

## CHAPTER 6

# Skin and Soft Tissue Infections Following Marine Injuries

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### 1. INTRODUCTION

Bacterial diseases following aquatic injuries occur frequently worldwide and usually develop on the extremities of fishermen and vacationers, who are exposed to freshwater and saltwater.<sup>1,2</sup>

Though plenty of bacterial species have been isolated from marine lesions, superficial soft tissue and invasive systemic infections after aquatic injuries and exposures are related to a restricted number of microorganisms including, in alphabetical order, *Aeromonas hydrophila*, *Chromobacterium violaceum*, *Edwardsiella tarda*, *Erysipelothrix rhusiopathiae*, *Mycobacterium fortuitum*, *Mycobacterium marinum*, *Shewanella* species, *Streptococcus iniae*, and *Vibrio vulnificus*.<sup>1,2</sup>

In particular, skin disorders represent the third most common cause of morbidity in returning travelers and are usually represented by bacterial infections.<sup>3–12</sup> Bacterial skin and soft tissue infectious conditions in travelers often follow insect bites and can show a wide range of clinical pictures including impetigo, ecthyma, erysipelas, abscesses, necrotizing cellulitis, myonecrosis.<sup>3–12</sup>

In general, even minor abrasions and lacerations sustained in marine waters should be considered potentially contaminated with marine bacteria.<sup>3–12</sup>

Despite variability of the causative agents and outcomes, the initial presentations of skin and soft tissue infections (SSTIs) complicating marine injuries are similar to those occurring after terrestrial exposures and usually include erysipelas, impetigo, cellulitis, and necrotizing infections.<sup>3</sup>

Erysipelas is characterized by fiery red, tender, painful plaques showing well-demarcated edges, and, though *Streptococcus pyogenes* is the major agent of this process, *E. rhusiopathiae* infections typically cause erysipeloid displays.<sup>3</sup>

Impetigo is initially characterized by bullous lesions and is usually due to *Staphylococcus aureus* or *S. pyogenes*. Nevertheless, *S. iniae* infections are also characterized by either impetigo or cellulitis.<sup>3</sup>

Marine necrotizing infections can be either monomicrobial or polymicrobial. In both cases, the process may advance quickly to necrotizing fasciitis and myonecrosis, especially

in patients with underlying chronic wounds, such as chronic dermatoses and venous stasis ulcers; otherwise this may occur in immunocompromised hosts on corticosteroid treatment or showing liver disease, diabetes mellitus, HIV infection, or cancer.<sup>3</sup>

Grossly contaminated or infected lesions and all puncture wounds should be cultured or biopsied immediately and, although an empirical antibiotic approach is warranted, all definitive antimicrobial therapy should be targeted on precise pathogen identification and in vitro susceptibility testing.<sup>3</sup>

The aim of this chapter is to draw a picture of salient aspects of marine water environment-related SSTIs, by focusing on major bacteria behind the curtain of these clinical conditions and on their habitats, microbiological features, and diseases they may cause.

## 2. EPIDEMIOLOGY

After acute and chronic management of SSTIs in tsunami survivors with contaminated aquatic injuries, the early predominance of Gram-negative aquatic organisms emerged in early-onset infections, while rapidly growing mycobacteria are mostly agents of sea-related late-onset infectious syndromes.<sup>1,2</sup>

Although Gram-positive bacteria such as *Staphylococcus aureus* and streptococci, as well as *Pseudomonas aeruginosa* (Gram-negative) and several other bacterial species, have been isolated from infected minor marine wounds, some of the more uniquely marine bacterial pathogens observed after more severe aquatic injuries include *Aeromonas* and *Shewanella* species, *Chromobacterium violaceum*, *Edwardsiella tarda*, *Vibrio vulnificus* and marine mycobacteria.<sup>1,2</sup>

Nonetheless, an empiric approach against SSTIs that develop shortly after marine water exposure should still cover *Streptococcus pyogenes* and *S. aureus*, not only marine water-related organisms.<sup>1,2</sup>

