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Infections Caused by Halophilic Marine *Vibrio* Bacteria

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Objective

The authors reviewed patients who developed sepsis or soft tissue infections caused by marine *Vibrio* bacteria in Florida.

Summary Background Data

Marine *Vibrio* bacteria are the most common bacteria found in seawater. They are concentrated in marine animals that feed by filtration such as oysters and clams. These bacteria can cause gastroenteritis, sepsis, cellulitis leading to necrotizing soft tissue infection after exposure to seawater or consumption of raw seafood.

Methods

The authors received 182 systemic infections that occurred in Florida between January 1, 1979, and December 31, 1991, which were treated by the authors or were reported to the Florida Department of Health and Rehabilitative Services. Patients were divided into two groups depending on whether they presented with primary bacteremia or soft tissue infection.

Results

Seventy-one patients had been exposed to these bacteria by eating raw seafood, 94 had direct exposure to seawater, and exposure was uncertain in 27 patients. *Vibrio* species were cultured from the blood of 103 patients and from wounds or soft tissues of 113. An additional 5 patients had cellulitis but bacteria were not cultured from these sites. In patients in whom it could be determined, 93 had primary soft tissue infections and 82 had primary bacteremia. Twenty-four patients had necrotizing soft tissue infections and required surgical debridement. Three of these 24 patients required amputation. Thirty-seven (20.3%) patients died. Severe liver disease occurred in 54 patients and 25 of these patients died.

Conclusions

Marine *Vibrio* bacteria can cause sepsis and soft tissue infections, especially in individuals with severe liver disease and other chronic illnesses such as diabetes mellitus. The authors believe all individuals, especially those with systemic illness, should be warned against eating raw seafood.

Marine animals can injure humans in several ways. Biting animals such as sharks, moray eels, and barracuda can be responsible for severe bite injuries, but these attacks are uncommon. Stings from animals such as Portuguese man-of-war, jellyfish, catfish, and coral, although painful, usually require little treatment.

Some animals cause injury by inducing infection. These infections result when oral bacteria are introduced into the tissues of victims who are bitten. Bacteria present within the tissues of marine animals can cause infection when they are ingested. In addition, seawater itself

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contains bacteria, so that skin and soft tissue injuries exposed to seawater may become secondarily injected. In Florida, marine bacteria ingested in seafood such as oysters and crab or which contaminate open wounds when people swim or wade cause more serious disease and death than do bites, stings, and other injuries caused by all marine animals combined. Most infections are caused by halophilic marine *Vibrio* bacteria. More infections due to halophilic marine *Vibrio* bacteria are reported in Florida than any other place in the United States or the world. Surgeons may be asked to treat these individuals infected with these bacteria because they can cause cellulitis and necrotizing soft tissue infections. They also can cause gastroenteritis and sepsis.

Infections caused by these bacteria must be reported to the Communicable Diseases Epidemiology Program of the Florida Department of Health and Rehabilitative Services. Patients reported to the Communicable Disease Epidemiology Program or seen at Shands Hospital at the University of Florida, Gainesville, form the basis for this report.

PATIENTS AND METHODS

Case report forms or hospital charts of patients with bacteremia and/or soft tissue infections or cultured from other tissue sites caused by halophilic marine *Vibrio* bacteria treated by the authors at Shands Hospital at the University of Florida or reported to the Communicable Diseases Epidemiology Program of the Florida Department of Health and Rehabilitative Services between January 1, 1979, and December 31, 1991, were reviewed. Virtually all cultures were confirmed by the Office of Laboratory Services, Department of Health and Rehabilitative Services. *Vibrio* species grow in nonselective media that contain at least 0.5% sodium chloride. *Vibrio* species are differentiated from one another by the ability to ferment a variety of sugars and grow in 10% sodium chloride.

