Vibrio Vulnificus Infections can be Avoided

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Vibrio Vulnificus is one of the most invasive and rapidly fatal human pathogens known. The first fatal *V. vulnificus* infection was possibly reported in the fifth century B.C. by Hippocrates [1]. He relates that the king of the island Thasos in the Aegean Sea sustained an acute infection characterized by a swollen foot with red and black skin lesions, rapidly progressive septicemia, and death on the second day. It is suggested that this infection was caused by *V. vulnificus* [1] The epidemiology and pathogenesis of this bacterium differs significantly from other members of the *vibrio* genus, particularly in its strong association with molluscan shellfish coupled with its extreme and rapid invasiveness and concomitant tissue destruction in susceptible human hosts. In this issue of *IMAJ*, Finkelstein and associates [2] describe the first fatal infections caused by this bacterium in Israel. These cases demonstrate our foremost fears of this bacterium, urging the need for enhanced awareness among the public to the life-threatening hazards of what seems to be a safe act, such as handling the *Tilapia* fish.

V. vulnificus is a naturally occurring, free-living inhabitant of estuarine and marine environments throughout the world, residing in high numbers in filter-feeding shellfish (oysters, clams, mussels). It prefers tropical to subtropical climates, and has been isolated from waters where temperatures range from 9 to 31°C. It proliferates in areas or during months where the water temperature exceeds 18°C [3]. Consequently, most reported cases of *V. vulnificus* infections occur during the warm months of the year, usually from May to October [4]. Low to moderate salinities are also associated with the presence of *V. vulnificus*, and higher salinities have adverse effects on the survival of the organism [5]. Currently, *V. vulnificus* is divided into three distinct biotypes based on phenotypic characteristics. Biotype 1 was the first to be described as pathogenic to humans [6], while biotype 2 is a major source of disease in eels. This biotype has been reported sporadically as an opportunistic pathogen in human infections [7], but is generally not regarded as a human pathogen [8]. Biotype 3 – also called the "Israeli biotype of *V. vulnificus*" – has been described only in Israel and was the responsible pathogen for the last outbreak that occurred in Israel in 1996–97 [9,10].

Human infections with *V. vulnificus* occur almost wherever the pathogen has been isolated, with reports from the United States, Europe, Australia, South America, Southeast Asia [11], and recently from Israel [9,10]. The two major types of infection caused by this bacterium are primary septicemia and wound infections. Gastrointestinal infection is very rare, accounting for only 1–3% of all reported cases involving *V. vulnificus* in the USA [12]. Primary septicemia is defined as a systemic illness characterized by fever, chills and hypotension, where *V. vulnificus* was isolated from blood or other sterile site and with a history of raw shellfish consumption but no wound infection preceding illness. This type of infection comprises approximately 40–45% of all infections with *V. vulnificus* in the USA and Southeast Asia [12,13] where eating raw or undercooked seafood is a common practice. Among susceptible hosts (see below) the mortality rates may reach up to 40–60% of all cases with primary septicemia [14]. Another form of infection with *V. vulnificus* is cutaneous infections, which usually occur in connection with puncture wounds after handling raw seafood, or trauma and exposure to saline environments [15]. Wound infections range from mild self-limiting lesions to rapidly progressing erythema, cellulitis and necrosis, occasionally developing to secondary septicemia. *V. vulnificus* can cause wound infection by penetrating into minor abrasions or lacerations (usually overlooked by patients) during the handling of raw seafood or exposure to water containing the organism. This was probably the port of entry for infection in case 1 described by Finkelstein et al. [2]. The fatality rate for wound infections may reach up to 25%, with deaths occurring primarily among susceptible persons.

