Exogenous endophthalmitis caused by *Enterococcus casseliflavus*: A case report and discussion regarding treatment of intraocular infection with vancomycin-resistant enterococci

Byron M Berenger MD[1,2], Shobhana Kulkarni MD[3,4], Brad J Hinz MD[5], Sarah E Forgie MD[1,6]

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BACKGROUND: Endophthalmitis caused by enterococci is rare, and cases involving vancomycin-resistant enterococci are even more so. Due to the poor bioavailability of many antibiotics in the vitreous chamber, special considerations are required when choosing antibiotics to treat these infections. The authors report the first case of exogenous endophthalmitis caused by *Enterococcus casseliflavus* via the unique mechanism of high-velocity water stream trauma from a toy water gun.

A previously healthy four-year old boy presented with endophthalmitis of the left eye after injury from a water gun. Empirical treatment for endophthalmitis was started on presentation to the ophthalmologist. After the identification of the pathogen and a review of the literature, the antibiotic regimen was changed to include intravitreal ampicillin and amikacin with systemic linezolid.

Endophthalmitis caused by *E casseliflavus* and other vancomycin-resistant enterococci are challenging to treat. Rapid identification of vancomycin-resistant enterococcal endophthalmitis is important to guide appropriate antibiotic therapy. Systemic linezolid achieves excellent intravitreal concentrations, and should be used in combination with intravitreal and topical antibiotics.

Key Words: *Endophthalmitis;* Enterococcus; Enterococcus casseliflavus; *Vancomycin-resistant*

L'endophtalmie exogène attribuable à l'*Enterococcus casseliflavus* : rapport de cas et exposé sur le traitement de l'infection intra-oculaire par des entérocoques résistant à la vancomycine

HISTORIQUE : L'endophtalmie est rarement attribuable aux entérocoques, et les cas découlant d'entérocoques résistant à la vancomycine le sont encore plus. Étant donné la piètre biodisponibilité de nombreux antibiotiques dans la cavité vitréenne, il faut tenir compte de facteurs particuliers lors de la sélection du traitement de ces infections. Les auteurs présentent le premier cas d'endophtalmie exogène causée par une *Enterococcus casseliflavus* contractée après un traumatisme imputable au mécanisme unique de jet d'eau à grande vitesse propulsé par un pistolet à eau.

Un garçon de quatre ans auparavant en santé a consulté à cause d'une endophtalmie de l'œil gauche après une blessure contractée par un pistolet à eau. L'ophtalmologiste a prescrit un traitement empirique dès la consultation. Après avoir confirmé l'agent pathogène et analysé les publications, il a modifié la posologie antibiotique pour inclure de l'ampicilline intravitréenne et de l'amikacine combinée à de la linézolide systémique.

L'endophtalmie causée par l'*E casseliflavus* et d'autres entérocoques résistant à la vancomycine est difficile à traiter. Il est important de déceler rapidement l'endophtalmie par entérocoque résistant à la vancomycine pour orienter l'antibiothérapie. La linézolide systémique, qui assure d'excellentes concentrations intravitréennes, devrait être combinée à des antibiotiques intravitréens et topiques.

Endophthalmitis is caused by the introduction of a pathogen into the intraocular space via trauma, ocular surgery, or direct extension of a superficial eye infection (exogenous endophthalmitis) or hematogenously (endogenous endophthalmitis). Endophthalmitis caused by vancomycin-resistant enterococci (VRE) is rare, described in only a few published case reports. One type of VRE, *Enterococcus casseliflavus* is inherently resistant to vancomycin due to the chromosomally encoded *vanC* gene, and has been reported once as a cause of endogenous endophthalmitis (1,2). We report the first case of exogenous endophthalmitis caused by *E casseliflavus* via the unique mechanism of high-velocity water stream trauma from a toy water gun.

For VRE infections, ampicillin or amoxicillin are reasonable antibiotic choices if the isolate is susceptible. In the absence of high-level aminoglycoside resistance, ampicillin may be combined with an aminoglycoside for a synergistic effect (3). Other clinically available antibiotics with activity against VRE include: linezolid, daptomycin and tigecycline (4,5).

