# A PEÇA QUE FALTA NO DIA-A-DIA DOS SEUS DOENTES...

MSD
INVENTING FOR LIFE

Merck Sharp & Dohme, Lda. | www.msd.pt | Tel. 214 465 700
Quinta da Fonte, 19 - Edifício Vasco da Gama, 2770-192 Paço de Arcos | NIPC 500 191 360


PT-DOV-00091 10/2020

# DORAVIRINA FAZ PARTE DO DIA-A-DIA

dos doentes VIH-1 com diferentes necessidades

**Eficácia**
robusta e duradoura, independentemente da carga vírica basal[1,2]

**Perfil de segurança**
favorável e geralmente bem tolerado[1,2]

**Resistência**
Baixas taxas de resistência e perfil de resistência único[1,3]

**Perfil de interações**
medicamentosas favorável[4,5]

**Toma única diária**
a qualquer hora do dia[6]

**Administração**
com ou sem alimentos[6]

Pifeltro®
doravirina

MSD
INVENTING FOR LIFE

Merck Sharp & Dohme, Lda. | www.msd.pt | Tel. 214 465 700
Quinta da Fonte, 19 - Edifício Vasco da Gama, 2770-192 Paço de Arcos | NIPC 500 191 360


PT-DOV-00048 04/2020

**Referências: 1**. Molina JM, *et al.* Lancet HIV. 2018;5(5):e211-e220. **2**. Orkin C, *et al.* Clin Infect Dis. 2019;68(4):535-544. **3**. Pham HT, *et al.* Drugs in Context 2020; 9: 2019-11-4.
**4**. Khalilieh SG, *et al.* Antimicrob Agents Chemother Apr 2019, 63 (5) e02016-18. **5**. Wilby, KJ, *et al.* Eur J Drug Metab Pharmacokinet 43, 637–644 (2018).
**6**. Resumo das Características do Medicamento Pifeltro. Novembro 2019.

**Nome do medicamento:** PIFELTRO® (Doravirina) **Forma farmacêutica e composição:** comprimidos revestidos por película com 100 mg; um inibidor não nucleosídeo da transcriptase reversa (NNRTI), ativo contra o vírus da imunodeficiência humana (VIH-1). **Indicações terapêuticas:** PIFELTRO é indicado em associação com outros medicamentos antirretrovíricos para o tratamento da infeção Por VIH-1 sem evidência prévia ou presente de resistência à classe NNRTI. **Posologia e modo de administração:** Comprimido de 100 mg, via oral, 1 vez ao dia, com ou sem alimentos. **Contraindicações, Advertências e precauções especiais de utilização:** hipersensibilidade à substância ativa ou a qualquer um dos excipientes. PIFELTRO contém lactose. A administração concomitante com medicamentos que sejam fortes indutores da enzima do citocromo P450 CYP3A é contraindicada, uma vez que se espera que ocorram diminuições significativas nas concentrações plasmáticas de doravirina, o que pode diminuir a eficácia de PIFELTRO. Estes medicamentos incluem, mas não se limitam aos seguintes: carbamazepina, oxcarbazepina, fenobarbital, fenitoína, rifampicina, rifapentina, hipericão (Hypericum perforatum),mitotano e enzalutamida. Sempre que possível, PIFELTRO deve ser administrado com duas outras terapêuticas antivíricas (TARV) ativas para minimizar o potencial para uma falência virológica e o desenvolvimento de resistência. . No contexto da síndrome de reativação imunológica foram reportados doenças autoimunes como a doença de Graves, hepatite autoimune, polimiosite e síndrome de Guillain-Barré, que podem ocorrer vários meses após o início do tratamento. **Efeitos indesejáveis:** As reações adversas frequentemente notificadas (≥1%) incluíram: sonhos anormais e insónias, cefaleias, tonturas e sonolência, náuseas, diarreia, flatulência, dor abdominal e vómitos, erupção cutânea, fadiga e aumento da ALT. **Interações medicamentosas e outras formas de interação:** A doravirina é principalmente metabolizada pelo CYP3A, e espera-se que os medicamentos que induzem ou inibem o CYP3A afetem a depuração da doravirina. A administração concomitante com o indutor moderado de CYP3A, rifabutina, diminuiu as concentrações de doravirina. Quando a doravirina é administrada concomitantemente com rifabutina, a dose de doravirina deve ser aumentada para 100 mg duas vezes por dia (estas doses devem ser tomadas com um intervalo aproximado de 12 horas). A administração concomitante de doravirina com outros indutores moderados do CYP3A não foi avaliada, mas são esperadas diminuições nas concentrações de doravirina. Se não for possível evitar a administração concomitante com outros indutores moderados do CYP3A (ex. dabrafenib, lesinurad, bosentano, tioridazina, nafcilina, modafinil, telotristate de etilo), a dose de doravirina deve ser aumentada para 100 mg duas vezes por dia (estas doses devem ser tomadas com um intervalo aproximado de 12 horas).**Titular de AIM:** Merck Sharp & Dohme B.V. **Data de revisão do texto:** Novembro de 2019.
**Para mais informações deverá contactar o titular da autorização de introdução no mercado. Medicamento sujeito a receita médica restrita de utilização reservada a certos meios especializados.**

