

# *Enterococcus casseliflavus* Infection: A Review of Clinical Features and Treatment

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**Abstract:** Some *Enterococcus* species, including *Enterococcus faecalis* and *E. faecium*, are increasingly becoming a common cause of nosocomial infections, accounting for the majority of human enterococcal infections, while other species, such as *E. casseliflavus*, have also been shown to be pathogenic to humans due to the increase in immunocompromised patients. These infections vary widely in their mode of transmission, symptoms, and other characteristics. Treatment is difficult in some cases because enterococci are resistant to numerous antimicrobial agents. *Enterococcus faecalis* and *E. faecium* are the best-known opportunistic pathogens, but others, including *E. casseliflavus*, occasionally cause opportunistic infections. This review summarizes the clinical features of *E. casseliflavus* infections and discusses effective therapeutic strategies. Bacteremia was the most common form of *E. casseliflavus* infections. Because *E. casseliflavus* carries the VanC gene, which confers resistance to vancomycin, less resistant drugs such as ampicillin were found more effective in treating the bacteremia. The second most common form of *E. casseliflavus* infection was trauma-induced endophthalmitis. This was commonly reported in active young to middle-aged patients. Vitreoretinal surgery and local or systemic administration of sensitive antimicrobial agents seem to be key to successful treatment. Other conditions such as infective endocarditis, meningitis, peritonitis, and pyothorax have also been reported as forms of *E. casseliflavus* infection. This review clarifies the clinical features of *E. casseliflavus* infection and provides important insights into its treatment.

**Keywords:** nosocomial infections, bacteremia, endophthalmitis, vancomycin

## Introduction

Enterococci, a group of widespread Gram-positive facultative anaerobic bacteria, have more than 40 described species. Although previously considered to belong to the Streptococci group, DNA homology studies have suggested that *Enterococcus* is a distinct genus.<sup>1</sup> These bacteria are usually found in the intestines of humans and animals, on the surfaces of plants, and in dairy products.<sup>2</sup> They persist in the environment because of their ability to survive under a range of conditions, including drying, extreme temperatures, high osmolarity, and the presence of disinfectants.<sup>3</sup> Moreover, enterococci are also used in food production as probiotic products to monitor fecal contamination.<sup>4</sup>

However, some species of the bacteria are an increasingly common cause of nosocomial infections, such as *Enterococcus faecalis* and *E. faecium*, accounting for the majority of human enterococcal infections, while others like *E. casseliflavus* have also been shown to be pathogenic to humans.<sup>5</sup> *E. casseliflavus* has been assigned the species status in 1984; it is a motile bacterium that produces a yellow pigment.<sup>6</sup> *E. casseliflavus* is rarely found in clinical samples (<1.3%);<sup>7</sup> however, it is an opportunistic pathogen that targets individuals who are immunocompromised or chronically ill and is sometimes nosocomially acquired.<sup>8</sup> Although uncommon, *E. casseliflavus* infection can be seriously invasive. Yet, few studies have summarized the characteristics of these infections.

Here, reports of *E. casseliflavus* infections and their features are reviewed. Furthermore, I summarize commonly reported manifestations of *E. casseliflavus* infections, along with discussions of case studies and clinical therapies. All *E. casseliflavus*-related clinical manuscripts written in English listed on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) were included.

## Bacteremia

Bacteremia was the most common form of *E. casseliflavus* infection. Eleven case reports and 12 retrospective cohort studies/case series of *E. casseliflavus* bacteremia were reviewed.<sup>9–31</sup> The treatment courses of all 11 reported cases were summarized in Table 1. Specific background factors of bacteremia cases, including cirrhosis, chronic obstructive pulmonary disease, cancers (including those on chemotherapy) and its complications, advanced age, and steroid use, were identified in the case reports. Ten of eleven patients had at least one of these background factors. Retrospective cohort studies showed that 40.12–48.8% of the patients with bacteremia due to *E. casseliflavus* had solid tumors as a complication.<sup>27,30</sup> A study evaluating *E. casseliflavus* and *E. gallinarum* bacteremia cases showed that malignancy (70.0%) and diabetes mellitus (20.0%) were the most common complications in these bacteremia cases.<sup>31</sup> These results indicate that *E. casseliflavus* bacteremia is more likely to occur in immunocompromised hosts. Case reports suggest that the susceptible age for this bacteremia is mainly 60–80 years; however, neonatal cases have also been reported.<sup>14</sup>

The most important organs related to *E. casseliflavus* bacteremia are the biliary tract and liver. Infective endocarditis was the primary infection site in two cases,<sup>9,10</sup> and cholangitis was reported as the primary infection site in one case.<sup>12</sup> A retrospective cohort study of biliary infections with bacteremia found that *E. casseliflavus* constituted 12.5% of the Gram-positive bacteremia.<sup>20</sup> Three of the eleven patients had biliary tract infections prior to the onset of *E. casseliflavus* bacteremia.<sup>16,18,19</sup> In one case, surgery of the biliary system had been performed before the onset of *E. casseliflavus* bacteremia.<sup>15</sup> A retrospective cohort study of post-liver transplant cases found 7.8% of the patients to be infected with enterococcal bacteremia.<sup>21</sup> These results suggest that this microbe has a high affinity for the biliary system.