Then, in general, treatment could include a first-generation cephalosporin or clindamycin combined with levofloxacin or ciprofloxacin plus doxycycline (if an increased risk for acquiring *V. vulnificus* exists).<sup>1,2</sup>

### 2.1 *Aeromonas* Species

The genus *Aeromonas* includes Gram-negative bacilli inhabiting warm soil together with fresh and brackish waters worldwide and behaving both as aquatic animal commensals and pathogens.<sup>13</sup>

Most can produce enterotoxins and hemolysins, thus causing acute hemorrhagic diarrheal syndrome and invasive SSTIs in both immunocompetent and immunocompromised hosts exposed to an aquatic environment, including near-drowning.<sup>13</sup>

*Aeromonas* wound infections may develop after freshwater traumatic lesions, i.e., alligator, fish, snake and leech bites; infected injuries usually involve extremities or other bodily sites where open wounds were immersed in contaminated freshwater in warmer

months.<sup>13,14</sup> Within 24 h, erythema, edema and purulent discharge (indistinguishable from streptococcal cellulitis) can be observed.<sup>3</sup> There may be fever and progression to invasive infections, especially in the immunocompromised population, with necrotizing fasciitis, necrotizing myositis and bone involvement.<sup>13,14</sup>

Although most *Aeromonas* SSTIs follow aquatic immersions, an outbreak of *A. hydrophila* wound infections after mud exposure in 26 football players was reported in 2002. None of the players had any immunocompromising underlying condition, and all recovered with antibiotics.<sup>14</sup>

In general, *Aeromonas* strains from human infections are susceptible to aminoglycosides, carbapenems, fluoroquinolones, aztreonam, tetracyclines, as well as third- and fourth-generation cephalosporins, while variable levels of activity have been reported for cotrimoxazole.<sup>15</sup>

In addition to wound drainage and debridement, *Aeromonas* wound infections should be faced initially with either a third-generation cephalosporin or a fluoroquinolone, possibly combined with an aminoglycoside pending antibiotic susceptibility testing and culture results.<sup>15,16</sup>

## 2.2 *Chromobacterium violaceum*

*Chromobacterium violaceum* is a Gram-negative, aerobic rod, behaving as a ubiquitous saprophyte in soil and water in tropical and subtropical regions all over the world.<sup>17,18</sup> In spite of its wide geographical distribution, it is a low-grade pathogen that is responsible for few cases of infection in immunocompetent people and is often dismissed as a contaminant at examination of cultures.<sup>17</sup>

The organism is presumptively recognized by the violet color of colonies it forms, with nonpigmented strains being less common.<sup>17–19</sup>

Most cases occur in temperate and tropical regions and are characterized by high fatality rates in immunocompromised patients and the possibility of neutrophil impairment should be taken into consideration when managing patients with fulminant infections of *C. violaceum*.<sup>20</sup> The portal of entry is generally a skin lesion secondary to a laceration or fish bite, followed by contamination with brackish or stagnant water. An ulcerated lesion with a bluish purulent discharge is usually observed at the initial injury site with regional swelling on an extremity. In the following days, bacteremia may occur, more commonly in the immunocompromised hosts, with disseminated macular cutaneous lesions progressing to abscesses; these may also involve bone, liver, and lung as well as spleen. Due to the rarity of this infection, availability of treatment recommendations is still lacking.<sup>18,19</sup>

*C. violaceum* is usually susceptible to aminoglycosides, carbapenems, chloramphenicol, cotrimoxazole, fluoroquinolones and tetracyclines, but resistant to most penicillins and cephalosporins.<sup>18,19</sup> Because of high mortality rates, treatment of suspected *C. violaceum* infections should start immediately and be based on drainage of purulent

abscesses and empiric combination of intravenous antibiotics, which will be narrowed after susceptibility testing results are provided.<sup>19</sup>

