Aeromonas hydrophila*. Psychrophilic strains that grew better at lower temperatures (22°C to 28°C) and primarily caused infections in fish, such as salmonids, were designated *Aeromonas salmonicida*. These two groups were phenotypically quite distinct and could easily be distinguished from one another on the basis of a number of properties, including optimal growth temperatures, motility, production of indole, and elaboration of a melanin-like pigment on tyrosine agar.

While the taxonomy of the psychrophilic strains has remained fairly stable with minor exceptions, the number of mesophilic species has mushroomed over the past decade or so. These changes have been pioneered by three groups,
Table 1. Significant events in the evolution of *Aeromonas* as a genus of human pathogens.

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1891</td>
<td>Sanarelli</td>
<td>Aeromonads linked to bacteremic &quot;red leg&quot; disease in frogs</td>
</tr>
<tr>
<td>1936</td>
<td>Kluyver, van Niel</td>
<td>Proposal of the genus <em>Aeromonas</em></td>
</tr>
<tr>
<td>1954</td>
<td>Hill, Caselitz, Moody</td>
<td>First human case of disease linked to <em>Aeromonas</em> (acute fulminating metastatic myositis)</td>
</tr>
<tr>
<td>1964</td>
<td>Rosner</td>
<td>First well-described case linking <em>Aeromonas</em> with diarrhea</td>
</tr>
<tr>
<td>1965</td>
<td>Véron</td>
<td>Proposal to include <em>Aeromonas</em> in the family Vibrionaceae</td>
</tr>
<tr>
<td>1968</td>
<td>von Graevenitz, Mensch</td>
<td>First large clinical series of aeromonas infections associated with a variety of illnesses</td>
</tr>
<tr>
<td>1980</td>
<td>von Graevenitz</td>
<td>Association of <em>Aeromonas</em> with three major types of infections (diarrhea, wound infections, and gastroenteritis)</td>
</tr>
<tr>
<td>1976</td>
<td>Popoff, Véron</td>
<td>Genus <em>Aeromonas</em> genetically heterogeneous at species level</td>
</tr>
<tr>
<td>1981</td>
<td>Popoff, Coynault, Kiredjian, Lemelin</td>
<td>Same</td>
</tr>
<tr>
<td>1986</td>
<td>Colwell, MacDonell, De Ley</td>
<td>Proposal to place <em>Aeromonas</em> in its own family</td>
</tr>
</tbody>
</table>

**NOTE.** This table is based on data from [2–9].

Despite the plethora of new *Aeromonas* species, few of these at present appear to have clinical significance. Only five *Aeromonas* species, including one with two biotypes, have been unquestionably established as human pathogens, by virtue of their isolation (in pure culture) from extraintestinal infections (table 2). Of these, two species and one biotype of a third species account for \(>85\)% of all clinical isolates [14]. When only clinically significant isolates are considered, the total percentage of strains represented by HGs 1, 4, and 8 is probably even higher.

Hänninnen and Siitonen [37] recently analyzed 93 isolates of *Aeromonas* recovered from feces (in symptomatic and asymptomatic cases) and blood and found that 89 (96%) of these were identified as *A. hydrophila*, *A. caviae*, or *A. veronii* [37]. Thus, it appears that since the definition of the original 12 DNA groups, no new taxa of major medical significance in the genus *Aeromonas* have been discovered. Of the remaining nine species, most have been predominantly recovered from a variety of nonhuman sources such as water, the gastrointestinal contents of birds and other animals, and fish.

The three *Aeromonas* species predominantly recovered from clinical material (*A. hydrophila*, *A. caviae*, and *A. veronii* biotype sobria) have been involved in a wide array of extraintestinal and systemic infections, including sepsis, wound infections, meningitis, peritonitis, and hepatobiliary disease. However, for the newly described species, very little information is presently available regarding their occurrence in clinical specimens and ability to provoke disease (table 3). Most documented cases of infection involve bacteremias or wound infections.

...
recovered from European eels from Valencia, Spain [31], while the most recent addition to the genus, *A. popoffii*, was described on the basis of 8 isolates recovered from drinking water samples at five sites in Belgium and Scotland [32]. In both instances it is unclear whether the isolates analyzed were in fact separate strains or whether they simply represented multiple isolations of the same strain from the same site. The limited number of strains analyzed in the case of *A. encheleia* has already led to its redefinition [36]; precise phenotypic definition has been precluded by the discovery of biochemically aberrant strains (LMG 13075 and LMG 13076) that fall within the genetic definition of the species ($\geq 80\%$ relatedness to type strain).

A third confounding problem involves strains that previously fell within the *A. hydrophila* complex (HGs 1–3). This group has been found to be much more complex than originally thought. There appear to exist many “bridge organisms” that fall just below cutoff criteria by DNA hybridization for inclusion within a species yet share phenotypic features consistent with the genomospecies [28, 32]. It thus appears that there exists a continuum of rare strains that fall between established species that now make up this complex (*A. hydrophila, A. bestiarum, A. salmonicida*, and *A. popoffii*). These could in essence represent new species but from a practical and medical standpoint should probably be referred to as genomovars or nomenspecies [43], unless a large enough number of strains from diverse sources can be found that generate a minimum of at least two differential tests for precise identification.

