International Journal of Infectious Diseases 25 (2014) 26–31

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Central nervous system infections due to vancomycin-resistant enterococci: case series and review of the literature

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ARTICLE INFO

Article history:
Received 25 November 2013
Received in revised form 7 January 2014
Accepted 10 January 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Vancomycin-resistant enterococci
Meningitis
Ventriculitis

SUMMARY

Objectives: To evaluate reported cases of central nervous system (CNS) infections due to vancomycin-resistant enterococci (VRE) and describe the data necessary to better understand clinical characteristics of this rare disease process.
Methods: We report two cases of VRE CNS infection and review 36 cases reported in the literature.
Results: Eighty-two percent (31/38) of cases were due to *Enterococcus faecium*. The median length of stay prior to diagnosis was 14 days (interquartile range 9–33). Fifty-eight percent (22/38) of cases had significant underlying non-malignant CNS disease processes and 63% (24/38) had CNS devices in situ. Forty percent (15/38) of patients had other positive culture sites. Ninety-two percent (35/38) of patients experienced microbiological cure and 74% (28/38) experienced clinical and microbiological cure following a variety of antimicrobial therapies. Seventy-four percent (14/19) of patients who experienced clinical/microbiological cure with CNS devices had them either removed or replaced. Eighteen percent (7/38) died from VRE CNS infections.
Conclusions: VRE CNS infections are uncommon nosocomial infections that most commonly affect patients with underlying CNS disease processes. The vast majority of cases are due to *E. faecium*, and many cases involve multiple positive culture sites. Optimal antimicrobial therapy remains undefined, but should be coupled with removal or replacement of indwelling CNS devices.

1. Introduction

The enterococci have emerged in recent years as significant pathogens causing infections in both nosocomial and community settings. Once thought to be relatively harmless commensals, they are now the third leading cause of nosocomial bloodstream infections.[1] Antimicrobial resistance in enterococci has been reported increasingly, with the first case of vancomycin resistance documented in 1988.[2] Vancomycin resistance occurs in 60% of *Enterococcus faecium* isolates causing nosocomial bloodstream infections.[1] Enterococcal meningitis is relatively uncommon, accounting for only 0.3% to 4% of cases of bacterial meningitis.[3] Vancomycin-resistant enterococci (VRE) as a cause of central nervous system (CNS) infection is extremely rare, and has been described in the literature primarily as individual case reports and small case series. Herein, we report two cases of CNS infections due to VRE and review 36 cases of VRE CNS infections reported in the literature. To our knowledge, we provide the most comprehensive review of VRE CNS infections to date, including underlying comorbid conditions, clinical features, cerebrospinal fluid (CSF) characteristics, treatment regimens, and outcomes.

2. Case reports

2.1. Case 1

A 19-year-old woman with acute myelogenous leukemia was admitted for umbilical cord blood transplantation. Her post-transplant course was complicated by viral infections (cytomegalovirus (CMV),

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http://dx.doi.org/10.1016/j.ijid.2014.01.009

BK virus), mucositis, and graft-versus-host disease. Eight days post-transplant she developed fever, and two sets of blood cultures yielded *Enterococcus spp* resistant to vancomycin (minimum inhibitory concentration (MIC) ≥32 μg/ml) and ampicillin (MIC ≥16 μg/ml), and susceptible to quinupristin–dalfopristin (MIC ≤0.5 μg/ml), linezolid (MIC 2 μg/ml), and high-level gentamicin (MIC <500 μg/ml). Daptomycin (6 mg/kg intravenous (IV) daily) and gentamicin (1 mg/kg IV every 8 h) were started and her Hickman catheter was removed. Eight days later she remained bacteremic and linezolid (600 mg per os (PO) every 12 h) was added. Subsequent blood cultures revealed that the VRE isolate had become resistant to linezolid (MIC 8 μg/ml), therefore it was stopped and rifampin (300 mg PO every 8 h) was added.

She remained bacteremic and 23 days after starting antimicrobials became unresponsive and demonstrated left gaze deviation and tonic/clonic movements of the extremities. A head computed tomography (CT) scan revealed hydrocephalus and an external ventricular drain was placed. CSF cultures obtained at the time of ventriculostomy placement yielded VRE, with a susceptibility profile consistent with the previous blood isolate. At this time, the VRE treatment regimen was changed to chloramphenicol (500 mg IV every 6 h), daptomycin (increased to 8 mg/kg IV daily), gentamicin (1 mg/kg IV every 8 h), and rifampin (300 mg PO every 8 h). On day 27, gentamicin was discontinued due to decreased urine output. After multiple CSF cultures revealed vancomycin-susceptible enterococci and the presence of multiple enterococcal species could not be excluded, vancomycin (15 mg intraventricular (VT) daily) and gentamicin (4 mg VT daily) were added to her therapy (on days 29 and 30, respectively). On day 35, all cultures (blood and CSF) were vancomycin-resistant; consequently VT vancomycin was discontinued and replaced with quinupristin–dalfopristin (2 mg VT daily). Intraventricular quinupristin–dalfopristin was discontinued after 6 days of therapy and changed to daptomycin (5 mg VT every 48 h) since CSF cultures continued to be positive for VRE. On day 40 and day 52, blood and CSF cultures, respectively, were finally sterile. Transthoracic echocardiography did not reveal any evidence of endocarditis. The patient was treated for an additional 6 weeks of antibiotic therapy, which consisted of daptomycin (IV), chloramphenicol (IV), rifampin (PO), daptomycin (VT), and gentamicin.