Treatment of bacterial endophthalmitis is difficult due to the severe and rapid retinal damage that occurs as a result of bacterial growth and inflammatory response, and it involves a combination of intravitreal and systemic antibiotics with vitrectomy (6). Although there is a lack of strong evidence supporting an added benefit of systemic antibiotics, they are recommended in severe cases of endophthalmitis and routinely for exogenous endophthalmitis (6,7). Poor penetration of systemic or topical antibiotics into the vitreous chamber makes administration of antibiotics to prevent further bacterial growth challenging, especially in the context of resistant organisms such as VRE.

CASE PRESENTATION

A previously healthy, fully immunized, four-year-old boy, with no previous visual issues, presented with endophthalmitis of the left eye. He and his siblings had been playing with water guns several hours before presentation, and water was squirted into his eye. The water was from

[1]*Department of Medical Microbiology and Immunology, University of Alberta;* [2]*Alberta Provincial Laboratory for Public Health;* [3] *DynaLIFE$_{Dx}$ Diagnostic Laboratory Services;* [4]*Department of Laboratory Medicine and Pathology;* [5]*Department of Ophthamology;* [6]*Department of Pediatrics, University of Alberta, Edmonton, Alberta*

Correspondence: Dr Sarah Forgie, Department of Pediatrics, Edmonton Clinic Health Academy, 3-558D 11405 87 Avenue, Edmonton, Alberta T6G 2J3. Telephone 780-248-5540, e-mail s.forgie@ualberta.ca

a wading pool that had been filled with tap water the same day. The child experienced acute onset of pain and, approximately 2 h later, reported 'white dots' obscuring his vision. Six hours after the initial insult, his mother noticed that his left cornea was cloudy and his conjunctiva was red. He was immediately taken to his local hospital and assessed promptly by the local ophthalmologist. His pupils were asymmetric, his conjunctiva was injected on the left and there was corneal opacity. The remainder of his physical examination was unremarkable. Given the mechanism of the injury, the diagnosis was not clear, and the ophthalmologist transferred him to a tertiary eye care centre 5 h away for further management. The child presented to the tertiary care centre with severe anterior chamber inflammation, miosis and inferior hypopyon. The vitreous cavity was filled with purulent debris with no view of the fundus. B-scan ultrasonography revealed vitritis with no foreign body. Given the unusual mechanism of injury, it was not clear whether this was endophthalmitis or a severe inflammatory response to trauma. The Retina Service was consulted and, after assessment, the child was scheduled for surgery

Approximately 26 h after the injury, the child underwent anterior chamber exploration and pars plana vitrectomy. Vitrectomy allowed visualization of white retinal infiltrates and the absence of a foreign body. After vitrectomy wash out, the vitreous chamber was injected with 1 mg vancomycin, 2.25 mg ceftazidime and 1 mg dexamethasone (routine drugs administered for exogenous endophthalmitis) (8). Topical and systemic medications were also administered including: one drop 0.5% moxifloxacin hourly, one drop 1% prednisolone daily, one drop 2% homatropine every 12 h, 30 mg/kg/day oral ciprofloxacin divided every 12 h and 60 mg/kg/day intravenous vancomycin divided every 6 h.

Gram stain of the vitreous fluid revealed >25 polymorphonuclear leukocytes and >25 Gram-positive cocci in pairs and chains (intracellular and extracellular) per 1000× field. After 18 h of incubation on blood agar, there was growth of yellow-pigmented, alpha-hemolytic colonies, which were Gram-positive cocci in pairs and chains. Mass spectrometry (Vitek MS BioMérieux, France) identified the organism as *E casseliflavus* (99.9% certainty) within 45 min. The medical microbiologist was immediately alerted of the identification of this intrinsically vancomycin-resistant organism and treatment options were discussed with the pediatric infectious disease and ophthalmology physicians.

