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# Multidrug-Resistant *Enterococcus Faecium* Meningitis in a Toddler:

## Characterization of the Organism and Successful Treatment with Intraventricular Daptomycin and Intravenous Tigecycline

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## Abstract

A case of enterococcal meningitis in a toddler is presented. The organism was highly resistant to all drugs previously used for pediatric Gram-positive meningitis. She was successfully treated with intraventricular and intravenous daptomycin and intravenous tigecycline. The organism was characterized as a member of CC17, a notorious emerging nosocomial clone of *Enterococcus faecium.*

### Keywords

vancomycin-resistant *Enterococcus*; tigecycline; daptomycin; meningitis; children

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A21-month-old girl received an HLA-matched, haploidentical peripheral blood stem cell transplant with natural killer cell add-back for treatment of refractory acute bilineage leukemia. She received intense myelosuppression with a total of 14 daily doses of OKT3 (muromonab). On the third post-transplant day, she developed fever. Peripheral blood culture obtained via central venous catheter (CVC) had growth *of Enterococcus faecium* resistant to vancomycin (Table 1, isolate 1). Vancomycin-resistant enterococci (VRE) had been recovered from her stool on routine surveillance one month earlier. Linezolid was administered intravenously in a dosage of 10 mg/kg every 8 hours, but fever persisted and blood cultures showed growth of *E. faecium*, even after removal of the CVC 4 days after starting antimicrobial therapy. Daptomycin (4 mg/kg every 12 hours) was added to the regimen 6 days after linezolid therapy was initiated. Antibiotic susceptibility testing of the organism was repeated and had not changed since Day 0 (Table 1, isolate 2).

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When peripheral blood cultures demonstrated continued growth of VRE, an echocardiogram was obtained, ten days after start of antimicrobial therapy. The study identified echogenic linear foci in the innominate vein, likely representing sheath thrombi from the previously removed CVC. An intravenous heparin drip was initiated to prevent extension of the thrombus. After 20 days of therapy with Linezolid, 14 days with daptomycin, and 7 days with heparin, blood cultures were sterilized, with the last positive blood culture having been obtained 20 days after the first (Table 1, isolate 3). A repeat echocardiogram showed the innominate vein thrombi to be smaller.

Despite sterile blood cultures, the patient continued to have fevers and developed emesis. Eight days after the last positive blood culture, she developed acute mental status changes. When computed tomography of the head showed acute hydrocephalus, an external ventriculostomy drain (EVD) was emergently placed. Microscopic examination of cerebrospinal fluid (CSF) revealed Gram-positive cocci, and culture subsequently demonstrated growth of *E. faecium* (Table 1, isolate 4). When antimicrobial susceptibility testing revealed that the CSF isolate was resistant to Linezolid, this drug was discontinued. Other antibiotic options were limited. Because of the poor penetration of systemic daptomycin into the CSF,[1] the risks and benefits of direct intraventricular daptomycin therapy via ventriculostomy were discussed with the family, who agreed to proceed with this therapy.

On the basis of a previous report of intraventricular daptomycin use in an adult,[2] daptomycin 2.5 mg in 5 mL normal saline was administered via ventriculostomy tubing every 24 hours, locked for 30 minutes, and then reopened to continue CSF drainage. To reduce the risk of chemical meningitis due to direct instillation of the antimicrobial, we initiated intravenous dexamethasone, 1 mg every 6 hours for 5 days, on day 2 of intraventricular daptomycin. No clinical signs of increased central nervous system irritation (such as increased emesis or irritability) were observed, nor were increases in CSF pleocytosis or protein noted on daily monitoring. Peak and trough concentrations of daptomycin measured in CSF specimens from the EVD at the end of the intraventricular infusion and 30 minutes before the next dose were 24.44 and 2.97 mg/L, respectively. The measurements were obtained at the Center for Anti-Infective Research and Development (Hartford, CT), using high-performance liquid chromatography (HPLC).

Gram stain and culture of the CSF remained positive during the first 3 days of intraventricular therapy. The only remaining agent to which the isolate was susceptible was tigecycline. Based on standard adult dosing and a report of a mean site-to-serum area under the concentration-time curve (AUC) ratio of 0.11 for tigecycline in CSF of patients with noninflamed meninges,[3] a loading dose of 3 mg/kg i.v. was extrapolated, with maintenance dosing of 2 mg/kg i.v. every 8 hours to maximize CSF penetration. Two days after tigecycline was added, the patient's CSF sterilized. Platelet and white blood cell counts were monitored daily and remained at baseline. Mildly elevated hepatic transaminases developed on treatment day 8 of tigecycline, but the patient was receiving concomitant hepatotoxic drugs. Serum tigecycline concentrations were measured by HPLC at 0.75, 4, and 7 hours after the half-hour drug infusion, and an AUC of 8.7 mg h/L for an 8-hour dosing interval was calculated using the trapezoidal method. Tigecycline concentrations in CSF collected

from the EVD at 0.75 and 4 hours postinfusion were below the detectable level of 0.05 mg/L.

Intraventicular daptomycin was continued for 7 days after the date of the first negative CSF culture, although the dosage was decreased to 2 mg every 24 hours for 2 days before stopping, to minimize the risk of toxicity. Tigecycline was given for a total of 14 days. A ventriculoperitoneal shunt was placed after 10 days of sterile CSF cultures. Parenteral daptomycin was continued for 6 weeks after the first sterile blood culture due to the thrombotic nidus of infection. The patient returned to her baseline neurologic functioning.