The patient was discharged 101 days following transplant; however, she was readmitted on day 133 post-transplant for treatment of lower gastrointestinal bleeding, CMV viremia, and *Streptococcus viridans* bacteremia. She subsequently developed altered mental status, left-sided weakness, lethargy and headache, and status epilepticus requiring pentobarbital coma. However, the VRE infection did not recur after completion of therapy, demonstrated by negative blood and CSF cultures. On post-transplant day 162, the patient was transitioned to palliative care and died.

2.2. Case 2

A 51-year-old woman with systemic sclerosis status post chemotherapy, total body irradiation, cyclophosphamide, equine anti-thymocyte globulin, autologous stem cell transplant, and subsequent myelodysplastic syndrome was transferred from an outside hospital after treatment with azacitidine led to febrile pancytopenia and bilateral pulmonary infiltrates. Culture from bronchoscopy obtained prior to transfer revealed one colony of *Enterococcus spp* (no susceptibility testing was performed). The patient was treated with ceftriaxone and vancomycin at the outside hospital, but was subsequently switched to daptomycin 6 mg/kg IV daily and cefepime upon transfer. The patient developed VRE bacteremia and a transthoracic echocardiogram noted vegetations on the aortic and mitral valves. Gentamicin 1 mg/kg IV every 8 h was added. The patient later developed confusion and a CT scan of the head revealed non-communicating hydrocephalus. Head magnetic resonance angiography and venography did not show any evidence of cerebral aneurysm. CSF cultures were negative. The patient's altered mental status improved after lumbar puncture but she again developed confusion, with a subsequent head CT revealing a subarachnoid hemorrhage. A repeat lumbar puncture was performed and VRE was isolated from the CSF. Chloramphenicol 1000 mg IV every 6 h and rifampin 300 mg IV every 8 h were added to the antibiotic regimen. However, within 3 days the patient developed acute respiratory failure and subsequently died.

3. Methods

A literature review of VRE CNS infections was performed using the Medline/PubMed database. Multiple searches were performed, all of which were limited to English-language articles published from 1988 (the year in which vancomycin resistance in an enterococcal isolate was first reported) through June 2013. Search terms used were vancomycin-resistant Enterococcus meningitis, vancomycin-resistant enterococcal meningitis, glycopeptide-resistant Enterococcus meningitis, vancomycin-resistant Enterococcus ventriculitis, and vancomycin-resistant Enterococcus brain abscess. This search strategy yielded a total of 126 articles. All relevant articles were reviewed as were the references from pertinent articles to identify additional reports.

CNS infection was defined as the isolation of organisms from at least one CSF culture associated with clinical manifestations of meningitis or ventriculitis and classical CSF findings including pleocytosis (white blood cell (WBC) count $\geq 10 \times 10^6$/l), increased protein concentration (>45 mg/dl), or decreased glucose level (< 40 mg/dl). If the authors claimed a case of meningitis or ventriculitis and did not report the CSF parameters then the case was included. Vancomycin resistance was defined as a vancomycin MIC ≥32 μg/ml. If the authors claimed that the isolate was resistant to vancomycin without reporting the MIC, the case was included; however, if the reported MIC was <32 μg/ml, the case was excluded. Neutropenia was defined as an absolute neutrophil count $<1 \times 10^9$/l. Microbiological cure was defined as a negative CSF culture and clinical cure was defined as survival with clinical resolution of infection. Articles that presented aggregate patient data (e.g., clinical trials in which data on individual patients were not reported) were excluded. Cases reporting polymicrobial infections were also excluded.

Eleven cases were excluded from our analysis. In five cases the infecting organisms had a vancomycin MIC of <32 μg/ml;[4–8] in four cases the patient had polymicrobial CNS infection.[9–12] One case was presented in the setting of aggregate data with no specific case details presented and was therefore excluded.[3] One case was from an abstract reference that was not obtainable for review and was therefore excluded.[13] Our analysis yielded 36 cases of VRE CNS infections. Combined with our two additional cases, a total of 38 cases are presented herein.

Data were analyzed using JMP Pro version 10.0.0 (SAS Institute, Cary, NC, USA). Normality of data was assessed by visual inspection of the normal quantile plot. Normally distributed data were described using the mean (standard deviation (SD)), while non-normally distributed data were described with the median (interquartile range (IQR)).

4. Results

Case details are shown in Table 1.[14–43] The ages of affected individuals ranged from neonate (<4 weeks old) to 82 years old,