*E. casseliflavus* carries the VanC gene intrinsically and is moderately resistant to vancomycin (VCM).<sup>32</sup> Owing to this moderate resistance, the Clinical and Laboratory Standards Institute (CLSI) considers VCM concentrations below 4 mg/dL to be susceptible for *Enterococcus species*; therefore, the drug is not actively recommended in *E. casseliflavus* bacteremia treatment.<sup>33</sup> Indeed, a VCM minimum inhibitory concentration (MIC) of 4 mg/dL in three cases, 8 mg/dL in one case, and 3 mg/dL in two cases, were demonstrated.<sup>10,13,14,16,18,19</sup> It is important to note that even if microbiological

**Table 1** Summary of the Treatment Courses for All Reported Bacteremia Cases

No	Citation	Age (Years)	Gender	Diagnosis	Multiple Organisms Detected	Definitive Treatment for <i>Enterococcus casseliflavus</i> Bacteremia	Outcome
1	9	63	Male	Bacteremia/Infective endocarditis	Yes	Daptomycin for 6 weeks	Survived
2	10	86	Female	Bacteremia/Infective endocarditis	No	Ampicillin and gentamicin for 6 weeks	Survived
3	11	56	Male	Bacteremia/Spontaneous bacterial peritonitis	No	Meropenem (Duration unknown)	Survived
4	12	74	Male	Bacteremia/Cholangitis	Yes	Daptomycin for 2 weeks	Survived
5	13	72	Male	Bacteremia	No	Ampicillin for 6 weeks	Survived
6	14	24 weeks	Female	Bacteremia	No	Ampicillin and netilmicin for 12 days	Survived
7	15	39	Male	Bacteremia	Yes	Ertapenem for 6 weeks, followed by amoxicillin-clavulanate (duration unknown)	Survived
8	16	75	Male	Bacteremia	No	Ampicillin for 2 weeks	Survived
9	17	87	Male	Bacteremia	Yes	Ampicillin for about 2 weeks, followed by linezolid for 2 weeks	Survived
10	18	80	Female	Bacteremia	Yes	Ampicillin-sulbactam for 10 days	Survived
11	19	19	Female	Bacteremia	No	Ampicillin and teicoplanin for 2 weeks	Survived

tests show that this microorganism is susceptible to VCM, the actual therapeutic effect of VCM is likely to be low. In the case reports reviewed, all 11 patients were treated with antimicrobial agents other than VCM and survived. While five patients were treated with ampicillin-sulbactam or carbapenem from the beginning, five patients had been switched from VCM to ampicillin, and one patient had been switched from VCM to daptomycin, which had a favorable sensitivity result.<sup>9,10,13,14,16,17</sup> Some retrospective cohort studies report *E. casseliflavus* to be 79.5–100% sensitive to VCM, while others report VCM MICs as high as 4 mg/dL.<sup>26–28</sup> However, ampicillin was reported to have a 96% success rate against *E. casseliflavus* in a summary of 41 cases, indicating that this drug is a viable treatment option.<sup>30</sup>

Of the 11 case reports reviewed, five presented with bacteremia caused by *E. casseliflavus* and other organisms.<sup>9,12,15,17,18</sup> Cohort studies reported a high proportion (41.5–66.1%) of *E. casseliflavus* bacteremia cases with multiple bacterial species present, primarily other Gram-negative *Enterobacteriaceae*.<sup>27,28,30</sup> This feature is probably specific to *E. casseliflavus* bacteremia. Although all reported cases demonstrated favorable outcomes, *E. casseliflavus* bacteremia is typically accompanied by multiple bacterial species and consequently might have a poor prognosis.<sup>22,25</sup> The mortality rates have been reported as 24.4–24.8% for enterococcal bacteremia, 27.3–28.7% for non-*faecalis* non-*faecium* bacteremia, and 12.8–25.0% for *E. casseliflavus* bacteremia.<sup>22,23,27–30</sup> However, the mortality rate of *E. casseliflavus* bacteremia has only been reported in a small number of studies and it is not clear whether there is any difference in prognosis compared to other enterococci. Either way, enterococcal bacteremia, including that caused by *E. casseliflavus*, is associated with an overall poor prognosis.

