
REVIEW ARTICLE

Wound infections caused by *Vibrio vulnificus* and other marine bacteria

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SUMMARY

Infections caused by *Vibrio vulnificus* were first reported in 1979 by Blake et al. of the US Centers for Disease Control. At that time described as a ‘rare, unnamed halophilic lactose-fermenting *Vibrio* species’, *V. vulnificus* has emerged as the most virulent foodborne pathogen in the United States with a hospitalization rate of 0·910 and a case-fatality rate of 0·390. It is in addition a significant cause of potentially life-threatening wound infections. Infections following ingestion of raw or undercooked seafood, commonly raw oysters, can lead to a primary septicaemia with a fatality rate of 50–60%. An unusual symptom, occurring in 69% of 274 cases reviewed by Oliver, is the development of secondary lesions, typically on the extremities, which are generally severe (often a necrotizing fasciitis) and require tissue debridement or amputation. These cases occur almost exclusively in males over the age of 50 years. Interestingly, this gender specificity has been found to be due to the female hormone oestrogen, which in some manner provides protection against the lethal *V. vulnificus* endotoxin. Further, most cases occur in persons with certain underlying diseases which are either immunocompromising or which lead to elevated serum iron levels (e.g. liver cirrhosis, chronic hepatitis, haemochromatosis). *V. vulnificus* infections resulting in primary septicaemia have been extensively studied, and the subject of several reviews. This review concentrates on the wound infections caused by this marine bacterial pathogen, including the more recently described biotypes 2 and 3, with brief discussions of those caused by other marine vibrios, and the increasingly reported wound/skin infections caused by *Mycobacterium marinum*, *Erysipelothrix rhusiopathiae*, and *Aeromonas hydrophila*.

WOUND INFECTIONS CAUSED BY MARINE *VIBRIO* SPECIES

Almost all persons who develop vibrio wound infections do so following infection of a pre-existing wound (e.g. an ant bite or laceration) or one obtained while engaged in recreational or fishing activities in coastal waters. As reported by Howard et al. [1], typical examples cited were ‘bitten by stingray while

clamming’, ‘lacerated wrist while shucking oysters with oyster knife’, ‘bitten on finger by crab’, ‘salt-water fisherman cut thumb while fishing’, ‘lacerated foot on rocks in ocean’ and ‘bitten on leg by fire ants, still had on wet pants after wading in water’.

In the first review of soft-tissue infections due to halophilic vibrios [2], 49 of the 51 cases examined were men aged from 7 to 92 years (average 48·2 years). An underlying disease that might be expected to predispose them to a *Vibrio* infection was seen in 22 (44%) of the patients. As with primary septicaemia [3], the most common of these was cirrhosis due to chronic alcoholism [11 (50%) of those with

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underlying illnesses], cancer, steroid medication, heart failure, or diabetes mellitus [four each (17%)], and haemochromatosis or multiple myeloma (one of each). Cellulitis was seen in 39 (76%) of the patients, which usually appeared within 24–48 h of seawater exposure but also occurred as early as 4 h and as late as 12 days later. Half of the 22 patients with underlying diseases developed a necrotizing infection compared with only one of the 29 patients who did not have a predisposing illness ($P < 0.01$). *V. vulnificus*, at 43% (22 cases), was the *Vibrio* most commonly cultured from the 51 wound infections. *V. alginolyticus* was isolated from 26%, *V. parahaemolyticus* from 18%, and non-O1 *V. cholerae* from 10% (the species of *Vibrio* involved was not identified in one patient). Twelve of the 51 patients developed necrotizing infections requiring surgical debridement and *V. vulnificus* was responsible for 75% of these. Of the 51 cases, 13 (26%) patients died. Most commonly isolated from fatal cases was *V. vulnificus* (11/13 patients), with *V. parahaemolyticus* causing one death and non-O1 *V. cholerae* the other.

In a similar study, Levine et al. [4] found 29 out of 121 infections reported in 1989 during a coordinated *Vibrio* surveillance conducted in four Gulf Coast states to be wound infections. Of these, *V. vulnificus* was the most commonly isolated (eight cases), followed by *V. parahaemolyticus* (six), *V. alginolyticus* (five), and non-O1 strains of *V. cholerae* (four). Reflecting the frequent severity of such infections, 19 of the patients were hospitalized and two died. Of the 26 patients with known medical histories, 14 (54%) had an underlying illness.