### Clinical Infections

#### Gastroenteritis

The single greatest problematic topic concerning aeromonads is still the same unresolved issue that plagued the genus 10–15 years ago: the association of *Aeromonas* species with gastrointestinal disease. Proponents will point to numerous case reports and many case-control studies as supportive evidence for an etiologic relationship between these bacteria and diarrheal disease [44]. Furthermore, the detection of an enteropathogenic mechanism (enterotoxin) in many *Aeromonas* strains provides additional corroboration [14]. Likewise, opponents will cite some, albeit fewer, case-control investigations and the recognition of an asymptomatic carrier state as proof of its lack of enteropathogenicity. The fact that no well-described epidemiologically linked outbreaks of diarrheal disease attributed to *Aeromonas* have ever been reported and that Koch’s postulates have failed to be fulfilled (no animal model) provides strong credence to this latter stance [3, 14].

In the past, these conflicting viewpoints concerning the role of *Aeromonas* species in bacterial gastroenteritis were largely
attributed to an imprecise taxonomy and the supposition that only certain aeromonads possessed diarrheagenic potential. However, this does not now appear to be the case. First, the taxonomy of aeromonads has dramatically improved over the past 15 years, and the major species of clinical importance have been identified (see taxonomy section).

In studies on bacterial diarrhea, both symptomatic individuals and controls have been found to be colonized/infected with the three main species, *A. hydrophila*, *A. veronii* bt. sobria, and *A. caviae* [44–47]. Most isolates of the former two species have been demonstrated in vitro to have enterotoxigenic potential by their ability to express a cytolytic enterotoxin often referred to as a β-hemolysin [13, 14, 19]. Therefore, these early theories regarding why aeromonads were not definitively linked to diarrhea (taxonomy, “hot strains”) do not appear to be valid, on the basis of the best experimental evidence presently available.

In trying to assess the role *Aeromonas* species may or may not play in bacterial gastroenteritis, one must wade through myriad reports, many of which are anecdotal in nature. It appears that the best clinical evidence supporting a role for aeromonads in diarrheal disease comes from a handful of individual case reports in which there is additional documentation of the role of these agents in gastroenteritis, other than simply their isolation from a stool specimen (table 4). In virtually all of these cases, healthy persons without any other significant medical conditions came down with severe gastrointestinal infections, in conjunction with the isolation of *Aeromonas* in pure culture or as predominant flora in fecal and biopsy specimens.

In seven of these eight cases there was additional serological evidence of infection in the demonstration of agglutinating antibodies to the somatic antigen, neutralizing antibodies to the cytotoxin/enterotoxin, and/or immunoreactive antibodies by immunoblot against the whole-cell proteins of the infecting strain. In several cases [6, 48, 50, 51] antibody levels were followed over time, and either a ≥4-fold rise in titer or a concomitant decline during the convalescent period was demonstrated.

These data are further supported by several other immunologic investigations [53, 54] that support the role of aeromonads as enteric pathogens and by a number of case reports in which the resolution of abnormal bowel pathology (per sigmoidoscopy, colonoscopy, or small bowel radiographs) was accompanied by the disappearance of *Aeromonas* organisms from stool specimens as the only possible enteropathogens [55–57]. It seems highly likely, therefore, that at least some *Aeromonas* strains are enteropathogenic. Why then have no outbreaks of *Aeromonas*-associated gastroenteritis been identified? In 1990, Bloom and Bottone [58] described a 3-day outbreak of intestinal disease associated with 17 persons residing in a long-term care facility. Eleven of these patients were available to submit stool samples, and four (36%) yielded *A. hydrophila*. The authors speculated that the low positivity rate may have been due to improper collection techniques, storage, or transport of specimens. This seems unlikely. Unfortunately, the four *A. hydrophila* strains were not further characterized by biochemical, serological, or molecular techniques to determine whether or not a single strain was involved. These same authors [58] refer to another unpublished episode of diarrheal disease attributed to *Aeromonas* in four persons who consumed contaminated egg salad.

de la Morena et al. [59] studied *Aeromonas* isolates recovered from children involved in several outbreaks of gastroenteritis in day-care centers. In the largest of these episodes, *Aeromonas* was recovered as the sole pathogen from 6 (24%) of 25 children; 5 of these 6 children were symptomatic. However, molecular typing of these cultures by pulsed-field gel electrophoresis indicated that a majority of these isolates generated different chromosomal patterns, indicating involvement of different strains with multiple species (*A. hydrophila*, *A. caviae*). While this does not necessarily refute a disease association

