IDCases 36 (2024) e01995

Contents lists available at ScienceDirect

IDCases

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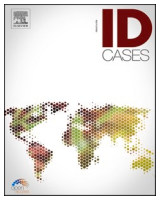

Case report

Vagococcus: An under-recognized and emerging cause of antibiotic-resistant infection

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ARTICLE INFO

Keywords:
Vagococcus fluvialis
Wound infection
Blast injury
Antibiotic susceptibility

ABSTRACT

Vagococcus, a bacterium generally isolated from fish and domestic animals, is a rarely reported human pathogen whose clinical characteristics and antimicrobial susceptibility remain uncertain. In this case report we describe a 19-year-old active-duty military sailor who suffered a blast injury to the left foot from a firework explosion. The injury was complicated by a polymicrobial wound infection that included *Vagococcus fluvialis*. *Vagococcus spp.* infections in humans are often associated with skin and soft tissue infection, including those resulting from trauma or blast injuries. This case serves to highlight this pathogen's role in causing invasive infections and as well as the importance of recognizing its clinical characteristics and antibiotic resistance profiles.

Background

Vagococcus is a Gram-positive, catalase-negative, facultative anaerobic coccus that is most commonly isolated from fish and domestic animals but is rarely encountered in clinical medicine as a cause of human infection [1,2]. It was first proposed as its own genus in 1989 and phenotypically resembles *Lactococcus* and *Enterococcus*. Initially it was distinguished by its motility (*vagus* meaning "wandering" in Latin) but non-motile species of *Vagococcus* have since been recognized in diverse settings ranging from rivers and agricultural areas to decomposing animals and various sea life [3,4]. The significance of *Vagococcus spp.* in human infections is difficult to assess, however, possibly owing to under-recognition. Its similarity to *Enterococcus.* may cause erroneous identification through conventional biochemical tests [1]. Nonetheless, *Vagococcus spp.* are being increasingly identified as causes of infection in humans. Here we present a case detailing one such infection with *Vagococcus fluvialis* in a military service member and discuss the implications of the infection through a brief review of relevant literature.

Case presentation

A 19-year-old male active military sailor with no significant medical history was admitted for surgical management of a left foot skin and soft tissue infection (SSTI). The wound occurred two days prior to presentation at a celebration in the patient's hometown in rural Kansas, when a stray firework exploded beneath the patient's left foot. The patient was wearing thick combat boots at the time and, while the boot itself remained intact, the concussive force and heat of the firework blast traumatized the patient's foot. The patient reported subsequently taking his foot out of the boot and cooling it in a mud puddle to alleviate the pain. Since he was still wearing a sock he was unaware that he had sustained an open wound where his heel had split open at his proximal plantar foot. Shortly thereafter he presented to a local emergency department where his wound was irrigated, closed with sutures, and treated empirically with a course of oral cephalexin (Fig. 1).

The following day the patient returned to his place of duty in San Diego, California where his ship's medical officer noted the wound to be purulent and inflamed. He was referred to the Naval Medical Center San Diego and admitted for further surgical care. On arrival the patient was afebrile with normal vital signs. He had a seven-centimeter laceration on the plantar aspect of his left heel, significant edema about the ankle and plantar aspect of his foot, and ecchymosis most prominent over the medial malleolus. Purulent drainage was expressed from the wound with compression, and initial lab work-up was remarkable for white blood cell count of 10,100 cells/mL and C-reactive protein levels of 19.9 mg/dL. The patient underwent surgical irrigation and debridement

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https://doi.org/10.1016/j.idcr.2024.e01995
Received 24 October 2023; Received in revised form 21 May 2024; Accepted 23 May 2024
Available online 24 May 2024

Fig. 1. The patient's left heel after initial wash out and suturing highlighting the splitting-type soft tissue injury sustained from the concussive force of the blast.

of the wound with drain placement and began intravenous antibiotic therapy with vancomycin and ceftriaxone.