### 2.3 *Edwardsiella tarda*

*Edwardsiella tarda* is a Gram-negative rod-shaped organism belonging to the family Enterobacteriaceae; it notoriously behaves as an aquaculture pathogen and causes emphysematous putrefactive disease in catfish.<sup>21</sup>

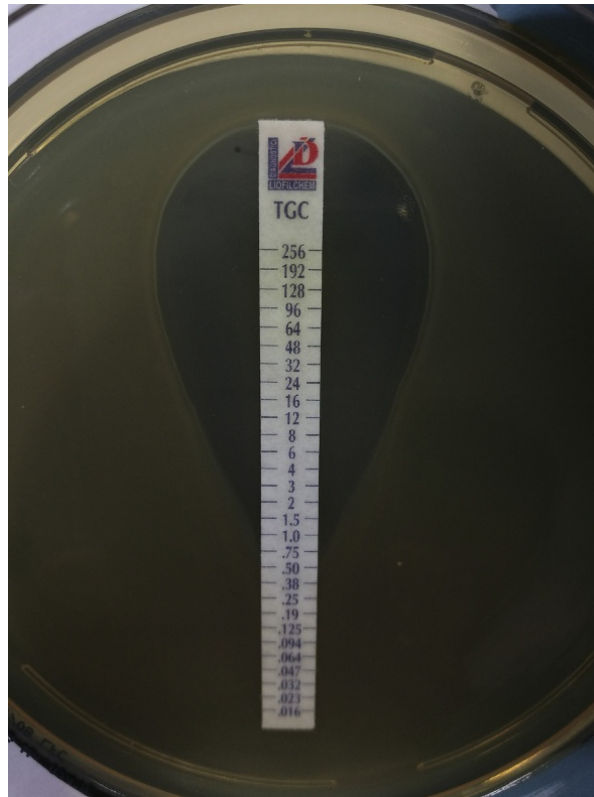
Extraintestinal *E. tarda* infections are uncommon compared with intestinal ones, and are frequently represented by wound abscesses needing surgical incision and drainage in patients with marine exposures or injuries; extensive myonecrosis and fatal septic shock may develop in immunocompromised hosts, especially those with chronic hepatopathy.<sup>22</sup>

### 2.4 *Shewanella* Species

The genus *Shewanella* includes saprophytic Gram-negative microorganisms inhabiting warm and temperate regions worldwide and which are part of the marine environment microflora. More than 50 species of *Shewanella* have been classified thus far, all of which produce yellowish-brown pigmented and mucoid colonies releasing hydrogen sulfide in culture.<sup>23,24</sup>

Several *Shewanella* species have been recently known to be emerging agents of soft tissue and invasive infections following seawater exposure, and these include *Shewanella algae* (which is the most common), *Shewanella haliotis*, *Shewanella putrefaciens* and *Shewanella xiamenensis*.<sup>23,24</sup>

The major clinical manifestations of shewanellosis are deep ulcers associated with hemorrhagic bullae on the lower extremities, otitis externa or media, biliary tract and bloodstream infection.<sup>23–25</sup> Nonhealing ulcers usually evolve to necrotizing fasciitis, compartment syndromes and osteomyelitis.<sup>25</sup> *Shewanella* bacteremia in the past has been complicated by endocarditis and meningitis, while lung infection, cholecystitis and peritonitis may follow aspiration or ingestion, respectively, of *Shewanella*-containing seawater in near-drowning.<sup>23,24</sup> Together with marine exposure and raw seafood ingestion, further common risk factors for shewanellosis are minor trauma or lacerations that occur in a marine environment, preexisting lower extremity ulcers and immune system impairment.<sup>25</sup> The diagnostics of shewanellosis rely on positive culture of blood or lesion aspirate samples, although reliable identification at a species level requires molecular characterization.<sup>23–25</sup> Most species respond in vitro to a broad range of antibiotics, such as third- and fourth-generation cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones. *S. algae*, particularly, is resistant to penicillins and cephalosporins belonging to the first and second generations.<sup>23</sup> Poor data are still available concerning in vitro activity of tigecycline versus *Shewanella* isolates and no species-specific EUCAST breakpoints for antibiotic susceptibility testing are available (Fig. 1).<sup>58</sup> Treatment of