### Table 4. Well-documented cases of *Aeromonas*-associated gastroenteritis.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Patient’s sex/age (y)</th>
<th>Gastrointestinal syndrome</th>
<th>Antigen</th>
<th>Acute</th>
<th>Convalescent</th>
<th>Biopsy</th>
<th>Aeromonas species</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [6]</td>
<td>F/10</td>
<td>Typhoid fever</td>
<td>O</td>
<td>3,000</td>
<td>7,000</td>
<td>None</td>
<td><em>A. hydrophila</em>¹</td>
</tr>
<tr>
<td>2 [48]</td>
<td>F/67</td>
<td>Cholera</td>
<td>HA</td>
<td>&lt;10</td>
<td>160</td>
<td>None</td>
<td><em>A. hydrophila</em>¹</td>
</tr>
<tr>
<td>3 [49]</td>
<td>M/35</td>
<td>Dysentery</td>
<td></td>
<td></td>
<td></td>
<td>Rectal</td>
<td><em>A. hydrophila</em>¹</td>
</tr>
<tr>
<td>4 [50]</td>
<td>F/67</td>
<td>Cholera</td>
<td>O</td>
<td>40</td>
<td>1,280</td>
<td></td>
<td><em>A. veronii</em></td>
</tr>
<tr>
<td>5 [51]</td>
<td>M/67</td>
<td>Enteritis</td>
<td>O</td>
<td>160</td>
<td>640</td>
<td>None</td>
<td><em>A. hydrophila</em>¹</td>
</tr>
<tr>
<td>6 [45]</td>
<td>F/30</td>
<td>Dysentery</td>
<td>O</td>
<td></td>
<td>128</td>
<td>None</td>
<td><em>A. media</em></td>
</tr>
<tr>
<td>7 [23]</td>
<td>M/80</td>
<td>Enteritis</td>
<td>O</td>
<td></td>
<td>512</td>
<td>None</td>
<td><em>A. veronii</em></td>
</tr>
<tr>
<td>8 [52]</td>
<td>F/24</td>
<td>Ulcerative colitis</td>
<td>O</td>
<td>16</td>
<td></td>
<td>Small intestine</td>
<td><em>A. veronii</em></td>
</tr>
</tbody>
</table>

**NOTE.** HA = hemolysin (cytotoxin); O = somatic; WC = whole-cell.

* Agglutination, neutralization, or immunoreactive (immunoblot) antibodies (titer).

¹ Identifications predate current taxonomy.

² ETEC O159:H34 also isolated.

³ *Plesiomonas shigelloides* also isolated.
between aeromonads and the outbreak, it does not provide strong support for the concept.

In a study by George and associates [60] in 1985, a wide variation in the quantitative numbers of aeromonads recovered from persons who had diarrhea (10³–10¹⁰ cfu per gram of feces) or did not (10³–10⁸ cfu/g) were noted during different sampling periods. Similarly, volunteer studies involving the ingestion of various Aeromonas strains found that only certain isolates were associated with colonization/shedding in most individuals when challenge doses exceeded 10⁸ cfu [61]. These observations, coupled with the severity of disease noted in table 5, suggest that certain strains at very high inocula can sometimes produce gastrointestinal disease in select individuals. If this is the case, conditions necessary to meet outbreak-related disease (single specific strain, very high concentrations in foods, susceptible individuals) are unlikely to be met except on a very sporadic basis.

**Hemolytic Uremic Syndrome**

A new syndrome associated with aeromonas infection has recently linked aeromonads with hemolytic uremic syndrome (HUS). Bogdanovic and colleagues [62] described a 23-month-old child that developed HUS 6 days after an episode of bloody diarrhea with abdominal pain caused by *A. hydrophila*. The cytotoxin of the infecting strain was active on Vero cells. Serum samples obtained from the young infant 23–58 days after the onset of HUS demonstrated increasing titers of neutralizing antibody to the *A. hydrophila* cytotoxin, ranging from 1:8 (at 17 days) to 1:256 (at 58 days). She underwent peritoneal dialysis and received antihypertensive drugs and packed RBC transfusions, and the outcome was favorable; most metabolic indicators returned to normal within 5 weeks of her illness.

A follow-up to this report by a Canadian group found that two of 82 typical cases of HUS were due to *A. hydrophila* [63]. Thus, although apparently rare, Aeromonas can now be added to this list of agents sporadically linked to diarrhea-associated HUS. However, this cytotoxin (cytolytic hemolysin or aerolysin) is genetically and antigenically unrelated to the shiga toxins produced by *Escherichia coli* O157:H7, as determined by gene probe, PCR amplification, and immunologic assays [14].

**Septicemia and New Bacteremic Syndromes**

Janda and Abbott [64] have proposed four major categories of persons associated with aeromonas septicemia, based upon portal of entry, underlying disease state, immunocompetency status, and exposure to sources of fresh water. By far, the two most common of these groups are immunocompromised adults and infants under 2 years of age with multiple underlying medical complications who develop aeromonas sepsis as a result of direct extension (seeding) of the organisms from their gastrointestinal tracts into the circulatory system.