In the largest study of its kind in the United States, Hlady & Klontz [5] summarized 690 *Vibrio* infections (including primary septicemia, gastroenteritis, and wound infections) reported in 675 persons in Florida over a period of 13 years. Of these, 168 (24%) involved wound infections. Typically, 86% of these occurred in the warm-water months between April and October, and in 98% of the cases the wounds were acquired while the patients were in or around water. *V. parahaemolyticus*, *V. vulnificus*, and *V. alginolyticus* accounted for 86% of the 168 wound cases, with 47 of the cases (28%) due to *V. vulnificus*. Of the *V. vulnificus*-induced wound illness, 72% of the patients were hospitalized, and 11% died (all male). Other vibrios isolated from wounds were non-O1 *V. cholerae*, *V. hollisae*, *V. fluvialis*, *V. damsela*, *V. metchnikovii*, and *V. mimicus*.

Table. *Symptoms and signs associated with Vibrio vulnificus wound infections**

Symptom/sign	%
Cellulitis at wound site	88
Bullae	88
Fever (>37.8 °C)	65
Chills	29
Mental status changes†	18
Ecchymosis	18
Hypotension‡	12
Diarrhoea	6
Vomiting	6

* Adapted from Klontz et al. [9] ($n = 168$).

† Obtundation, disorientation, or lethargy.

‡ Systolic blood pressure less than 90 mmHg.

Vibrio vulnificus

The first indication of the existence of a new *Vibrio* species pathogenic for humans (originally called the ‘L+’, or ‘lactose-positive *Vibrio*’) was in 1976 [6]. That study reported patients with leg lesions caused by this Gram-negative rod, but it is not clear whether the infections originated from a wound or followed ingestion of seafood containing the bacterium. The first report to differentiate the routes of infection appears to be that of Blake et al. [7], which reviewed 15 wound infections caused by *V. vulnificus*. Twelve of the 15 patients had a history of contact with seawater of a pre-existing wound, while two others sustained wounds while cleaning crabs. Symptoms began within 4 h to 4 days (median 12 h), and virtually all cases developed swelling, erythema, and often intense pain. The lesions generally involved a rapidly developing cellulitis that frequently evolved into vesicles or bullae, and sometimes became necrotic. Unlike primary septicemia however, infections were restricted to the primary wound site, with no spread to other areas of the body [8]. Other symptoms reported [7] were fever and chills, and occasionally hypotension and vomiting. Klontz et al. [9] have summarized these (see Table).

Of the 15 wound infections studied by Blake et al. [7], five had known underlying disease, including diabetes, alcoholism, chronic congestive heart failure, and chronic lymphocytic leukaemia. All of the patients were treated with antibiotics, and most underwent tissue debridement. One patient (with leukaemia), who had acquired *V. vulnificus* while cleaning crabs, developed bacteraemia, high fever, shock, and died 36 h after the first symptoms began.

As expected, 85% of the cases occurred in the warm season of the year, 90% of them in males, and 95% in those aged ≥ 40 years. Such an age distribution is typical: Howard and colleagues [1, 2, 10] reported that, except for a highly unusual case in a boy aged 7 years, the average age of the 51 cases they studied was 66.5 years. In a similar study on 17 patients with wound infections in Florida, Klontz et al. [9] reported a median age of 61 years; 16 (94%) were male. In 76% of the patients wounds were sustained while having direct contact with seawater, usually some fishing activity. Mortality in the wound infection group was 24%, and *V. vulnificus* was isolated from blood cultures of all of these. The median time between sustaining the wound and death was 4.5 days (range 3–9 days). Of the six patients with underlying chronic disease, four died (67%), compared with none of the 11 patients without chronic disease ($P=0.006$).

In an unpublished study, Oliver examined the incubation times reported in 16 studies covering over 100 cases of wound infections caused by *V. vulnificus*. These ranged from 3 h (an extreme, although eight cases had incubation periods of 12 or fewer hours) to 12 days (also an extreme, although three cases involved 10–12 days incubation). Most symptoms occurred around 24 h.