The high virulence of *V. vulnificus* cannot be assigned to a single factor but is likely influenced by capsule production, ability to acquire iron in human serum, lipopolysaccharide type, production of exoenzymes and exotoxins, and a susceptible host. Fortunately, most healthy people are resistant to infection with this bacterium. People who are most susceptible to *V. vulnificus* infection usually suffer from a chronic disease that affects liver function, mainly cirrhosis or alcoholic liver disease [14]. Several theories exist to explain the increased virulence of *V. vulnificus* among these patients. Cirrhotic patients often have immune system dysfunction: decreased complement levels, reduced phagocytic activity, chemotaxis, and opsonization, thus promoting the virulence of *V. vulnificus* [16]. Other conditions associated with increased susceptibility include hemochromatosis, underlying malignancy, diabetes mellitus, immunosuppressive therapy, and chronic renal failure [12,15]. For people who tend to eat raw or undercooked seafood and have low gastric acidity, either therapeutically induced or natural, are at increased risk for developing the primary septicemia type of infection [17]. The availability of iron appears to be crucial for the virulence of *V. vulnificus* in humans. The organism is unable to use transferrin-bound iron for growth; however, in patients with iron overload and transferrin saturation of 75% or higher, free iron is available for use. Therefore, transferrin saturation is a more important growth variable for *V. vulnificus* than total iron stores [18,19]. These findings may explain the unusual susceptibility of patients with chronic liver disease or hemochromatosis with high serum iron levels to having *V. vulnificus* septicemia.

Though the two cases described by Finkelstein et al. [2] were women, it is a well-known fact that infections with *V. vulnificus* are seen primarily in males over the age of 40. Little is known about the underlying mechanisms that result in a sexually dimorphic response to *V. vulnificus* endotoxic shock. Recently Merkel et al. [20] demonstrated in a rat model that gonadectomy in females results in increased mortality, and estrogen replacement results in decreased mortality in both gonadectomized males and females. These findings indicate that estrogen may provide some protection against *V. vulnificus* lipopolysaccharide-induced endotoxic shock.

Early debridement of the infected wound is crucial for successful therapy and is especially indicated to avoid amputation of fingers, toes or limbs. Because patients with wound infection may deteriorate rapidly, with development of necrotizing fasciitis or compartment syndrome, expeditious and serial surgical evaluation and intervention are required. Empiric combinational antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting. This approach ensures coverage for a broad range of organisms and polymicrobial infections. In addition, resistance by bacterial subpopulations is prevented, and additive or synergistic effects are provided; resistance among other biotypes of *V. vulnificus* has been described [21]. Once organisms and sensitivities are known, the use of antibiotic monotherapy is recommended. Currently the strains of *V. vulnificus* isolated in Israel are sensitive to all antibiotics used in the standard disk susceptibility test, except for sporadic resistance to gentamicin. The use of tetracycline in the treatment of *V. vulnificus* infections is based on a mouse model where it proved to be highly efficacious [22]. At HaEmek Medical Center in Afula in Israel, we used various beta-lactam antibiotics to successfully treat such patients. Antibiotic treatment is often ineffective unless initiated as soon as the first clinical symptoms appear [23]. However, in cases of serious wound infections, the primary treatment is proper surgical debridement, with antibiotics playing a secondary role [24]. A vaccine against *V. vulnificus* has been developed but has not been tested beyond the preclinical trials in mice [25,26]. The vaccine antiserum is raised against the capsule of *V. vulnificus* and the achieved protection is capsule type-specific. Clinical strains of *V. vulnificus* exhibit various capsule types and far from all types has yet been identified [27,28].

The preventive measures undertaken in the summer of 1998 [10] significantly decreased the number of reported cases, but unfortunately cases continue to appear. These preventive measures should apply to both fish farmers and consumers. Fish farmers should fully implement the guidelines set in 1998 by the Fish Farmers Association, and according to this policy, no fish of *Tilapia* species or carp harvested from fishponds should be sold alive; fins, scales and intestines should be removed (using specially designed gloves) before the fish are marketed; and the cold-chain should be maintained throughout processing. Consumers should be advised not to handle the fish bare-handed; that freezing can markedly decrease the amount of the bacteria to a minimum but does not eliminate it from the inner or outer surfaces of the fish; that heating is a safe procedure (temperatures above 45°C have been shown to kill the organism) [29]; and most important of all, susceptible persons should be prohibited from handling raw *Tilapia* or carp fish by any means (with no hazard at all from handling cooked or grilled fish).

V. vulnificus infections can be avoided by providing clear and sufficient information to the public, especially susceptible hosts, about the hazards of handling raw *Tilapia* and carp fish. Official guidelines issued by the health authorities to alert the public to these hazards during the warm months of the year are a necessity.

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