The most common underlying conditions associated with aeromonas septicemia in these patients are malignancy (40%–50%), hepatobiliary disease (15%–30%), and diabetes (3%–5%), as well as a variety of miscellaneous illnesses, including pancreatitis, trauma, cardiac anomalies, gastrointestinal disorders, anemia, and respiratory problems [64]. Mortality rates in these groups generally range from 25% to 50% [64–66]. Ko and Chuang [67] analyzed 58 cases of aeromonas bacteremia occurring at one medical center over a 5-year period in southern Taiwan. While the overall fatality rate was 36%, several factors were indicators of a poor outcome, including shock on admission, diabetes mellitus, spontaneous bacterial peritonitis, and a high Pugh score (hepatic decompensation).

A third group involves those that develop sepsis as a result of severe wound infections (myonecrosis) precipitated by traumatic events [64]. In these cases, infection comes from exogenous rather than endogenous sources, with exposure to fresh water the most common cause. For persons developing sepsis in conjunction with myonecrosis, the prognosis is extremely poor, >90% of patients succumb to their infections [64, 68].

A fourth group comprises an extremely small collection of cases involving adults with no underlying defects, exposure to freshwater sources, or recognized portal of entry for their bacteremia [64, 69]. Most of these infections have involved pulmonary disease with a fatal outcome (~75%). In one instance, a healthy 23-year-old college student who presented

<table>
<thead>
<tr>
<th>Trauma</th>
<th>Precipitating event(s)</th>
<th>Acquisition</th>
<th>Source of aeromonads</th>
<th>Immune status</th>
<th>Presentation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laceration/abration</td>
<td>Water sports</td>
<td>Community</td>
<td>Water, soil</td>
<td>Normal</td>
<td>Typically mild to moderate infections: cellulitis, abscess formation, ulceration</td>
</tr>
<tr>
<td>Puncture wound, penetrating injury</td>
<td>Occupational exposure</td>
<td>Community</td>
<td>Water, soil</td>
<td>Normal</td>
<td>Typically mild to moderate infections: cellulitis, abscess formation, ulceration</td>
</tr>
<tr>
<td>Crush injury</td>
<td>Motor vehicle accidents</td>
<td>Community</td>
<td>Soil, water</td>
<td>Normal</td>
<td>Often more severe: pyomyositis, gas gangrene, myonecrosis, osteomyelitis</td>
</tr>
<tr>
<td>Severe burn(s)</td>
<td>Occupational accidents</td>
<td>Community</td>
<td>Skin, muscle</td>
<td>Normal</td>
<td>Often more severe: pyomyositis, gas gangrene, myonecrosis, osteomyelitis</td>
</tr>
<tr>
<td>Invasive medical procedure(s)</td>
<td>Intraabdominal surgery, catheterization</td>
<td>Nosocomial</td>
<td>Feces, inanimate objects (?)</td>
<td>Often impaired</td>
<td>Varies: purulent exudate, abscess formation</td>
</tr>
<tr>
<td>None</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Impaired</td>
<td>Cellulitis, abscess, infected chronic ulcers</td>
</tr>
</tbody>
</table>

### Table 5. Clinical settings associated with aeromonas wound infections.

<table>
<thead>
<tr>
<th>Source of</th>
<th>Immune status</th>
<th>Presentation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Typically mild to moderate infections: cellulitis, abscess formation, ulceration</td>
<td></td>
</tr>
<tr>
<td>Soil</td>
<td>Typically mild to moderate infections: cellulitis, abscess formation, ulceration</td>
<td></td>
</tr>
<tr>
<td>Inanimate objects</td>
<td>Often more severe: pyomyositis, gas gangrene, myonecrosis, osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Varies: purulent exudate, abscess formation</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Cellulitis, abscess, infected chronic ulcers</td>
<td></td>
</tr>
</tbody>
</table>

None

Unknown

Unknown

Impaired

Typically mild to moderate infections: cellulitis, abscess formation, ulceration

Often more severe: pyomyositis, gas gangrene, myonecrosis, osteomyelitis

Varies: purulent exudate, abscess formation

Cellulitis, abscess, infected chronic ulcers

Typically mild to moderate infections: cellulitis, abscess formation, ulceration

Often more severe: pyomyositis, gas gangrene, myonecrosis, osteomyelitis

Varies: purulent exudate, abscess formation

Cellulitis, abscess, infected chronic ulcers
with *A. caviae* sepsis and subsequently developed ulcerative colitis, 3 months after the bacteremic episode [70]. This suggests that persons presenting with aeromonas sepsis with no apparent underlying defect should be extensively evaluated for cryptic processes that may not be clinically apparent.

While overall mortality rates from study to study vary significantly with regard to aeromonas sepsis, a better prognosis (<25% mortality rate) has generally been observed for immunocompetent individuals with diabetes or underlying biliary or miscellaneous anomalies who present with sepsis and without signs of peritonitis or ecthyma gangrenosum lesions [64].