Patients were divided into two groups depending on whether they presented with primary bacteremia or soft tissue infection. Thirty-six patients had bacteria cultured from both soft tissues and blood and are divided according to whether one likely led to the other. Thus, 15 of the 82 patients in the bacteremia group also had *Vibrio* species cultured from soft tissues but these 15 individuals had eaten raw seafood and did not have direct exposure to marine waters. On the other hand, 16 of 93 patients with primary soft tissue infections also had bacteremia. These individuals had been directly exposed to marine waters but had not eaten raw seafood. No such determination could be made for five patients, who had *Vibrio* species cultured from both blood and soft tissues. The chi-square test was used to test for statistical significance.

RESULTS

Between January 1, 1979, and December 31, 1991, 182 patients developed invasive infections due to marine *Vibrio* bacteria. Gastroenteritis due these bacteria developed in a similar number of patients, but these latter patients are not considered further. One hundred forty-six infections occurred during the summer months from May through October. Only 18 infections occurred before 1985. Since that time, 13 to 26 invasive infections have occurred each year.

There were 148 men and 34 women. One hundred seventy were white, nine were Black, two were Hispanic, and one was Oriental. Their ages were from 5 to 92 years old (mean: 50.6 yr). Eighty-eight patients were older than 50 years.

Seventy-one individuals were exposed to marine vibrios by eating raw seafood. Seventy had eaten raw oysters, and one had eaten raw crabs. Ninety were exposed directly to seawater or estuarine waters by bathing in the ocean or being injured by marine animals or inanimate objects. Six of these individuals had both eaten raw oysters and been directly exposed to marine water. *Vibrio* was cultured from the peritoneal cavity of one patient who was on peritoneal dialysis. She had been swimming in the ocean immediately preceding the development of peritonitis. Another individual had *Vibrio* cultured from her gallbladder after cholecystectomy for acute cholecystitis. She had eaten raw crabs and had gone fishing in the ocean before developing cholecystitis. The exposure was uncertain in 27 patients. These latter individuals had lived or traveled near marine waters but denied eating raw seafood or being directly exposed to marine water.

One hundred three individuals had *Vibrio* bacteria cultured from the blood. Bacteria were cultured from the area of inflammation or wounds in 113 patients. Cellulitis developed in an additional five patients with bacteremia, but bacteria were not cultured from these areas. In thirty-six individuals, *Vibrio* bacteria were cultured from both blood and wound.

Ninety-three patients had primary soft tissue infections and 82 had primary bacteremia. There were 82 men and 11 women in the soft tissue infection group and their mean age was 45.2 years (range: 5–92 yr). The bacteremia group had 61 men and 21 women with a mean age of 56.6 years (range: 18–90 yr).

Patients with primary bacteremia usually have abrupt onset of chills, fever, nausea, vomiting, diarrhea, which is frequently bloody, abdominal cramps, and intense muscle pains (Table 1). Twenty-seven patients also had soft tissue infections manifested by cellulitis, edema, bronze discoloration, and bullae (Fig. 1). Nine patients had necrotizing soft tissue infections. Patients with primary soft tissue infections had primarily soft tissue

Table 1. CLINICAL FINDINGS IN PATIENTS WITH PRIMARY BACTEREMIA OR SOFT TISSUE INFECTION

Clinical Finding	Primary Bacteremia (n = 82) (%)	Soft Tissue Infection (n = 93) (%)
Fever	76	40
Chills	9	4
Nausea	61	14
Vomiting	54	9
Diarrhea	54	8
Headache	27	4
Abdominal cramps	45	10
Muscle pain	40	34
Cellulitis	27	65
Bullae	11	11
Necrotizing infections	11	14

Table 2. CHARACTERISTICS OF PATIENTS WITH HALOPHILIC MARINE *VIBRIO* INFECTIONS

Characteristic	All Patients (n = 182)	Primary Bacteremia (n = 82)	Primary Soft Tissue Infection (n = 93)
Liver disease	54	39	12
Other chronic conditions*	20	10	10
No underlying illness	83	33	71
Exposure to seawater	88	10†	75§
Raw seafood consumption	71	63‡	6§
Exposure not identified	35	12	13
Died	37	22	12

* Chronic conditions includes diabetes mellitus, steroid medications, previous gastric surgery, and cancer in patients who did not have liver disease.
† $p < 0.01$ compared with primary soft tissue infection.
‡ Three patients ate raw seafood and were exposed to seawater.
§ One patient ate raw seafood and was exposed to seawater.

symptoms and signs but many of them had systemic manifestations as well (Table 1). Symptoms began 4 hours to 14 days after eating raw seafood or exposure to marine or estuarine water, with 48.3% of patients having symptoms within 24 hours and 66.7% within 48 hours.