RPDI
Janeiro > Abril 2021 / Vol. 16 > N.º 1

CASO CLÍNICO / *CLINICAL CASE*

# Fasciite Necrotizante Rapidamente Progressiva causada por *Photobacterium damselae*: Um caso clínico

# *Rapidly Advancing Necrotizing Fasciitis caused by* Photobacterium damselae*: A Case Report*

/ **Sofia Branco Ribeiro**[1] / **Luís Bento**[2]

[1] Serviço de Medicina Intensiva, Hospital de Faro, Centro Hospitalar Universitário do Algarve, Faro, Portugal

[2] Unidade de Urgência Médica – Hospital de São José, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal

Correspondência:
Sofia Branco Ribeiro
Email: apribeiro@chalgarve.min-saude.pt

Patrocínios:
O presente estudo não foi patrocinado por qualquer entidade.

*Artigo recebido em*
01/04/2020

*Artigo aceite para publicação em*
20/08/2020

## / Resumo

A bactéria *Photobacterium damselae* (previamente denominada *Vibrio damsela*) é um membro da família *Vibrionaceae* e constitui um agente patogénico de uma grande variedade de animais marinhos, incluindo peixes, crustáceos, moluscos e cetáceos. Em humanos, a infeção por *Photobacterium damselae* é rara, mas grave, podendo mesmo ter uma evolução fulminante e de elevada mortalidade. A maioria dos casos descritos na literatura teve origem na exposição de feridas à água do mar ou água salobra, infligidas durante atividades piscatórias ou recreativas. Dada a sua evolução extremamente agressiva, quaisquer atrasos no diagnóstico e/ou tratamento podem resultar numa maior mortalidade.

Os autores relatam o primeiro caso de fasceíte necrotizante por *Photobacterium damselae* descrito em Portugal. Apesar da sua gravidade e prognóstico habitualmente reservado, verificou-se uma evolução favorável após uma abordagem médico-cirúrgica precoce, que envolveu desbridamento cirúrgico, antibioterapia e realização de pensos diários.

Este caso pretende salientar a importância da inclusão da bactéria *Photobacterium damselae* no diagnóstico etiológico diferencial de infeções de tecidos moles, sobretudo quando há uma história de exposição marinha associada. Dada a sua evolução extremamente agressiva, o diagnóstico precoce, o desbridamento cirúrgico e a antibioterapia são essenciais para reduzir a mortalidade e melhorar o *outcome*.

**Palavras-chave:** *Photobacterium damselae*, *Vibrio damsela*, fasceíte necrotizante

## / Abstract

**Photobacterium damselae** *(formerly* **Vibrio damsela***) is a marine bacterium of the family Vibrionaceae that causes infections in a variety of marine animals including fish, crustaceans, mollusks, and cetaceans. Human diseases caused by* **Photobacterium** *damselae are rare and can lead to rapid, fulminant infections with a high rate of death. Most of the reported infections have their primary origin in wounds exposed to salt or brackish water, inflicted during fish and tools handling. Herein we describe the first case of* **Photobacterium damselae** *necrotizing fasciitis in Portugal, successfully treated with timely surgical debridement, antibiotic therapy and daily wound dressing. Considering that the majority of cases presenting with aggressive soft tissue wound infections are even fatal following progression into necrotizing fasciitis, the patient described in our case report showed a very favorable outcome.*

*This case aims to emphasize the importance of adding* **Photobacterium damselae** *to the differential diagnosis in patients with aggressive soft tissue wound infections and of obtaining a thorough history related to marine exposure, considering the exceedingly high mortality rate that ensues with any delay in source containment. In this extremely aggressive infection, early diagnosis, prompt surgical intervention and antibiotic treatment are essential to reduce mortality and improve outcomes.*


**Keywords:** **Photobacterium damselae**, **Vibrio damsela**, *necrotizing fasciitis*

## / Introduction

*Photobacterium damselae* (formerly *Vibrio damsela*) is a Gram-negative facultative anaerobe bacteria. Like other Vibrionaceae species its natural habitat is seawater. *Photobacterium damselae* behaves as a generalist pathogen, capable of living as a free-swimming bacterium, and as a pathogen, with the ability to cause disease in a wide range of animal phyla. Despite their relative infrequency, zoonotic infections by *Photobacterium damselae* have been reported. Literature search is cumbersome, since *P. damselae* has been renamed often with a number of synonyms in the past; however, even with all synonyms used as query terms, there are less than 20 cases published worldwide.