Regarding the histology of *V. vulnificus* wound infections, a typical scenario was described by Beckman et al. [11]. In this case, a 60-year-old man with advanced Laennec's cirrhosis went wading off the southern US Gulf Coast after receiving multiple fire ant stings to his leg. He was treated with antibiotics when the leg became infected about 48 h later, but the leg became oedematous with haemorrhagic bullae. Despite further administration of antibiotics, fasciotomy, and ultimately, amputation of the leg, he died 45 h after admission. Autopsy revealed the superficial dermis to be oedematous, and the entire dermis appeared devitalized and contained numerous bacteria. The subcutaneous tissue contained a dense cellulitis, extending into skeletal muscle with much tissue damage. Endothelial cells were hyperplastic and swollen.

In vitro and *in vivo* studies indicate *V. vulnificus* is sensitive to virtually all commonly employed antibiotics, including tetracycline and third-generation cephalosporins [12, 13] and many have been employed in the treatment of both primary septicaemia and wound infections caused by this bacterium [2]. Antibiotic treatment significantly improves case-fatality

rates, with the greater the delay between onset of illness and initiation of antibiotic treatment having a dramatic effect on survival rates. In a mouse model, it was found that tetracycline prevented most deaths if administered up to 2 h after subcutaneous injection of 10^8 *V. vulnificus* cells [14]. However, none of the animals survived when the antibiotic was administered 3 h after injection. In reviewing cases of *V. vulnificus* wound infection in Florida, Klontz et al. [9] observed that only two out of six patients receiving treatment less than 24 h after onset of illness died, compared with all of those with more than a 72-h delay.

An outbreak of *V. vulnificus* wound infection

The occurrence during July 2004 of seven cases of *V. vulnificus* wound infections in one estuarine area near Port O'Connor, Texas in the United States was, to my knowledge, the first and only time when more than one person has been infected with this bacterium in one location [15]. All cases were males aged 44–65 years and all involved infection of pre-existing wounds or those acquired during a fishing contest. Five of the six were hospitalized. One man who had a minor cut on his leg after slipping on a dock died despite being hospitalized for 26 days and having both legs amputated [16]. While *V. vulnificus* infections in Texas are fairly common (there were 14 *V. vulnificus* wound infections reported during 2003 in the entire state), such an outbreak is unprecedented. Whether unusual environmental conditions existed in these estuarine waters is not known.

Geographical distribution

V. vulnificus occurs naturally (and is not pollution associated) in temperate estuarine and coastal waters worldwide, but is most frequently isolated when water temperatures are above 20 °C and salinities are between 5 and 25‰ [17]. Because of such environmental restrictions, there have been few cases reported in the Mediterranean, presumably because the high salinity (38‰) of that water body is not amenable to *V. vulnificus* [18–20].

A brief summary of *V. vulnificus* wound infections reported in countries other than the United States follows.

Denmark

The first fatal case of a *V. vulnificus* infection in Denmark was reported by Bock et al. [21], in a

68-year-old man with a history of chronic lymphatic leukaemia and liver cirrhosis who became infected while catching eels in the sea. Dalsgaard et al. [12] subsequently described this and 10 additional patients admitted to Danish hospitals with *V. vulnificus* infections during the unusually warm summer of 1994. All had been infected after seawater exposure or fishing-associated activities.

Sweden

The first documented case in Sweden was reported by Melhus et al. [22] in 1995. The case involved a 90-year-old female who swam daily in the Baltic Sea, and developed infection in a pre-existing wound of the toe. She was discharged 10 days after admission.

Germany

Hoyer et al. [23] described the case of a woman who, during an unusually warm (>20 °C) August day, went wading in the Baltic Sea with a small wound on her lower leg. Five days later her leg became red, swollen, and developed haemorrhagic bullae. She became hypotensive and was in a critical care unit for 5 weeks.

Spain

Torres et al. [20] described an 84-year-old male who, despite having no underlying diseases, developed a fatal *V. vulnificus* wound infection following swimming on the Mediterranean coast. These authors noted that only three cases of *V. vulnificus* had been reported in Spain prior to this, which they attributed to the high salinity and relatively low temperatures of this sea.