A recently described syndrome involves aeromonas bacteremia in burn patients. Before 1988, reports of aeromonas septicemia secondary to infection of burn wounds were virtually nonexistent [13]. Subsequently, Purdue and Hunt [71] and Barillo et al. [72] reported on nine patients who became bacteremic with aeromonads after sustaining severe burn injuries to 38%–80% of their total body. Most of these burns resulted from motor vehicle accidents or accidental or self-inflicted injuries. Introduction of aeromonads into the injured site appeared to occur through contaminated soil or water in most instances.

In one case, quantitative cultures of wound biopsy specimens from a 17-year-old who sustained burns on 59% of his body through the accidental ignition of a can of gasoline yielded *Aeromonas* at a concentration of 10^8 cfu per gram of eschar [71]. In a 1995 study of 58 cases of septicemia, two patients (3%) with severe burn wounds subsequently became bacteremic with *Aeromonas* [67]. The overall fatality rate reported for published cases is ~67%.

Presently, four species of aeromonads are universally recognized to cause septicemia in the human host. These species are *A. hydrophila*, *A. veronii* (both biotypes), *A. caviae*, and *A. jandaei* [26, 40, 65, 66]. A fifth, *A. schubertii*, is implicated as a bloodborne pathogen, since two of the original seven described strains were recovered from the blood of a cancer patient and a person with Felty’s syndrome for whom no additional information is available [24]. Recently, the first case report of *A. schubertii* bacteremia, in a 64-year-old man with liver disease, was published [73]. He apparently acquired his infection from a seafood meal he had consumed several days before his septic crisis.

Most monomicrobial infections are caused by *A. hydrophila* (65%), followed by *A. veronii* (23%–31%) and *A. caviae* (4%–12%). Aeromonas polyomicrobial bacteremias often involve members of the Enterobacteriaceae family, *Pseudomonas*, and streptococci/enterococci [14, 65–67]. Of the ~100 serogroups of *Aeromonas* known to exist, four (O:11, O:16, O:18, and O:34) appear to account for most cases of septicemia (96%) [65]. Differences in the tendency of some *Aeromonas* species to be associated with certain underlying diseases or polyomicrobial infections have been noted in some surveys [65]. An example of this is *A. caviae*, which has been more often associated with polyomicrobial sepsis in cancer patients than either *A. hydrophila* or *A. veronii*.

### Meningitis

Meningitis is a rare complication of extraintestinal infection with *Aeromonas*. Parras et al. [74] recently described a case of aeromonas meningitis involving a 54-year-old man with liver disease and also reviewed the literature. Eight cases of aeromonas meningitis have been described, on the basis of selected clinical criteria; most were community-acquired. Four of these eight cases have occurred in young infants (age, 13 days to 2 years), two of whom had hematologic dyscrasias (sickle cell disease and β-thalassemia, respectively).

The remaining four reports describe aeromonas meningitis in adults (aged 34–66 years), all of whom had one or more underlying conditions (liver disease, ligation of hemorrhoids, and/or head trauma). In 5 of 8 cases (63%), *Aeromonas* was recovered from both the CSF and blood; in 2 instances, from CSF only; and in 1 case, from blood [74]. In two reports, *A. veronii* biotype sobria appeared to be the etiologic agent [74, 75], while *A. hydrophila* was probably involved in the other six cases (although this was not specified). In the most recent case report, in vitro markers associated with invasive *Aeromonas* strains (e.g., causing bacteremia) were demonstrated in the *A. veronii* isolate recovered from CSF [74].

### Peritonitis

Another uncommon yet serious secondary sequela of primary aeromonas infection/colonization is peritonitis. Aeromonas peritonitis can present in three distinct clinical settings: spontaneous bacterial peritonitis, chronic ambulatory peritoneal dialysis, or intestinal perforation [76]. More than 45 cases have been reported in the literature, of which the majority (>75%) have been associated with aeromonas bacteremia [67, 76–78]. Muñoz and associates [76] reviewed 34 cases of aeromonas peritonitis described in the literature. The majority of infections were in patients with chronic liver disease (73%), followed by persons undergoing chronic ambulatory peritoneal dialysis for renal failure (15%) and those with intestinal perforation (9%). All three of the major *Aeromonas* species have been implicated in peritonitis, but *A. hydrophila* predominates, as in most other extraintestinal infections [76–78]. The case-fatality rate for aeromonas peritonitis approaches 60% [76].

### Wounds

Following the gastrointestinal tract, wounds are the second most common source of clinical specimens yielding aeromonads. *Aeromonas*-associated wound infections can range from mild, uncomplicated processes primarily involving cutaneous surfaces (e.g., cellulitis and furunculosis) to more complex illnesses where fascia, tendons, muscle, joints, and bone may become infected [79–81]. Four new surveys have described an additional 85 cases of aeromonas skin or soft-tissue infections with concise reviews of the medical literature [80–83]. Based on these and other publi-
cations [3, 64], a clearer picture is emerging regarding the role these bacteria play in superficial and deep-seated wound infections in selected patient populations.