Forty-nine (59.7%) patients with primary bacteremia had underlying illnesses that may have increased their susceptibility to these infections (Table 2). Thirty-nine had severe liver disease and cirrhosis, and ten other patients without liver disease had other medical conditions (cancer, diabetes mellitus, steroid medications for arthritis, previous gastric surgery) that may have compromised their host defenses. Significantly fewer ($p < 0.01$) patients (12, 12.9%) with primary soft tissue infections had liver disease (Table 2). The number of patients in both groups with necrotizing soft tissue infections was similar. None of the nine patients with primary bacteremia who developed necrotizing infections had a history of exposure to seawater.

Figure 1. Typical appearance of a soft tissue infection caused by halophilic marine *Vibrio* bacteria. Note the bronze discoloration (dark skin of lower leg) and bullae (arrows).

The *Vibrio* species responsible for primary bacteremia or soft tissue infections were similar in both groups (Table 3). *V. vulnificus* was the most common species identified. *V. vulnificus* was responsible for a disproportionate number of deaths accounting for 11 of 12 (chi-square = 14.72, $p < 0.001$) deaths in patients with primary soft tissue infections and 17 of 22 deaths (chi-square = 7.44, $p < 0.01$) in patients with primary bacteremia.

Surgeons may be asked to treat these patients because they have sustained injuries from marine animals or because of lacerations or abrasions sustained in association with contamination by marine or estuarine water that may harbor *Vibrio* bacteria. Soft tissue infections can also occur in areas of previous minor injuries that result in breaks in the skin that are then exposed to seawater when the individual bathes in marine or estuarine waters. Fifty-six individuals had preexisting injuries that might have provided an entrance for *Vibrio* bacteria. Another 20 individuals sustained injuries in association with exposure to seawater.

Infections developed in 32 individuals after sustaining injuries from marine animals. These were usually cuts or puncture wounds from shells or fish barbs. To add insult to injury, a soft tissue infection developed in one man who had been bitten by a shark.

All wound infections and cellulitis due to *Vibrio* bacteria occurred in the extremities. The infection is characterized by intense erythremia progressing to bronze discoloration and bullae formation. Purulent drainage is

Table 3. *VIBRIO* SPECIES RESPONSIBLE FOR HALOPHILIC MARINE *VIBRIO* INFECTIONS

Vibrio Species	All Patients (n = 182)	Primary Bacteremia (n = 82)	Primary Soft Tissue infection (n = 93)
vulnificus	83	43	38
parahaemolyticus	39	11	26
alginolyticus	25	3	21
cholerae non-01	23	16	5
holliase	3	3	0
mimae	3	3	0
fluvalius	1	1	0
Not identified	5	2	3

not commonly found in patients with these infections. These patients may also have erythremia proximal to the site of infection. With infections in the lower extremity where they usually occur, there may be erythremia in the groin and flank.

Necrosis that may need debridement may develop in some patients. Necrotizing soft tissue infections that required debridement developed in 24 of the 118 patients with wound infections. *Vibrio* bacteria were cultured from the wounds of all 24 patients and from the blood of 14 patients. *V. vulnificus* was the most common species isolated from these patients (18 of 24), a significantly higher proportion (chi-square = 9.63, $p < 0.01$) than in patients with *Vibrio* infections who did not develop necrotizing infections. Twenty-two patients were men and two were women. Thirteen patients had eaten raw seafood in the period before necrotizing soft tissue infections developed and nine had direct exposure to seawater. Three of these patients had both direct exposure to seawater and had eaten raw oysters. Two patients were not exposed to raw oysters or to seawater. A fisherman who was driving near the Gulf of Mexico was riding in his pickup truck with his left hand hanging out the window and was bitten by an insect. A necrotizing soft tissue infection developed on the dorsum of his hand, and *V vulnificus* was cultured from the wound. The other individual was a 71-year-old man with diabetes mellitus who did not have a history of eating raw oysters or being exposed to seawater. A necrotizing soft tissue infection of his lower extremity developed caused by *V. alginolyticus*. Eight patients had a preexisting wounds in their lower extremity that might have provided an access for bacteria from seawater or might have provided a site where the bacteria could lodge. Twenty-two patients had necrotizing infections of the lower extremity, and two had necrosis of the skin, of the dorsum, and of the hand.