The discussion prompted an immediate return to the operating room for additional intravitreal antibiotics and a repeat vitreous washout. Using the local antibiogram for this organism, published susceptibilities and the experience of Hillier et al (9,10) treating an *E gallinarum* endophthalmitis secondary to a metallic foreign body, the treatment plan consisted of intravitreal ampicillin (50 mg) and amikacin (400 mg), as well as intravenous ampicillin (300 mg/kg/day divided every 6 h). Topical treatment consisted of 0.3% gentamicin (one drop four times per day) and 1% prednisolone (one drop four times per day). Twelve hours after the antibiotic change to ampicillin, linezolid (30 mg/kg/day divided every 8 h) was added. Systemic and topical antimicrobials were continued for 14 days. Table 1 summarized the antibiotic susceptibilities.

The patient was closely monitored in the ophthalmology clinic. The hypopyon did not recur and the vitreous cavity remained opaque with no view of the fundus at 10 days after the initial anterior chamber washout with vitrectomy. The visual acuity began to decrease three weeks postincident; however, clinical examination did not support repeat infection and it was likely due to development of outer cortical vitreous separation causing vitreous debris. Over time, the vitreous cavity and anterior segment cleared, and vision improved to 20/400 at seven weeks, 20/400 at 17 weeks and 20/70 at 16 months postincident.

TABLE 1
Susceptibilities of the *Enterococcus casseliflavus* isolate compared with EUCAST and CLSI breakpoints

Antibiotic	Isolate MIC	Interpretation	EUCAST†	CLSI‡
Ampicillin	≤2	Sensitive	≤4	≤8
Vancomycin	4	Resistant*	≤4	≤4
Gentamicin synergy	N/A	Sensitive	≤128	≤500
Linezolid	2	Sensitive	≤4	≤2

*Data presented as µg/mL. Minimum inhibitory concentrations (MICs) were determined using the Vitek 2, GP 67 card (BioMérieux, France). Vitek 2 reports gentamicin synergy as sensitive or resistant without an MIC. *Vancomycin was reported resistant due to the intrinsic carriage of VanC in* E casseliflavus. *†Data adapted from reference 7. ‡Data adapted from reference 6. CLSI Clinical Laboratory Standards Institute; EUCAST European Committee on Antimicrobial Susceptibility Testing; N/A Not available*

DISCUSSION

The present case highlights the importance of interdisciplinary medical care, and the effective use of laboratory technology to assure early and appropriate antimicrobial treatment. Rapid identification of this isolate was achieved using mass spectrometry, a process that previously would take 8 h to 12 h. In addition, effective communication between the medical microbiologist and the clinical team allowed prompt treatment changes. This stresses the importance of interdisciplinary teams in the health care environment, especially when dealing with challenging infections such as VRE endophthalmitis.

Early vitrectomy is an important component for treating severe endogenous or postsurgical endophthalmitis, and is routinely performed for exogenous endophthalmitis because it improves outcomes and enhances clearance of bacteria, inflammatory cells and debris (6,8). During vitrectomy, iatrogenic complications such as retinal detachment may occur; therefore, repeat vitrectomy is avoided unless intravitreal debris persist (8,11). In our case, vitrectomy was performed in an acceptable time frame given that the child came from a rural area and the initial diagnosis was initially ambiguous. Repeat vitreous washout and the administration of additional intravitreal antibiotics was performed because VRE was isolated and it was resistant to the initial intravitreal antibiotic regimen.

In exogenous endophthalmitis, vision is restored to 20/40 or better in 15% to 40% of cases and, in acute postoperative endophthalmitis, approximately 50% have visual acuity of 20/40 or better and 15% to 36% have visual acuity of 20/200 (6). Therefore, the outcome in the present case (visual acuity of 20/70) is acceptable given that the treatment of VRE is challenging, especially when the infection is in the vitreous chamber where there is poor penetration of systemic or topical antibiotics.