Four clinical settings account for the vast majority of wound infections attributed to *Aeromonas* species (table 5). By far the most common scenario involves healthy individuals who become infected with *Aeromonas* subsequent to an abrasion or penetrating injury that results in exposure to environmental sources containing aeromonads. In one study by Voss et al. [82], 82% of all aeromonas wound infections resulted from a penetrating injury; 43% of these illnesses were water-related.

Such injuries typically result from recreational (swimming, diving, or boating) or occupational (fishing) use of aquatic facilities. Traumas often occur (in 67%-90% of cases) in young men (age range, 32-44 years) who sustain such injuries while pursuing water-related activities [80, 82, 83]. The lower extremities (60%-65%) are the most common sites implicated in infection, followed by the scalp, hands, and arms [81, 82]. A common precipitating event for many of these wound infections is the striking of a submerged object (roots, tree branch, or rocks) while walking barefoot along the bank of a stream, river, or lake.

Semel and Trenholme [81] noted in a review of aquatic injuries that virtually all cases resulted from contact with freshwater, as opposed to the marine environment. This consistent finding is in spite of the fact that aeromonads can be recovered from seawater and seafood such as shrimp [84, 85]. Aeromonad densities do not appear to explain this singular association, as maximum concentrations of *Aeromonas* species in seawater and pristine freshwater habitats appear remarkably similar (\( \sim 10^2 \) cfu/mL), with high counts (\( \sim 10^7-8 \)) found only in fecally contaminated samples such as wastewater and crude sewage [84]. The other common source of *Aeromonas* causing wound infections is soil. In a review of 32 infections of the foot, at least one-third of all cases were related to the introduction of aeromonads via dirt or soil-contaminated inanimate objects such as broken glass, nails, and sticks [86].

A second category of wound infections is those associated with more severe traumas such as airplane, automobile, streetcar, and boating accidents [80, 82]. Often such injuries result in severe burns or compound fractures leading to myonecrosis, synergistic gas gangrene, or cryptic illnesses manifested months later as infections of the bone [71, 80, 82, 87]. In these instances, soil rather than water is the predominant reservoir for the *Aeromonas* causing infection (table 5).

While the vast majority of aeromonas soft-tissue and skin infections are community-acquired, nosocomially transmitted wound infections do occur. Many of these are precipitated by the translocation of inappropriate infections (such as in the gastrointestinal tract) to sterile tissues by the breaching of normally intact anatomic barriers or through medical intervention. Vukmir [88] described a case of *A. hydrophila* spontaneous myonecrosis of the left calf with sepsis in a 41-year-old man with a history of alcohol abuse, hematemesis, and melena. Previous episodes of gastrointestinal bleeding point to possible dissemination through ruptured esophageal varices. A second similar case of *A. veroni* (‘*sobria*’) acute rhabdomyolysis of the lower extremities with bacteremia occurred in a 56-year-old man with alcoholic liver disease [89]. Again, esophageal varices were suspected as the initial focus, with seeding to extraintestinal sites. Although he partially recovered from his septic episode and associated soft-tissue infection, he eventually succumbed to hepatic and renal failure.

Catheter-related infections, including sepsis due to indwelling medical devices, are rarely caused by *Aeromonas* species. Gold and Salit [80] described two wound infections at the excision site of males who had recently undergone intraabdominal surgery. Kelly et al. [83] reported the isolation of aeromonads from intravascular catheter sites in two men with liver disease and malignant melanoma; a third strain was isolated from an intercostal catheter site in a young man with complications following a craniotomy.

Recently, a case report describing *A. hydrophila* myonecrosis in a 50-year-old man with diabetes, cirrhosis, and esophageal varices was published [90]. Forty-eight hours following insertion of an intravenous cannula into the long saphenous vein, the patient developed spiking fevers with bilateral edema of both legs, subcutaneous gas, and bullae formation. The gangrenous infection progressed rapidly, resulting in death within 5 hours of the initial symptoms in his legs. Aspirated fluid from both legs yielded *A. hydrophila*. The gastrointestinal tract was the presumed source of infection.

Finally, although less frequent, aeromonas wound infections related to the use of leech therapy continue to be reported. One current highlighted case involved a 58-year-old man with a basal cell carcinoma of the scalp who after surgery developed a necrotic flap with aeromonas bacteremia after the use of medicinal leeches to relieve venous congestion [91].

Although uncommon, aeromonas wound infections can develop in persons without any recognizable preceding trauma. In a study of 28 patients with musculoskeletal and soft-tissue involvement due to *Aeromonas*, five individuals (18%) had no history of an injury [82]. Three of these patients had abscesses/cellulitis, while the other two had infections of chronic ulcers. In three of these five patients, underlying disorders were detected, including chronic vascular insufficiency, diabetes mellitus, and chronic lymphocytic leukemia.