To determine the phylogenetic background and confirm the clonality of the VRE isolates, multilocus sequence typing was performed as previously described.[4] According to the publicly available multilocus sequence typing database (http://efaecium.mlst.net/), all of the tested clinical isolates belonged to ST412, which is a member of the epidemic clonal complex 17 (CC17). CC17 is now widely recognized as a hospital-adapted *E. faecium* subpopulation,[5] and member strains typically carry multiple virulence-associated traits.

## Discussion

We believe that this is the first reported case of pediatric meningitis successfully treated with intraventricular daptomycin. It is also the first report of tigecycline use in a toddler. While use of these agents in combination precludes crediting one or the other with the predominant curative role, both were well tolerated, and the patient's CSF was successfully sterilized of this highly-resistant isolate, with no evidence of recurrence at 3 months of follow-up.

Vancomycin-resistant *E. faecium* is an emerging pathogen for hospitalized and immunocompromised patients. Most enterococci have intrinsic resistance to multiple classes of antimicrobial agents, including cephalosporins and semisynthetic penicillinase-resistant penicillins (eg, oxacillin), as well as to clinically achievable serum concentrations of aminoglycosides. The toxicity of chloramphenicol has proscribed its use in most industrialized countries. Therefore, until recently, antimicrobial therapy for the treatment of VRE was limited. Although more options have become available with the approval of novel antimicrobial agents, there is usually a delay in approval of such agents for use in children. Linezolid was approved by the Food and Drug Administration for use in children in 2002,[6] but as of this writing, daptomycin has not been so approved, although a clinical trial is underway (available at: http://clinicaltrials.gov/ct2/show/NCT00136292). Tigecycline is a treatment option for adults with serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or VRE. Pharmacokinetic data from the manufacturer indicate that a dose of 1 mg/kg every 12 hours in pediatric patients 8 years of age and older provides an AUC that is comparable to that for standard adult dosing (Wyeth Laboratory). No data are available on the safety of this drug in pediatrics, as use of the related agent tetracycline in children less than 8 years of age has the potential risk of tooth discoloration. Daptomycin has been used for children with MRSA and VRE infections in situations where few alternatives exist. In a retrospective review of children with VRE or MRSA infections

(median age, 6.5 years), doses of 4 to 6 mg/kg of daptomycin were used as adjunct therapy with successful outcomes.[7]

Options for the treatment of *E. faecium* meningitis in children are further limited, as many of the available drugs do not reach therapeutic CSF concentrations. Linezolid achieves excellent CSF penetration, with a CSF-to-serum ratio of 0.92.[8] Linezolid has been used successfully for central nervous system infections with *E. faecium* in children.[9] The organism isolated from the CSF in this case was resistant to Linezolid. Daptomycin has not been studied for meningitis in humans. In experimental animal meningitis models, CSF penetration is 5% with inflamed meninges.[1] It has been used intraventricularly in one reported case in an adult.[2] At that patient's l dose of 5 mg every 3 days, peak and trough levels from the CSF were 13.9 and 9.9 mg/L. Sterile CSF and survival of infection were achieved. Our patient's CSF drug concentrations were substantially lower, yet still achieved a good outcome.

Although CSF tigecycline was 11% of the serum concentration in healthy adult patients receiving a 100 mg dose,[3] in our case, the intraventricular concentration of tigecycline was below the limit of detection. It is unclear why this was the case given that peripheral blood concentrations were substantial. There are no studies assessing the impact of meningeal inflammation on CSF levels of the drug, but since we obtained the measured CSF sample several days after completion of dexamethasone therapy (and when CSF cultures were sterile), there was unlikely to have been any inflammation of the meninges which could have affected CSF penetration. The AUC calculated from our patient's serum drug concentrations was higher than the mean AUC in the adult study,[3] and what is reported in the drug's package insert for 24 hours after a single loading dose of 100 mg.[10] Nonetheless, doses of 1 mg/kg every 12 hours would be sufficient for patients less than 8 years old in a situation where no other options exist, although it is unclear whether the tigecycline had any therapeutic benefit for our patient's meningitis.

Decrease in enterococcal susceptibility to Linezolid after exposure to this drug has previously been reported[11] to be the result of a single gene mutation. In this report, resistance to quinupristin/dalfopristin, chloramphenicol, and doxycycline also emerged, despite lack of exposure to these agents. CC17, the group to which our isolate belongs, is a notorious emerging hospital-acquired pathogen, with multiple inducible chromosomal and plasmid-located resistance and virulence genes.[5]

This case emphasizes the urgent need for pediatric clinical trials of antibiotics for emerging resistant organisms. It also provides clinical guidance in the use of i.v. tigecycline or intraventricular daptomycin in children where there are no better alternatives.

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## Table 1

**Evolution of the Susceptibilities of the *Enterococcus* Isolates From Blood and CSF**

| Drug | Isolate 1 Blood Day 0 MIC | Isolate 2 Blood Day 7 MIC | Isolate 3 Blood Day 15 MIC | Isolate 4 CSF Day 25 MIC |
|---|---|---|---|---|
| Vancomycin | >256 (R) | >256 (R) | >256 (R) | >256 (R) |
| Chloramphenicol* | S | I | I | R |
| Doxycycline* | S | S | S | R |
| Linezolid* | S | S | S | R |
| Synercid* | S | S | S | R |
| Rifampin* | R | R | R | R |
| Daptomycin | 1 (S) | NT | NT | 2 (S) |
| Tigecycline | NT | 0.25 (NI) | 0.05 (NI) | 0.125 (NI) |

*Susceptibility testing for these antimicrobials were performed using disk diffusion method and therefore MICs are not available.

MIC indicates minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; NT, not tested; CSF, cerebral spinal fluid; NI, no interpretation available.