Taiwan

In a survey of 84 cases of *V. vulnificus* infection that occurred in Taiwan between 1995 and 2000, Hsueh et al. [24] found that 68% were wound infections. Of these, 50% involved necrotizing fasciitis and another 18% cellulitis.

Australia and New Zealand

Ghosh & Bowen [25] reported on 16 cases of *Vibrio* infection occurring in Australian Pacific coastal areas, of which three involved *V. vulnificus*. Interestingly, in one case *V. vulnificus* was isolated from a purulent sputum sample, in another from a pelvic peritoneum swab associated with an inflamed fallopian tube, and

in a third case sinuses associated with staphylococcal osteomyelitis. Wise & Newton [26] reported on a 60-year-old alcoholic who lacerated his leg while collecting rock oysters from a river on the eastern coast of Australia and died 5 h after presentation. Upton & Taylor [27] described a man who died of *V. vulnificus* infection following swimming in waters off Auckland, New Zealand.

Other *V. vulnificus* infection sites

Infections with *V. vulnificus* other than of wounds or primary septicaemias following ingestion of raw seafood include osteomyelitis [25, 28, 29], pneumonia (typically following near drownings [25, 28]), endometritis (following engaging in sexual intercourse while in the sea in Galveston Bay [30]) or fallopian tube infections [25], and corneal ulceration [31]. *V. vulnificus* was also isolated from urine on one occasion [32].

Biotype 2

This biotype of *V. vulnificus*, first reported by Tison et al. [33], differs from biotype 1 (the originally described strains) in several biochemical reactions (e.g. being indole negative) and in having a different Lipopolysaccharide type. This strain is almost exclusively associated with infection of commercially raised eels [34], although several cases of biotype-2 infections in humans have been reported [5, 35]. Veenstra et al. [36] described a 63-year-old man admitted to hospital 24 h after eviscerating fresh eels, with biotype-2 *V. vulnificus* isolated from his wounds and blood. Interestingly, these researchers could isolate biotype 1, but not biotype 2, from the adjacent seawater.

Biotype 3

First isolated in 1999, biotype-3 strains of *V. vulnificus* differ from biotypes 1 and 2 in several biochemical traits (e.g. lack of salicin and cellobiose fermentation) [37, 38]. The clinical, epidemiological, and microbiological features of wound infections caused by these strains have been reviewed by Bisharat et al. [37]. Of the 62 cases they studied, 57 developed cellulitis, four necrotizing fasciitis, and one osteomyelitis. Most cases were reported during the summer season, with a median incubation time of 12 h (range 3–48 h) and a median hospital stay of 8 days (0–41 days). Underlying disorders were observed in 40% of the

patients, including cirrhosis (13%), diabetes (19%), and malignant disease (8%). Surgical debridement was required for 66% of the patients, but no deaths were reported.

Infection was associated with the handling of St Peter's fish (*Tilapia*) in all but one of the cases described above; a single case involved handling of carp. *Tilapia* is the most commonly consumed fish in Israel and other Mediterranean countries [37], and cases so far have only been reported in the northern regions of Israel. In an unusual case of *V. vulnificus* wound infection, Tal et al. [39] reported on a 38-year-old woman with a chronic leg ulcer that became infected with *V. vulnificus* when contaminated fish blood was applied to the ulcer by a 'traditional healer'. Although the biotype was not determined, this was probably a biotype-3 strain, since the case occurred in Israel and involved infected fish.

It is interesting and problematic that samples taken from fish-pond waters and from both the skin and intestines of the *Tilapia* associated with these infections yielded only biotype-1 strains of *V. vulnificus*. This inability to culture biotype-3 strains from the environment is similar to the difficulty in isolating biotype-2 strains from eel-pond waters. An additional concern with biotype-3 strains is their identification. Colodner et al. [38] compared a variety of rapid identification systems, and found the ID-GNB Vitek (bioMérieux, Marcy l'Etoile, France) system correctly identified all but one of the 51 strains tested, whereas Microscan Neg Combo 20 (Dade Behring Inc., Liederbach, Germany) and API 20 NE (bioMérieux) systems were unable to correctly identify any of the strains. The authors suggest that this is due to the 'significantly smaller' number of phenotypic traits that are tested with the latter systems, as well as a smaller number of positive results with the traits tested.