Laboratory analysis of wound specimens found to contain aeromonads indicated a polymicrobial etiology, with only 17%-52% of all cultures yielding pure growth of *Aeromonas* [81-83]. Organisms commonly associated with *Aeromonas* include enteric bacilli, clostridia, *Bacteroides*, and enterococci. All three of the major *Aeromonas* species have been associated with wound infections, but *A. hydrophila* (71%) predominates [83]. Differences in species pathogenicity were not observed in this investigation.

In one study, fever was a prominent clinical finding, with an elevated WBC count detected in 8 of 9 cases [80]. Common modalities used to treat aeromonas wound infections include su-
medical procedures (chest radiography, CT) and sputum analysis for respiratory tract pathogens includes findings from a variety of Aeromonas species.

Aeromonas hydrophila was reported in the literature as a respiratory tract pathogen. Initial empirical therapy did not satisfactorily cover aeromonads in patients with underlying diseases whose infections often appear to arise from hematogenous dissemination of aeromonads from the gastrointestinal tract to the respiratory tree. Documentation of its possible role as a pulmonary pathogen has been complicated by the fact that it was often isolated from sputum in conjunction with other microbial pathogens and in the absence of frank bacteremia. Furthermore, sputum isolates of Aeromonas were almost invariably judged to represent transient colonization, as oral secretions often harbored aeromonads for short periods as a result of the ingestion of contaminated potable water during warmer months.

This viewpoint has radically changed over the past decade because of the dramatic increase in the number of detailed case reports documenting Aeromonas as a respiratory tract pathogen (table 6). These illnesses have ranged from life-threatening acute rapidly progressing infection, and concomitant sepsis, to overt pulmonary disease including lung abscesses, pneumonia, and empyema. Patients with aeromonas respiratory tract disease basically fall into two categories. One group is immunocompetent individuals who develop symptoms after contact with aquatic environments through vehicular accidents or swimming. A recent publication suggests the possible use of hyperbaric oxygen to treat cases of A. hydrophila cellulitis that are refractory to surgical debridement and antibiotic therapy.

The overall mortality rate is \( \sim 16\%-22\% \) of all cases, initial empirical therapy did not satisfactorily cover aeromonads, and, in virtually all other recent cases, in the absence of frank bacteremia. Furthermore, sputum isolates of Aeromonas were almost invariably judged to represent transient colonization, as oral secretions often harbored aeromonads for short periods as a result of the ingestion of contaminated potable water during warmer months.

Patients with aeromonas respiratory tract disease basically fall into two categories. One group is immunocompetent individuals who develop symptoms after contact with aquatic environments through vehicular accidents or swimming. A recent publication suggests the possible use of hyperbaric oxygen to treat cases of A. hydrophila cellulitis that are refractory to surgical debridement and antibiotic therapy.

Respiratory Tract Disease

Less than a decade ago, only a handful of legitimate cases of pulmonary disease due to Aeromonas had been reported in the literature. Documentation of its possible role as a pulmonary pathogen has been complicated by the fact that it was often isolated from sputum in conjunction with other microbial pathogens and in the absence of frank bacteremia. Furthermore, sputum isolates of Aeromonas were almost invariably judged to represent transient colonization, as oral secretions often harbored aeromonads for short periods as a result of the ingestion of contaminated potable water during warmer months.

This viewpoint has radically changed over the past decade because of the dramatic increase in the number of detailed case reports documenting Aeromonas as a respiratory tract pathogen (table 6). These illnesses have ranged from life-threatening complications involving soft tissues (parapharyngeal, epiglottitis) to overt pulmonary disease including lung abscesses, pneumonia, and empyema. Evidence supporting aeromonads as respiratory tract pathogens includes findings from a variety of medical procedures (chest radiography, CT) and sputum analysis (polymorphonuclear neutrophils, predominant gram-negative bacilli), as well as the concomitant isolation of Aeromonas from sterile body sites such as blood.
of the eye (blepharoconjunctivitis), more serious disease can occur, including corneal ulcers and endophthalmitis [102–104]. While histories of water-related traumas to the eye in such instances are common (struck by a reed), there are a surprising number of infections with no apparent preceding injury [104] or only an anecdotal comment from the patient regarding the possible source of the illness [103].

Laboratory Identification

Species Determination

An area of active research over the past decade has been the development of numerous methodologies for the rapid and accurate identification (to the species level) of aeromonads recovered from clinical, animal, and environmental sources. These studies have been fueled by the explosion in the number of genotypes, subspecies, and biotypes described for members of this genus. A number of molecular techniques have been exploited to type isolates or identify them to genomospecies level, and these include PCR amplification assays [105, 106], rDNA restriction patterns [107], restriction fragment length polymorphism [108], and pulsed-field gel electrophoresis [109]. However, these procedures are expensive and technically demanding and presently do not provide any useful clinical information. Furthermore, since no defined outbreaks of diarrheal disease have ever been reported, use of molecular technologies to fingerprint Aeromonas strains in the clinical laboratory is unwarranted. However, rRNA gene restriction patterns (rDNA) have been useful in one instance to trace the point source of sporadic diarrhea in a 38-year-old man who consumed shrimp cocktail [110].