**Fig. 1** Tigecycline in vitro activity versus a *Shewanella algae* isolate from the Clinical Microbiology and Virology Unit, Spirito Santo Hospital of Pescara, Italy. MIC has been determined by MIC Test Strip (Liofilchem<sup>®</sup>, Italy). The isolate is resistant, according to EUCAST 2017 non-species related breakpoints. It is susceptible if breakpoints for Enterobacteriaceae are considered.

invasive infections, especially in immunocompromised hosts, should include, according to most authors, initial intravenous betalactam antibiotics (i.e., cefotaxime, ceftazidime, cefepime) combined with either an aminoglycoside or a fluoroquinolone (ciprofloxacin or levofloxacin), then switch to an antibiotic susceptibility testing-based oral antibiotic therapy.<sup>23–25</sup> An early surgical approach is recommended as well, for drainage of bullous lesions, debridement of ulcers and evaluation of potential compartment syndromes that must be treated with decompressive fasciotomy.<sup>23–25</sup>

## 2.5 *Vibrio vulnificus*

*Vibrio vulnificus* has emerged as a highly virulent organism causing three kinds of disease, that is: (1) acute gastroenteritis after consuming raw or undercooked shellfish; (2) invasive septicemia following ingestion of raw or undercooked shellfish, mostly oysters; (3) necrotizing wound infections after marine injuries and exposures.<sup>26,27</sup>

*V. vulnificus* is a Gram-negative, halophilic bacillus that is free living in marine waters characterized by low to moderate salinities, especially above 18°C.<sup>26–30</sup> Men are uniquely predisposed to infections by *V. vulnificus* due to both recreational and occupational exposures to fish and shellfish, higher blood iron levels, higher rates of alcoholism and chronic epathopathy along with lower levels of protective estrogens.<sup>29,31</sup> Further predisposing factors that are not gender-related include all conditions increasing serum iron levels (such as hemochromatosis and thalassemia major), chronic liver disease (i.e., cirrhosis, hepatoma) and liver transplant, diabetes mellitus, end-stage kidney disease and underlying immunosuppression due to chemotherapy, splenectomy, steroids and HIV infection.<sup>30–32</sup>

*V. vulnificus* will be cultivated from blood cultures in 30% of wound infections with secondary bacteremia and in 70%–100% of episodes of primary sepsis.<sup>29,32</sup> As delay in starting antibiotics has been related to increasing fatality (until 100% for delays >72 h), treatment should be given in a timely manner by using ceftazidime plus doxycycline as an initial empiric combination for suspected *V. vulnificus* infections.<sup>33</sup> Ceftriaxone and cefotaxime may be used as an alternative, combined with a tetracycline; fluoroquinolones have proven to be effective, too.<sup>29,32,34–36</sup> Early wound debridement and surgical monitoring for compartment syndromes are also recommended and this approach has been shown to decrease mortality rates.<sup>33–35</sup>

## 2.6 *Erysipelothrix rhusiopathiae*

*Erysipelothrix rhusiopathiae* is a Gram-positive, nonsporulating rod-shaped bacterium which is frequently misidentified under a microscope as *Lactobacillus* or *Listeria monocytogenes*.<sup>37</sup>

On blood-based culture plates, instead, *E. rhusiopathiae* can be confused with *viridans* streptococci, as it is  $\alpha$ -hemolytic.<sup>37</sup>

In fish, the organism persists silently for long periods in the exterior slime.<sup>37</sup> Diseases it causes typically manifest 1–2 days after skin lesions occurred while handling or preparing fish.<sup>37</sup> Most of them, in man, are represented by a localized (erysipeloid) or generalized cutaneous infection; both forms are characterized by pain, throbbing erythema and strong pruritus.<sup>37</sup>