Of the 24 individuals with necrotizing soft tissue infections, 18 of them had at least one medical problem that might have made them a compromised host. Twelve had severe liver disease, 12 had diabetes, and 6 had cancer. Only six seem to be without a medical disease that might have compromised their host defenses. Eleven (45.8%) of the 24 patients with necrotizing soft tissue infections died. *V. vulnificus* was responsible for 9 (81.8%) of the 11 deaths (chi-square = 16.93, $p < 0.001$).

These necrotizing soft tissue infections usually involve the skin and soft tissue but not the underlying muscle. Treatment consists of debridement of the necrotic tissue. Three patients required amputation. In one of the three, the muscle was not involved, but the surgeon performed bilateral above-knee amputation after three previous limited debridements of the necrotic skin and underlying subcutaneous fat did not halt progression of the necrosis.

Thirty-seven (20.3%) of the 182 patients died. Twenty-nine of the patients who died were men and eight were women. Thirteen had *Vibrio* cultured from their blood alone, 7 from the wound but not from blood, and 17 had *Vibrio* cultured from both the wound and blood. An additional patient had a wound infection in addition to *Vibrio* being cultured from the blood, but the bacteria was not cultured from the wound. *V. vulnificus* was responsible for 28 (75.6%) deaths and was significantly (chi-square = 16.929, $p < 0.001$) more likely to cause death than infection with other *Vibrio* species. Death occurred from 1 day to 12 days after eating raw seafood or exposure to seawater (median: 1.9 days).

Antibiotic therapy and supportive treatment are required for all invasive infections due to halophilic marine vibrios. These bacteria are susceptible to most common antimicrobials including tetracyclines, erythromycin, cephalosporins, and extended spectrum penicillins. The infection frequently appears to progress despite what seems to be appropriate antibiotic therapy based on *in vitro* laboratory testing, leading to changes in antibiotic therapy. Other supportive measures may be required when hypotension or organ failure occurs. Operation is required if tissue necrosis is found.

DISCUSSION

Until recently *Vibrio cholerae* 01, the cause of epidemic cholera, was believed to be the only pathogenic *Vibrio* species. Other *Vibrio* species were dismissed as "nonagglutinable" because they did not agglutinate in antiserum to *V. cholerae*. In 1964, the Center for Disease Control received vibrio isolates from extraintestinal sites, which were later identified as *V. vulnificus*.[5] *V. parahaemolyticus* and *V. alginolyticus* were recognized as causes of extraintestinal infections in 1969 and 1973.[6,7] The clinical syndrome associated with *V. vulnificus* was

first described in 1979.[8] *V. cholerae* non-01, a different serotype of *V. cholerae*, does not cause epidemic diarrhea and is a halophilic marine vibrio.

Halophilic marine *Vibrio* bacteria can be found in coastal waters, estuaries, and marine animals throughout the world.[9,10] They are the most common bacteria found in marine waters where they account for 31.2% of all bacteria and reach concentrations of 35 to 710 colony-forming units (cfu) per 100 ml.[9] These bacteria are concentrated in animals such as oysters and other shellfish that feed by filtration. They account for 38% of all bacteria that can be cultured from oysters and 4.6×10^6 cfu can be cultured from a single oyster. The viability of vibrios decreases in refrigerated oysters to 10^5 cfu/oyster at 6 hours and 10^3 cfu/oyster at 24 hours.[11] They can also be cultured from crabs and other fish. These bacteria are readily killed by cooking. People who eat raw seafood, especially oysters, and those who are exposed to seawater, usually those with a preexisting cutaneous injury or who sustain an injury in the water can develop infections due to these bacteria.