Fortunately, most aeromonads (>95%) can be accurately identified biochemically to the genomospecies level nowadays with conventional, albeit unusual, phenotypic tests in some instances. Commercial systems are much less accurate [73], although new versions of software by a number of manufacturers show possible improvement in this area [111]. Dichotomous schemes to identify the major Aeromonas species involved in human infections have been proposed [112], as have others that identify all aeromonads with a high degree of accuracy but require an extensive number of phenotypic tests (>15) [113, 114]. Both of these formats are probably not justifiable for routine use in clinical laboratories because of expense, length of incubation required (~72 hours) for final identifications in many instances, and technical time involved.

How should laboratories identify aeromonads? One possibility is to continue to identify Aeromonas species to the phenospecies level, e.g., to the A. hydrophila, A. caviae, A. veronii (“sobria”) complexes. This would in all likelihood result in a misidentification rate of <15% and would have little, if any, impact on treatment or prognosis. A slightly extended format of this version would be to include the two other species pathogenic for humans (A. jandaei and A. schubertii).

Table 7 lists relevant biochemical reactions to separate these five species. Most of these tests are present in common manual and automated microbial identification systems, with minor exceptions (Vitek lacks the Voges-Proskauer test), so that isolates should be able to be identified to species level even if newer groups are not included in current matrices. For publication of case reports/studies, Aeromonas strains should be definitively identified to genomospecies, with species confirmation by a recognized reference or research laboratory.

Identification and Reporting

Given the type of identification protocols available, how should laboratories report the isolation and identification of aeromonads recovered from human material and, in particular, feces? Since it is presently unclear whether or not each fecal isolate of Aeromonas is involved in gastroenteritis, it should be incumbent upon the laboratory to provide the best laboratory data to physicians, upon which a clinical decision can be made. One recent editorial suggests that a supplemental comment that aeromonads have been implicated as a cause of gastroenteritis be attached to laboratory reports indicating the presence of these organisms in feces [115]. The authors suggest that in such instances the significance of this laboratory report be correlated with clinical findings.

Institutions with rates of fecal isolation of aeromonads of 0.5% to ≥1.0% should probably include a selective media (cefsulodin-irgasan-novobiocin [CIN]) for the specific recovery of Aeromonas in their enteric workups. Isolates should probably be identified to at least the phenospecies level instead of as “Aeromonas species,” and the relative number of colonies present on direct plating should be given (numerous, many, few). There are several reasons for this.

Certain phenospecies are inherently more pathogenic (e.g., A. hydrophila and A. veronii) than others and are associated with higher fatality rates among immunocompromised individuals [65]. Persons with underlying malignancies may be preferentially colonized by aeromonads [116], and monitoring the feces of such individuals for invasive Aeromonas strains may be justifiable in light of their tendency to disseminate to extra-intestinal sites.

Chronic diarrhea exceeding 1 year’s duration due to A. caviae [117] or A. hydrophila [118] has been reported, and the diagnosis is substantiated by the repeated isolation of the same species from stools over protracted periods of time. Alternatively, the isolation of Aeromonas from a single bloody stool may mask more important underlying gastrointestinal abnormalities such as inflammatory bowel disease and colonic carcinoma [119, 120]. Thus, established protocols for the isolation and identification of aeromonads from feces are needed in order to ensure the maximum cost/benefit ratio for the patient.

Antimicrobial Susceptibility

One key area that has received little attention lately has been the in vitro susceptibility of Aeromonas species to chemothera-
peutic agents. Although most aeromonads continue to be susceptible to tetracyclines, aminoglycosides, trimethoprim-sulfamethoxazole, third-generation cephalosporins, and the quinolones [44, 121], a 1996 study found increasing resistance to sulfamethoxazole, third-generation cephalosporins, and the genus Aeromonas. Regardless, new syndromes associated with specific strains, high assessment of the genera Aeromonas, and infectious syndromes associated with the genus Aeromonas have yet been published.

Conclusions

As with any unending saga, some questions are answered, others surface. While we now know the major Aeromonas species involved in human disease, we still are uncertain if other genomospecies can cause human infections. Also unclear is whether certain pathogenic groups such as A. schuberti or A. jandaei are associated with specific clinical syndromes. New studies on the susceptibility of the less frequently isolated newer taxa (A. veronii biotype veronii, A. schuberti, and A. jandaei) to select antimicrobial agents have yet been published.

Table 7. Identification of Aeromonas species of clinical significance.

<table>
<thead>
<tr>
<th>Test</th>
<th>A. hydrophila</th>
<th>A. caviae</th>
<th>bt veronii</th>
<th>bt sobria</th>
<th>A. jandaei</th>
<th>A. schuberti</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDC</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ODC</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>ADH</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>VP</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Esculin</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sucrose</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mannitol</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NOTE. ADH = arginine dihydrolase; bt = biotype; LDC = lysine decarboxylase; ODC = ornithine decarboxylase; VP = Voges-Proskauer; + = >85% positive; – = <15% positive.

References

Aeromonas


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