Invasive systemic *E. rhusiopathiae* diseases are uncommon and characterized by bacteremia, and potentially, associated infective endocarditis (IE); the latter, when sustained by *E. rhusiopathiae*, commonly involves the aortic valve.<sup>38</sup>

The organism is susceptible to penicillins, cephalosporins, carbapenems, clindamycin, fluoroquinolones and daptomycin and is typically resistant to aminoglycosides, sulfonamides and vancomycin.<sup>39</sup>

Since this glycopeptide is frequently used as empirical treatment of presumed IE, prompt microbiological differentiation of *E. rhusiopathiae* from other Gram-positive organisms is crucial.<sup>38</sup>

## 2.7 *Mycobacterium* Species

The aquatic, so-called atypical mycobacteria are the acid-fast causative agents of piscine mycobacteriosis and are responsible for both external and solid organ granulomas in more than 150 fish species.<sup>40,41</sup> Aquatic mycobacteria live at temperatures of 30–33°C in fresh and marine waters and are resistant to chlorine and iodine.<sup>41</sup>

*Mycobacterium marinum* has been historically associated with exposure to fish, aquariums, swimming pools, or marine fauna other than fish, and is the most frequent cause of external granulomas in those who are professionally exposed as they handle fish or work as aquarium operators.<sup>41–44</sup> Infections it causes typically start as localized zones of red-violet verrucous or crusted plaques that develop at skin inoculation sites 7 or more days after puncture wounds or minor injuries occurred in marine environments on the cooler, distal areas of the extremities.<sup>42,43</sup>

Solitary or multiple granulomatous nodules will be later observed in the inoculation site that may ulcerate with production of a yellowish pus.<sup>42,43</sup> In some occasions, metastatic nodular lesions develop according to a linear or sporotrichoid manner along the proximally draining lymphatic vessels; then they may ulcerate and undergo secondary infection.<sup>43</sup>

Deeper, invasive infectious processes such as bursitis, osteoarthritis, septic arthritis, and tenosynovitis may occur in indolent and untreated cases and, less commonly, in the immunocompromised population.<sup>43</sup> Of particular interest, a case of left wrist tenosynovitis and elbow bursitis following a puncture injury and exposure to coal mine water has been recently reported.<sup>44</sup>

Diagnostics rely on acid-fast staining, of course, along with culture of nodule discharge, aspirate or biopsy and molecular identification of the causative agent.<sup>41–44</sup>

Unlike *M. marinum*, other more rapidly growing marine mycobacterial species (i.e., *Mycobacterium abscessus*, *Mycobacterium fortuitum*, *Mycobacterium perigrinum*, and *Mycobacterium mageritense*) have been clearly related to persistent furunculosis after marine injuries in tsunami survivors.<sup>2</sup>

Among the more unusual outbreaks of mycobacterial furunculosis, rapidly growing *M. fortuitum* infections have occurred after freshwater footbaths and pedicures.<sup>45</sup> Also, razor-shaving of the lower legs has been identified as a relevant risk factor for mycobacterial infections compared with having pedicures without shaving.<sup>45</sup>

Further unusual outbreaks of mycobacterial furunculosis have been caused by rapidly growing *M. fortuitum* and followed ichthyotherapy with freshwater doctor fish (*Garra rufa*) in the United Kingdom.<sup>46</sup> The latter is a freshwater cyprinoid fish that naturally inhabits the river basins of central Eurasia; of interest, it is imported in large numbers to nail and foot spas all over the world for the removal of dead or hyperkeratotic foot skin during ichthyotherapy.<sup>46</sup>

*M. marinum* is typically susceptible to macrolides (i.e., clarithromycin), sulfonamides, cotrimoxazole, ethambutol and rifampin/rifabutin. A typical therapy regimen includes



two of these agents in combination (e.g., clarithromycin plus ethambutol or clarithromycin plus rifampin) for about 3–4 months (until 4–8 weeks post-clinical resolution).<sup>44,47</sup>