Based on these results, when *E. casseliflavus* is identified by blood culture, the biliary system should be evaluated, the antimicrobial susceptibility of the organism should be confirmed, and an effective antimicrobial agent other than VCM, such as ampicillin, should be administered promptly. Particularly, if multiple organisms are identified, attention should be paid to the choice of antimicrobial agents and the treatment course. In several reports summarizing enterococcal bacteremia due to nosocomial infections, risk factors for poor prognosis included catheter-related bloodstream infections, steroid-associated immunosuppression, severe illness at onset, and advanced age. These factors may also require evaluation at the time of diagnosis.<sup>22–24,27</sup>

## Endophthalmitis

Endophthalmitis is the second most frequently reported type of *E. casseliflavus* infection. Six reports of endophthalmitis caused by *E. casseliflavus* and one retrospective cohort study were reviewed.<sup>34–40</sup> In the cohort study, 14 (48.3%) of 29 cases of enterococcal endophthalmitis were attributed to this organism, suggesting that intraocular tissues were particularly susceptible to *E. casseliflavus*.<sup>40</sup> The case reports showed that most of the cases were traumatic endophthalmitis, with a wide range of trauma types, including attacks from domestic animals, such as pigs and horses, water gunshot wounds, among others.<sup>34,36–39</sup> A farm-related component was identified in three of six cases, such as trauma related to lawnmowers and attacks from livestock. Therefore, in farm injury-based endophthalmitis, it is necessary to consider the possibility that this microorganism is the causative agent.<sup>34,38,39</sup> No specific risk factors for infection were identified in these cases. Endophthalmitis caused by *E. casseliflavus* occurs in a wide age range (4–54); the incidence seems to be higher among active young and middle-aged individuals.

In five of the six cases, vitreoretinal surgery was performed, followed by intraocular administration of VCM/ceftazidime and steroids, followed by other more effective antimicrobial agents after the strain was identified. One patient initially refused vitreoretinal surgery, with the surgery being finally performed after the disease worsened. This suggests that endophthalmitis caused by *E. casseliflavus* requires vitreoretinal surgery.<sup>39</sup>

VCM is routinely administered intraocularly for endophthalmitis; however, if the organism is identified, additional measures, such as systemic or intraocular administration of an appropriate antimicrobial agent may be required. One cohort study showed that as an endophthalmitis pathogen, *E. casseliflavus* was resistant to new quinolones, including 64.3% resistance to ciprofloxacin and 100% resistance to VCM. Administration of systemic ampicillin was required as treatment in two cases and systemic linezolid in one case after intraocular administration of VCM and ceftazidime.<sup>36–38</sup> As noted previously, *E. casseliflavus* possesses an intrinsic VanC gene; therefore, VCM should not be used as a therapeutic agent for endophthalmitis caused by this species. Furthermore, three of the six patients underwent reoperation for vitreoretinal extraction, indicating the need for appropriate postoperative follow-up.<sup>34,35,38</sup> Although

proposing an appropriate treatment is challenging due to the paucity of case reports, the optimal approach for managing *E. casseliflavus*-caused endophthalmitis seems to be through vitreoretinal surgery, systemic administration of the suitable antimicrobial (eg, ampicillin) based on antimicrobial susceptibility testing, and adequate postoperative follow-up.

## Others

As mentioned previously, two bacteremia cases also resulted in infective endocarditis.<sup>9,10</sup> Although chronic kidney disease (CKD) was common to both cases and other risks such as age and being immunosuppressed were apparent, no clear common risk was identified. Vegetation was observed on the aortic valve in both cases. In both cases, the causative microorganism was assumed to be resistant to VCM, although MIC of VCM was 4 mg/dL in one report and that of VCM was unknown in the other report. Both cases resulted in recovery; one case was treated with daptomycin based on the susceptibility results and the other was treated with ampicillin. These two cases suggest that this organism, although rare, may be a causative agent of infective endocarditis.

Two cases of infectious meningitis have also been reported.<sup>41,42</sup> No similarities in background diseases or causes were observed. Moreover, VCM resistance was observed in both cases; one patient was treated with linezolid and the other with meropenem and ampicillin-sulbactam, both resulting in full recovery.

Two cases of peritonitis were also reviewed.<sup>11,43</sup> One patient had spontaneous bacterial peritonitis associated with alcoholic cirrhosis and ascites, and the other had peritonitis associated with peritoneal dialysis. *E. casseliflavus* can colonize the intestine and cause peritonitis. Finally, one case report was found of empyema caused by *E. casseliflavus* in association with a chronic expanding hematoma, but the details were not clear in this case.<sup>43</sup>

## Conclusion

This review clarified that *E. casseliflavus* can be a causative microorganism in various infections, including bacteremia and endophthalmitis. A review of cases also revealed that the bacterium intrinsically possesses the *VanC* gene and can be mildly to moderately resistant to VCM, highlighting the importance of selecting appropriate antimicrobial agents. In most cases, the organism demonstrated sensitivity to ampicillin, which has been recommended as one of the most suitable antimicrobial agents for *E. casseliflavus* infections.

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## Disclosure

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