Most of the reported infections caused by *Photobacterium damselae* in humans occurred in coastal areas of the United States of America, Australia, and Japan. They usually have their primary origin in wounds exposed to salt or brackish water, inflicted during fish and tools handling. Infected wounds can be followed by bullae formation and marked edema and may progress into a necrotizing fasciitis with multiple organ failure. In fact, most of those cases presenting with severe wound infection are even fatal following progression into necrotizing fasciitis. Unusual cases of infection after ingestion of raw seafood have also been reported.

Physicians must be aware that in patients presenting with wound infections and reporting contact to seawater and fish or exposure to seafood, this pathogen may be the cause of infection. In such cases, prompt surgical source control and early empiric antibiotic treatment are essential to reduce mortality and improve outcomes. Recommended antibiotic therapy includes a 7 to 14-day total course of doxycycline and a third-generation cephalosporin.

This report describes the first case of *Photobacterium damselae* necrotizing fasciitis in Portugal, in a 65-year-old fisherman, who had a favorable outcome after treatment with timely surgical debridement, antibiotic therapy and daily wound dressing.

## / Case report

A 65-year-old fisherman with prostate cancer and end-stage renal disease on regular maintenance hemodialysis presented to the emergency department of a local hospital with excruciating pain and rapidly progressive swelling of his right hand, caused by a small wound in the right first digit made accidentally approximately 4 hours earlier that day while he was cutting fish. He was given analgesics and empiric antibiotic coverage with flucloxacillin, ceftriaxone and metronidazole, and was quickly transferred to our hospital to be evaluated by Plastic and Reconstructive Surgery.

On evaluation, the patient was awake, alert and hemodynamically stable. The temperature was 37.4°C, the blood pressure 137/72

mmHg, the heart rate 93 beats per minute, the respiratory rate 21 breaths per minute, and the oxygen saturation 96% while he was breathing ambient air. His right hand was extremely edematous and tender. Sensation and pulses were intact, but there was decreased mobility in all five digits. Laboratory testing revealed a normal white blood cell count, a creatinine level of 8,36 mg/dL (increased from his baseline level of 6,40 mg/dL) and an elevated C-reactive protein (110 mg/L, normal <5). He was diagnosed with compartment syndrome of the hand, presumably from a severe cellulitis or necrotizing fasciitis, and was taken to the operating room where a right-hand fasciotomy was performed. Empiric antibiotic therapy with flucloxacillin, ceftriaxone and metronidazole were maintained. However, within the following hours, widespread tissue destruction developed and progressed into his entire right forearm, with friability of the superficial fascia and a dishwater-gray exudate without pus. Given the clear progression of signs and symptoms, the plastic and reconstructive surgeons returned the patient to the operating room for the second time within 24 hours to perform extensive surgical debridement. Specimens for Gram's staining and culture were obtained. While still in the operating room, the patient became hemodynamically unstable, requiring vasopressors, and was then admitted in the Intensive Care Unit (ICU) for postoperative monitoring.

On admission to the ICU, he was extubated, awake and alert, but requiring norepinephrine to maintain the mean arterial pressure > 65 mmHg. Empiric antimicrobial therapy with flucloxacillin, ceftriaxone and metronidazole were maintained. On the next day after admission to the ICU, a single wound culture grew a pan sensitive *Photobacterium damselae*. The antibiotic therapy was then altered to doxycycline and ceftriaxone, as recommended by a microbiologist consultant. Management with daily wound dressing and antibiotic therapy (doxycycline and ceftriaxone) led to a progressive improvement, with vasopressors being entirely discontinued on postoperative day 3. He was discharged to the Plastic and Reconstructive Surgery ward on the 4$^{th}$ postoperative day, where he completed a 14-day total course of doxycycline (intravenous, twice a day) and ceftriaxone (intravenous, every 8 hours). Multiple skin grafting surgeries were performed during the remainder of the hospitalization, and his wound finally healed after 65 days from admission. He was discharged home on day 71.