Intraoperative wound cultures revealed a polymicrobial infection with multiple Gram-negative species including *Enterobacter cloacae*, *Citrobacter freundii* and *Acinetobacter sp.;* and multiple Gram-positive isolates including *Enterococcus faecalis* and *Vagococcus fluvialis* (Fig. 2). All isolates were identified with matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS). Given concern for potential resistance in the Gram-negative isolates the patient's ceftriaxone was broadened to meropenem, while vancomycin was continued. Antimicrobial susceptibility testing for most isolates was done using the VITEK 2 system (BioMérieux) but testing for *Vagococcus fluvialis* was performed manually by disk diffusion on Mueller Hinton agar with 5 % sheep blood (Fig. 3). For interpretation of the results the Clinical and Laboratory Standards Institute (CLSI) cut-offs for *Enterococcus spp.* were used since no official cut offs are available for *Vagococcus spp*. This showed disk diffusions as follows: ampicillin (25 mm – susceptible), minocycline (25 mm – susceptible), trimethoprim- sulfamethoxazole (TMP-SMX) (0 mm – resistant), levofloxacin (11 mm – resistant), linezolid (29 mm – susceptible), vancomycin (18 mm – susceptible); and one MIC_{90} via BioMérieux E-Test for vancomycin ($MIC_{90} \leq 4$ μg/mL – susceptible).

By hospital day three the patient was clinically improving with resolving leukocytosis and inflammatory markers. There was low concern for osteomyelitis. After his surgical drain was removed he transitioned to a regimen of oral levofloxacin and minocycline. Antibiotic treatment course totaled 28 days of therapy starting from the date of surgery and at subsequent follow-up one month after discharge the patient had resolution of his symptoms.

Fig. 2. Wound culture on blood agar (tryptic soy agar with 5 % sheep's blood) obtained intraoperatively showing colonies of *Enterococcus faecalis* (lighter arrow) and *Vagococcus sp.* (darker arrow) that demonstrate an α-hemolytic pattern.

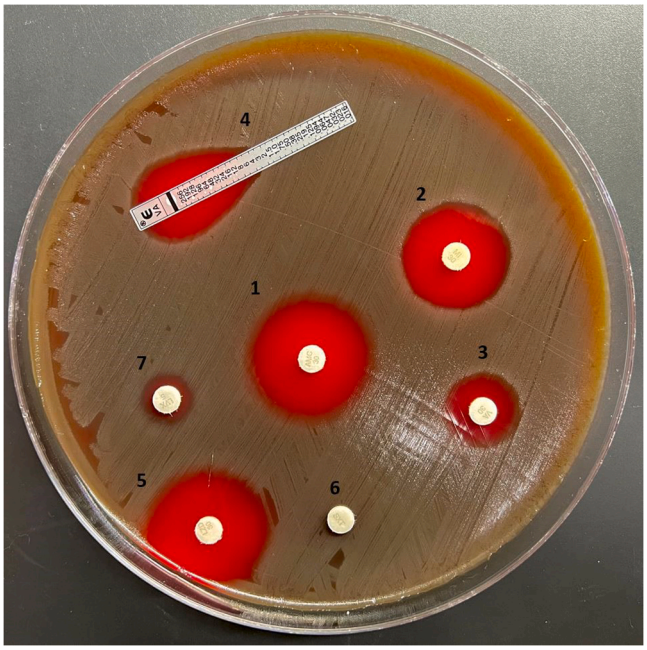

Fig. 3. Antimicrobial susceptibility testing for *Vagococcus* sp. performed manually by disk diffusion and via BioMérieux E-Test for vancomycin on Mueller Hinton agar with 5 % sheep blood demonstrating susceptibility to (1) ampicillin (25 mm), (2) minocycline (25 mm), (3,4) vancomycin (18 mm, $MIC_{90} \leq 4$ μg/mL) and (5) linezolid (29 mm), but resistance to TMP-SMX (0 mm) and levofloxacin (11 mm).

Discussion

Vagococcus spp. infections in humans are rare and this case describes an invasive SSTI in an immunocompetent male that highlights several key aspects of these infections. The first human infections with *Vagococcus spp.* were reported by Teixeira et al. in 1997 who described a

variety of infections including multiple SSTIs and cases of bacteremia, as well as one case of peritonitis and one case of meningitis [1]. Matsuo et al. reported a patient with bacteremia and a decubitus ulcer in addition to detailing 12 other cases of human infection in the literature (including the 6 cases from Teixeira et al.) with the majority being some form of SSTI [5]. The largest case series of human infection with *Vagococcus spp.* was described by Racero et al. who reported 15 cases in Argentina between 2014–2019, 14 of which were either SSTI, osteomyelitis, or a combination of the two [6]. With the addition of the case presented above, it appears that the most common form of human infection with *Vagococcus spp.* is SSTI.