Extraintestinal infections from these bacteria have been reported from North America, South America, Europe, Asia, and Austria.[12] More infections due to these bacteria occur in Florida than anywhere else in the world. With more than 1350 miles of coastline, of which more than 1000 miles are sandy beaches, a long bathing season, and a large tourist population, ample opportunity exists for contact between man and marine waters. In addition, the Gulf Coast of Florida is home to a thriving oyster harvesting industry that provides fresh oysters to restaurants throughout the state. These infections are extremely uncommon considering the large number of individuals exposed to marine waters or who eat raw seafood. One is nevertheless struck by the virulent nature of these infections when they occur. Symptoms frequently occur within hours after eating raw seafood or exposure to seawater. Shock and death can occur rapidly and half of the patients who died did so within 2 days. These bacteria are usually responsive to several antibiotics. Erythromycin, tetracycline, cephalosporins, and extended spectrum penicillins are all effective in the laboratory.[13,14] Nevertheless, infection and death commonly occur in spite of what seems to be appropriate antibiotic therapy. Because of the extremely virulent nature of these infections, we have been inclined to treat individuals with two antibiotics.

The surgeon is not usually required to treat these patients unless tissue necrosis has occurred. Even then, the necrosis usually involves skin and underlying fat but not the underlying muscle. Three patients in this series, however, did require amputation to control their infections.

Patients with cirrhosis, diabetes, cancer, and other diseases that may compromise their host of defenses appear to be particularly susceptible to these infections and 99 of the 182 patients in this series were compromised hosts. Patients with cirrhosis and hemochromatosis may have alterations and iron metabolism and elevated serum iron concentrations. Iron is required for bacterial growth and the ability to obtain iron from the host is essential for pathogenicity. In experimental studies, Wright et al.[15] demonstrated that *V. vulnificus* could grow well in rabbit serum that has a transferrin that is 60% saturated with iron, whereas human serum that is 30% saturated was bactericidal. They also demonstrated that administration of iron to mice could reduce the inoculum of bacteria required to kill 50% of the animals from 10^6 cfu to a single cfu.

Patients with cirrhosis also have portal hypertension, allowing bacteria that translocate from the gastrointestinal tract to bypass the phagocytic reticuloendothelial system in the liver. Bacteria may thus gain access to the systemic circulation. In animals studies with *V. vulnificus* we have shown that bacterial translocation occurs within 4 hours of inoculation into the duodenum. Bacteria can then cause bacteremia or may locate in an area of the skin where local host defenses have been comprised by a break in the skin leading to cellulitis and soft tissue infections. Because of their increased susceptibility to infection with *Vibrio* bacteria, we believe individuals, with severe liver disease and other systemic illnesses, should be warned not to eat raw seafood. The Florida Department of Health and Rehabilitative Services has warned all individuals not to eat raw oysters because of the risk of infection and death due to marine *Vibrio* bacteria.

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Discussion

DR. MARK A. MALANGONI (Cleveland, Ohio): I'd like to congratulate Dr. Howard and Dr. Bennett on sharing your unique experience with marine vibrio infections with us. I preface my comments by saying I have absolutely no experience treating these infections and therefore I probably serve as an adequate representative of today's audience, since I suspect most of you don't see any or many of these in your practice. I'd like to ask some questions to help us understand the pathophysiology of the soft tissue infections. Although not all patients who develop soft tissue infections were exposed to sea water, most were. I presume that many if not all of these patients had some cutaneous portal of entry. Thus, my question is, can the likelihood of infection be related to some threshold concentration of vibrio in the sea water itself. In this case certain public health measures such as closure of beaches, decontamination of water and the like might be effective in preventing these infections. Hematogenous spread is a very unusual cause for necrotizing soft tissue infections. I don't really understand the mechanism for the cutaneous and soft tissue infection occurrence in patients whose only risk factor was eating raw oysters. Could you clarify how this occurs and if there is a particular characteristic of *Vibrio vulnificus* that accounts for its predisposition to cause most of these infections? Bacteremia and necrotizing soft tissue infection was an ominous combination and had an associated mortality of almost 50%. Was this due entirely to the underlying disease or was there some delay in surgical therapy that accounted for the high rate of death? Only 20% of patients determined to have cutaneous involvement required debridement. Can you identify for us any particular indication for operation that differs from patients with other types of necrotizing soft tissue infections, and indeed what are your indications for debridement in this patient group? Lastly, can you tell us which two antibiotics you would suggest when you treat your next vibrio infection?