Other marine bacteria causing wound infections

V. parahaemolyticus

There is now ample evidence implicating *V. parahaemolyticus* in extraintestinal infections, including infections of the ear, eye, blood, and wounds [40]. As noted above, Howard & Lieb [2] reported 18% of the 51 wound infections they studied were caused by *V. parahaemolyticus*, an identical percentage to that found by Bonner et al. [41] in their 17 cases. Hlady & Klontz [5] found 33% of 168 wound infections in Florida to be due to *V. parahaemolyticus*. Of the

eight deaths resulting from these infections, three were caused by this pathogen. Most (88%) of the wound infections were in patients exposed to seawater within 7 days of illness, and a definite seasonality was observed, with infections peaking in the warm-weather months. Bonner et al. [41] reported a similar seasonality, with all but one wound incurred in a marine environment or during contact with seafood.

V. alginolyticus

V. alginolyticus was first recognized as a human pathogen in 1973 and has since been implicated as the cause of wound and ear infections [42]. Howard & Lieb [2] reported 13 (26%) of the 49 wound infections in their series to be caused by *V. alginolyticus*. Similarly, 22% of the 168 *Vibrio* wound infections in the Hlady & Klontz series [5] were caused by this organism, whereas Ghosh & Bowen [25] found 10 (63%) of their 16 *Vibrio* wound and ear infections in Australia to be caused by *V. alginolyticus*. The bacterium occurs in significant numbers in seawater and shellfish, and wound infections reflect these reservoirs. Most infections clear within a few days without antibiotic treatment [42], and none of the patients described by Howard & Lieb [2] or Hlady & Klontz [5] died.

Vibrio cholerae non-O1

While *V. cholerae* (generally the O1 serotypes) is generally associated with epidemic cholera, the far more numerous 'non-O1' strains found in coastal waters are often considered to be of no medical concern. However, Simpson et al. [43] studied 12 strains of non-O1 *V. cholerae* injected by the subcutaneous route (0.2 ml of 10⁷ c.f.u.) into mice, and found seven to result in a high mortality rate. All strains caused oedema and lesions at the inoculum site, and these often became necrotic, appearing similar to those produced by *V. vulnificus*. In contrast, only one of the 10 *V. cholerae* O1 strains tested was highly lethal. These experimental results are in agreement with clinical studies that have reported non-O1 strains to be isolated from blood, wounds, ear infections, bile, peritoneal fluid, sputum, and cerebral spinal fluid [44]. In the survey by Hlady & Klontz [5], 11 (6.5%) out of 168 wound infections were caused by non-O1 *V. cholerae* strains, similar to the 6% observed by Bonner et al. [41]. Further, and unlike O1 *V. cholerae* strains which rarely cause infection outside the gastrointestinal tract, a survey of non-O1 *V. cholerae*

extraintestinal infections by Safrin et al. [45] found over 60% of 23 cases that resulted in bacteraemia were fatal. In one instance [46], a man fell and abraded his shins while fishing. He developed fever, chills, and bilateral leg pain and swelling the next day. He was admitted to hospital, where the bilateral cellulitis continued to progress. After 4 weeks of therapy with oral tetracycline the cellulitis resolved, but he was left with permanent lymphoedema of one leg. Most wound infections are seawater-associated [47, 48].

It must also be noted that, while uncommon, wound infections with non-toxigenic strains of the O1 serogroup of *V. cholerae* have also been reported. Rodrigue et al. [49], for example, described 14 cases involving this serogroup, two of which were wound infections. One of these probably came from an oyster, while the other involved a post-surgical wound following hip surgery. Both cases occurred in the US Gulf Coast.