Environmental contamination of existing wounds likely represents the primary mechanism for these infections as *Vagococcus spp.* have been identified in a wide range of terrestrial and aquatic wildlife [1,2,4]. Another notable pathway to infection is speculated to be through consumption of contaminated food, which could lead to endodontic infections in predisposed individuals and possibly secondary bacteremia or endocarditis [7,8]. While individuals with comorbidities or immunocompromising conditions - such as diabetes, as demonstrated by Racero et al. - may be at increased risk of infection, there has been no clear evidence to support a nosocomial component to human infections with *Vagococcus spp.*

Microbiological identification of *Vagococcus spp.* can be challenging as conventional biochemical testing may confuse *Vagococcus spp.* with *Enterococcus spp.* [5]. Alternatively, MALDI-TOF MS can reliably identify *Vagococcus* to the genus and species level and was able to identify *Vagococcus fluvialis* in the present case. Some studies also described routinely using PCR of 16S rRNA to confirm identification and while this may be the most accurate approach the practicality and cost-effectiveness of this method can be a limiting factor [5,6].

Although it has been decades since *Vagococcus* was classified as a genus, the relative rarity with which it causes human infection means that little is known about its susceptibility to various antibiotics. Teixeira et al. studied nine strains of *Vagococcus spp.* in 1997 and found all to be susceptible to ampicillin, cefotaxime, TMP-SMX, and vancomycin whereas all were resistant to clindamycin, lomefloxacin, and ofloxacin [1]. The analysis of 15 *Vagococcus spp.* isolates by Racero et al. found the most active antibiotics to be ampicillin, TMP-SMX, vancomycin, teicoplanin and linezolid, while resistance to fluoroquinolones was observed in six isolates, resistance to macrolides in 11, and resistance to tetracyclines in 12 [6]. Other case reports have similarly identified susceptibility to penicillin G, ampicillin, cefotaxime, vancomycin, TMP-SMX and gentamicin; and resistance to, erythromycin, azithromycin, and ofloxacin [5,7]. The *Vagococcus fluvialis* isolate in the present study showed susceptibility (see above) to ampicillin, minocycline, vancomycin and linezolid, but resistance to TMP-SMX and levofloxacin. While *Vagococcus spp.* seem to be generally susceptible to ampicillin, vancomycin, and linezolid, the variable resistance to macrolides, fluoroquinolones, tetracyclines and TMP-SMX makes empiric antibiotic therapy selection for these infections more complex. A reasonable approach for most infections with *Vagococcus spp.* would be empiric therapy with an aminopenicillin or vancomycin while conducting full susceptibility testing.

A final consideration in the present case is its applicability to the populations at risk of trauma and blast exposure, such as military personnel. The mechanism of infection for the patient presented above was a blast injury that became infected by environmental pathogens. A recent review of the Trauma Infectious Disease Outcomes Study Initiative of Multidrug Resistant and Virulent Organisms (TIDOS MDR/VO) highlighted the importance of polymicrobial and multidrug resistant wound infections in American military service members with traumatic injuries sustained during the wars in Iraq and Afghanistan between 2009 and 2014 [9]. Interestingly, among 211 *Enterococcus*-positive polymicrobial combat-related extremity wound infections, two were positive for either *Lactobacillus spp.* or *Vagococcus spp*. While infection is certainly uncommon, this does lend credence to the possibly unrecognized presence of *Vagococcus spp.* in environments across the globe. Although identified cases of *Vagococcus spp.* as a cause of human infection have increased in the past two decades, it is unclear if this is because *Vagococcus spp.* may be an emerging pathogen or if this is a byproduct of improving microbiological identification methods. Nonetheless, special care is needed when identifying *Vagococcus spp.* given its similarity to other more common bacteria and when choosing empiric antibiotic therapy in light of the complex and variable resistance profiles they typically exhibit.

Ethical approval

This paper was approved for release by Naval Health Research Command on 17 Apr 2023.

Funding

There were no sources of funding required or used for this research.

CRediT authorship contribution statement

James Brunswick: Writing – original draft. **Jeffrey Spiro:** Writing – review & editing. **Piotr Wisniewski:** Writing – review & editing.

Declaration of Competing Interest

None.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Acknowledgments

None.

Declarations

None.

Disclaimer

The views expressed in this material are those of the authors, and do not reflect the official policy or position of the U.S. Government, the Department of Defense, or the Department of the Army.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Prior presentation

Not applicable.

Institutional Review Board (human subjects)

Not applicable.

Institutional Animal Care and Use Committee (IACUC)

Not applicable.

Institutional clearance

Institutional clearance approved.

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