DR. ANTHONY A. MEYER (Chapel Hill, North Carolina): I'd also like to congratulate Dr. Howard on an excellent presentation. Despite getting my start in surgery in San Francisco, we didn't see much vibrio, although I saw a considerable number of soft tissue infections more associated with drug use than with oyster abuse. The questions that I have relate to my experience that necrotizing soft tissue infections are associated with negligence frequently on the part of the patient and occasionally on the part of the physician who watches it for a period of time until it gets to be quite obvious that something isn't right. Did you notice considerable delay in treating your population of patients and to what extent did that delay contribute to their poor outcome? Furthermore, did they come to you with evidence already of organ system failure that would go along with the kind of mortality that you saw with those patients? Like Dr. Malangoni, my experience with necrotizing infections of other types has been that radical excisional debridement, a very aggressive debridement in the operating room and frequently repeated trips to the operating room are necessary to get ahead of the infection. In your experience with this specific type of infection, is this handled differently? Is the organism and the infection it has caused enough different that you need a different surgical approach?

DR. EDWIN A. DEITCH (Shreveport, Louisiana): I would like thank Dick Howard for the opportunity to review this manuscript well ahead of the time of this meeting. However, I must say that I found this message of not eating the oysters or going into the water quite disconcerting as I was packing my swimming suit and anticipating ingestion of prodigious amounts of raw oysters. Nonetheless, I believe that we owe Dick a debt of gratitude for bringing the little appreciated but highly dangerous infectious process to our attention. This is especially true since these oysters clearly are not indigenous only to Florida. The people who eat them also travel to other states. Since this disease can run a gamut from a shocklike disease of sudden onset to indolent soft tissue infection, I think we all need to be aware of it and thus we owe him our gratitude. I have several questions. The first question deals with antibiotic choice. As you mention in your talk, in your manuscript and as addressed by Dr. Malangoni, you stated that these patients frequently do not respond to antibiotics to which the organisms appear sensitive in the laboratory. I wonder why this is and I also wonder whether this may not represent a case of the gut being the reservoir of these bacteria. That is, if the antibiotics that are administered do not clear the gut as a reservoir whether we can, in fact, eradicate the infection. Thus, I ask you if you have any data on colonization rates of these patients versus the normal population? Secondly, can you give us any idea of how to diagnose these infections early? Clearly these seem to be very similar to a number of nondescript disease processes and I wonder if based on your experience you can give us any hints. Thirdly, as you gained experience treating these patients, has survival improved? If so, to what clinical maneuvers do you attribute this improvement in survival. Lastly, I'd like to ask Dick if these organisms are sensitive to alcohol and, if so, does he advise the prophylactic consumption of alcoholic beverages to prevent infection when eating raw oysters?

DR. BASIL A. PRUITT, JR. (San Antonio, Texas): Dr. Howard, I enjoyed your paper and I rise to review, in brief, our experience with infections in burn patients caused by members of the Vibrionaceae family. In 1977, Dr. Lindberg from our laboratory described a patient in whom Vibrio alginolyticus was recovered from both blood and burn wounds. Since then, we've had nine patients from whom Aeromonas, a member of the Vibrionaceae family, has been recovered from the blood. The five patients who died had an average burn of 60% which is an extent of injury associated with immunosuppression. Ac-