Aeromonas hydrophila

A. hydrophila is a Gram-negative rod widely distributed in both fresh and salt waters and is a common fish pathogen [50]. In humans, it is known to cause gastroenteritis and a variety of extraintestinal infections, including endocarditis, pneumonia, conjunctivitis, and urinary tract infections, as well as wound infections [51]. The latter generally remain localized, but may be fatal in immunocompromised patients where infection can lead to gas gangrene and septicaemia [51–53]. Most of these patients have chronic underlying syndromes, such as leukaemia, solid tumours, cirrhosis, or renal failure [51, 53]. However, unlike those caused by *V. vulnificus*, extraintestinal infections caused by *A. hydrophila* frequently occur in children and adolescents. While some of these infections may originate from the gastrointestinal tract [53], many are linked to water-associated injuries or aquatic recreational activities [54–57]. Simple wound infections are rather easily treated with antibiotics (fluoroquinolones or trimethoprim–sulphamethoxazole are drugs of choice), generally coupled with incision and drainage of the wound [50].

Mycobacterium marinum

M. marinum, an acid-fast bacillus found worldwide in freshwater and saltwater, is the cause of ‘fish-tank granuloma’ or ‘swimming-pool granuloma’ [50]. The average number of cases is estimated in the United States to be close to 200, and this and related

Mycobacterium infections are considered ‘emerging infections’ (see review of Dobos et al. [58], for a discussion of this and other *Mycobacterium* spp. causing necrotizing skin lesions). The infections occur most typically in healthy males between 35 and 42 years of age [59], but with extremes of 14 and 85 years being reported [60]. In a survey of 652 cases, Jernigan & Farr [61] reported 49% involved both freshwater and saltwater aquaria in the patients’ homes, 27% following fish or shellfish injuries, and 9% involving injuries associated with saltwater or brackish waters. The bacterium is slow growing (7–14 days at 30–32 °C), and as a consequence lesions require 2–6 weeks to develop after wound infection [50]. Jernigan & Farr [61] found a median of 21 days (range 5–270 days) in 40 cases with known incubation periods. The lesions typically develop on the fingers, hands, knees, and elbows, a result of exposure of the wounds at these sites to the bacteria in water. As with *V. vulnificus*, lesions are typically solitary, but unlike *V. vulnificus* are generally not significantly painful. In 20–40% of patients, the lesion may develop in a sporotrichoid pattern with additional nodular or ulcerating lesions appearing [62]. Once thought rare, lesions that had penetrated to tendons, bones, and joints were found by Aubry et al. [63] in 18 (29%) of the 63 cases they studied; such penetration appears limited to immunocompromised patients [48]. Antibiotic treatment is effective, with clarithromycin being the drug of choice [50, 63], although prolonged treatment is necessary [60, 63]. Ang et al. [60] reported the duration of disease to be 1–132 months, with a mean of 19 months, although lesions in untreated cases have been reported to last for decades [50, 63].

Erysipelothrix rhusiopathiae

E. rhusiopathiae is a Gram-positive rod that has worldwide distribution and is generally associated with a variety of birds, fish and shellfish, with swine considered the primary animal reservoir [50, 64]. Disease caused by this pathogen has been reported from virtually all countries of the world, including Europe [65]. The most common form, known as erysipeloid, results in localized cutaneous eruptions on the fingers or hands, and is often referred to as ‘shrimp picker’s disease’, ‘crab poisoning’, or ‘fish poisoning’ [66]. This typically occurs in workers (e.g. farmers, butchers, fishermen, and especially seafood packers) coming into regular contact with infected animals [50, 64]. The incubation period is 4–7 days,

and the disease usually resolves in 3–4 weeks, even without treatment [50]. A rare but highly fatal disseminated form of the disease involving endocarditis is also recognized, but this generally does not involve a preceding wound infection [64]. As with *V. vulnificus*, disseminated cases typically involve a history of alcohol abuse. Because of the possibility of dissemination, antibiotic treatment is recommended, with penicillins being the drugs of choice.

Summary and recommendations

Wound infections caused by marine bacteria, especially of the genus *Vibrio*, appear to be increasing in frequency and recognition. Many require some underlying syndrome, most commonly involving liver disease, but others appear able to infect fully immunocompetent and healthy individuals. Some, such as *V. vulnificus*, are potentially fatal, and require rapid and aggressive treatment. The pathogens described in this review should always be considered when wound infections are seen in persons with a history of seawater or seafood exposure.

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