## / Discussion

*Photobacterium damselae* is an autochthonous member of aquatic systems and one of the most common bacteria found in marine waters. Although rare, human infections by this pathogen have been reported in both immunocompromised and healthy hosts, and they generally result from subcutaneous tissue exposure to contaminated seawater or wounds inflicted by marine animals living in such an environment.

However, wounds sustained in marine environment are exposed to a milieu of bacteria rarely encountered in different settings. These include *Vibrio spp.*, *Aeromonas spp.*, *Shewanella spp.*, *Erysipelothrix rhusiopathiae*, *Mycobacterium marinum*, *Streptococcus iniae*, and other microbes. Failure to recognize and treat these uncommon pathogens in a timely manner may result in significant morbidity or death. The spectrum of manifestations is wide, varying from cases of mild cellulitis, to severe life-threatening necrotizing fasciitis, to sepsis and death.

A high index of suspicion is therefore necessary for the diagnosis of a *Photobacterium damselae* infection, since the only hallmark feature appears to be the history of marine exposure and its extremely fulminant course. In fact, most of those cases presenting with aggressive soft tissue wound infections are even fatal following progression into necrotizing fasciitis. Taking this into account, the patient described in our case report showed a very favorable outcome.

There are three critical elements in the management of patients with necrotizing soft tissue infections, essential to reduce mortality and improve outcomes: early diagnosis, prompt surgical intervention and appropriate antibiotic treatment. Prompt surgical exploration is especially important for three reasons: to determine the extent of infection, to assess the need for debridement or amputation, and to obtain specimens for Gram's staining and culture.

Similarly, to other *Vibrio* species, *Photobacterium damselae* is a halophilic, Gram-negative facultative anaerobe, often difficult to isolate on Gram stain. Antibiotic treatment recommendations for *Vibrio spp.* infections include tetracyclines (for example, doxycycline and tetracycline), fluoroquinolones (ciprofloxacin and levofloxacin), third-generation cephalosporins (cefotaxime, ceftazidime and ceftriaxone), aminoglycosides (amikacin, gentamicin) and folate pathway inhibitors (trimethoprim-sulfamethoxazole). The *Centers for Disease Control and Prevention* (CDC) recommends a treatment course of doxycycline (oral or intravenous twice a day for 7-14 days) and a third-generation cephalosporin (intravenous or intramuscular every 8 hours for 7-14 days).

Our case report aims to emphasize that, in establishing a diagnosis, it is critical to consider the anatomical features of skin and soft tissue infections; to assess epidemiologic risk factors by asking patients about animal exposures, travel history, underlying diseases, recent trauma, bites, burns, and water exposure; and to recognize the signs of different types of infection in an effort to limit the spectrum of causes to a more reasonable differential diagnosis. At times, even simple activities such as handling fish may represent a risk for serious skin and soft tissue infections, depending on the pathogen.

## / References


1. Rivas AJ, Lemos ML, Osorio CR. *Photobacterium damselae subsp. damselae*, a bacterium pathogenic for marine animals and humans. Front Microbiol. 2013 Sep 25; 4:283. DOI: 10.3389/fmicb.2013.00283.

2. Hundenborn J, Thurig S, Kommerell M, Haag H, Nolte O. Severe Wound Infection with *Photobacterium damselae ssp. damselae* and *Vibrio harveyi*, following a Laceration Injury in Marine Environment: A Case Report and Review of the Literature. Case Rep Med. 2013. DOI: 10.1155/2013/610632.

3. Barber GR, Swygert JS. Necrotizing fasciitis due to Photobacterium damselae in a man lashed by a stingray. N Engl J Med. 2000; 342(11):824. DOI: 10.1056/NEJM200003163421118.

4. Baker-Austin C, Oliver JD, Alam M, Ali A, Waldor MK, Qadri F, Martinez-Urtaza J. Vibrio spp infections. Nat Rev Dis Primers 2018 Jul 12; 4(1):8. DOI: 10.1038/s41572-018-0005-8.

5. Diaz JH, Lopez FA. Skin, Soft Tissue and Systemic Bacterial Infections Following Aquatic Injuries and Exposures. Am J Med Sci 2015; 349(3):269-275. DOI: 10.1097/MAJ.0000000000000366.

6. Nakamura Y et al. Necrotizing fasciitis of the leg due to *Photobacterium damsela*. J Dermatol. 2008; 35: 44–45. DOI: 10.1111/j.1346-8138.2007.00412.x .

7. Osorio CR, Vences A, Matanza XM, Terceti MS. Photobacterium damselae subsp. damselae, a Generalist Pathogen with Unique Virulence Factors and High Genetic Diversity. J Bacteriol. 2018; 200: e00002-18. DOI: 10.1128/JB.00002-18.