There are no published data regarding the penetration of ampicillin into the human vitreous chamber. Animal data reveal that when administered intravenously, levels of ampicillin in the vitreous fluid were approximately 2-log less than in the serum (12), and when administered orally, amoxicillin levels in the vitreous fluid were approximately 1.5- to 2-log less effective at killing *Micrococcus luteus* than levels in serum (13). Therefore, extrapolating from animal data, there is poor penetration of ampicillin and amoxicillin into the vitreous fluid.

Gentamicin also has poor penetration into the vitreous fluid. Human studies reveal no detectable gentamicin in the vitreous fluid when doses were administered intramuscularly (1.6 mg/kg) or subconjunctivally (40 mg) (14). These data are supported with animal studies (15). Furthermore, intravitreal gentamicin has been linked to macular infarction; however, intravitreal amikacin has a lower incidence of macular infarction (16).

Linezolid resistance in *Enterococcus* is rare and there is evidence that it penetrates the vitreous chamber. Administration of two doses of oral linezolid (600 mg every 12 h) in noninflamed eyes, achieved a mean (±SD) concentration in the vitreous fluid of 5.7±2.7 µg/mL (versus 10.3±4.1 µg/mL in the serum) 6 h postdose (see Table 1 for susceptibility breakpoints). Using the same linezolid regimen, Horcadjada et al (17) found concentrations in the vitreous fluid to be higher than 4 µg/mL in the majority of patients studied, 12 h after the second dose. When only one dose was administered, it was difficult to achieve levels higher than 2 µg/mL (17-19). Unlike systemic linezolid,

topical administration of linezolid in animal studies revealed negligible penetration into the vitreous fluid (20). Therefore, when administered orally or intravenously, linezolid concentrations in the vitreous chamber are above the minimum inhibitory concentration for most *Enterococci*.

Daptomycin is another alternative for treatment of VRE; however, there are limited data regarding its penetration into the vitreous chamber. One case of endogenous endophthalmitis caused by methicillin-resistant *Staphylococcus aureus* bacteremia, refractory to vancomycin and linezolid treatment in a patient experiencing chronic renal failure demonstrated vitreous fluid levels three times the Clinical and Laboratory Standards Institute susceptible breakpoint of ≤4 µg/mL 42 h after one dose of intravenous daptomycin (21).

Tigecycline is a potential antibiotic to use for VRE infections; however, topical or systemic use of tigecycline for eye infections has not been investigated. Tigecycline also has an unfavourable side effect profile and a United States Food and Drug Administration black box warning against its intravenous use (22).

In the present case, no source of the endophthalmitis other than the water stream trauma from the toy water gun was identified. Water toys and squirt guns are capable of generating pressurized water streams that pose a risk for increased intraocular pressure and ocular injury (23). While *Enterococci* are not typically associated with water, we speculate that the wading pool (that was used to fill the water guns) may have been contaminated with fecal matter. Given the timing of the insult, the clinical presentation and the lack of another identifiable source, the present case is likely one of *E casseliflavus* exogenous endophthalmitis caused by high-velocity water stream trauma from a toy water gun.

CONCLUSION

Endophthalmitis caused by *E casseliflavus* and other VRE are challenging to treat, due to reduced antimicrobial options and the poor penetration of topical and systemic antibiotics into the vitreal space. Therefore, rapid identification of the organism and knowledge of antimicrobial penetration into the vitreal space is important to guide therapy. Systemic linezolid alone may achieve intravitreal concentrations above the minimum inhibitory concentration for VRE; however, based on the literature, a combination of antibiotics delivered via intravitreal injection, systemic and topical routes should be used to treat VRE endophthalmitis.

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AUTHOR CONTRIBUTIONS: All authors read and approved the final manuscript. BMB was involved in the clinical management of the patient, performed literature review and drafted the manuscript. SF was the pediatric infectious disease consultant in the present case. BH was the opthalmologist involved in the case and obtained consent from the patient's parents. SK was the medical microbiologist in the present case. All authors were involved in critical appraisal and revision of the manuscript.

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