*M. fortuitum* responds instead to fluoroquinolones such as ciprofloxacin and levofloxacin, newer macrolides like azithromycin and clarithromycin, sulfonamides, tetracyclines (minocycline, doxycycline) and amikacin.<sup>44</sup> A 4-month (at least) combined therapy with at least two drugs is recommended.<sup>44</sup>

Similar oral antibiotic combinations may treat nonserious SSTIs by *M. abscessus*. Severe skin diseases caused by this organism are instead initially managed with a combination of intravenous amikacin plus ceftiofur with the possible addition of the carbapenem imipenem.<sup>44</sup>

In general, infections with rapidly growing mycobacteria may benefit from prompt recognition of acquired fluoroquinolone and macrolide resistance, if present.<sup>44</sup>

## 2.8 *Streptococcus iniae*

*Streptococcus iniae* is  $\beta$ -hemolytic and has not yet been assigned to a Lancefield group.

It was first identified in 1976 as the etiologic agent of subcutaneous abscesses in Amazon freshwater dolphins living in US aquariums and is nowadays known as a major fish pathogen. Particularly, it may cause epizootic outbreaks of invasive infection in farm-raised fish.<sup>48–50</sup>

The organism initially colonizes the fish surface, thus causing cellulitis, and possible subsequent invasive meningoenzephalitis, responsible for 30%–50% mortality in aquaculture ponds.<sup>49</sup>

The first cases of invasive disease described in humans date back to 1996 in Toronto and involved patients who had recently handled live or freshly killed fish.<sup>41</sup> Affected patients developed cellulitis of the hands, or endocarditis (in one case) or arthritis; some of these patients, particularly, had percutaneous injuries while preparing fish and developed cellulitis within 24 h of the injuries' occurrence.<sup>51</sup>

In all such 11 cases, human *S. iniae* isolates matched (by pulse-field gel electrophoresis) to those cultivated from surfaces of infected tilapia from local aquaculture farms.<sup>51</sup> Also, all human isolates showed susceptibility to penicillins, cephalosporins, macrolides, aminoglycosides, and cotrimoxazole.<sup>51</sup>

## 3. CONTROL AND PREVENTION OF AQUATIC INFECTIONS

People with well-established risk factors for high seriousness of aquatic infections, including subjects with open wounds, immune system deficit, diabetes mellitus, epathopathy, hemochromatosis, alcoholism, hematological disorders, chronic renal diseases, HIV infection and cancer, should be alerted about the risks of infectious conditions due to marine bacteria mediated by exposure to both marine animals and seawater, along with



preparation of live or freshly killed seafood and, of course, seawater ingestion or eating of raw or undercooked seafood, especially oysters.

Clinicians, in the meantime, should be aware of potentially catastrophic bacterial infections following marine injuries and exposures.

Initial antibiotic treatment should rely on clinical signs and symptoms (impetigo, erysipelas, pyoderma, cellulitis, necrotizing soft tissue infection), pending culture and antibiotic susceptibility testing results.

Except for minor marine wounds showing localized cellulitis or spreading erysipeloid-type appearance, most other marine-related infectious diseases and all Gram-negative and mycobacterial marine infections will need combined antibiotic approaches, and quite often will benefit from surgical management.

#### 4. CONCLUSION AND FUTURE PERSPECTIVES

Together with consciousness of the risk of insect-related virus infections, travelers should be aware of diseases that may develop following contact with water-inhabiting bacteria. Therefore, it is warranted that travel medicine practitioners maintain a high index of suspicion concerning potentially catastrophic bacterial infections complicating water injuries and exposures, especially those caused by *Vibrio vulnificus* in the Gulf of Mexico, *Chromobacterium violaceum* in the Western Pacific, and *Shewanella* in the Mediterranean and Western Pacific.<sup>3,52–57</sup>

Due to the increasing frequency of travel, both for work and holiday reasons as well as due to migration from war zones, microbiologists should be ready to face unusual diagnostic queries, like those surrounding infections with “foreign,” unexpected, bacteria, in a world with fewer and fewer frontiers and barriers.

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