

## Long-Acting Lipoglycopeptides for Gram-Positive Bacteremia at the End of Life to Facilitate Hospice Care: A Report of 3 Cases

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Administering and monitoring intravenous antimicrobials may cause discomfort in patients at the end of life and delay transition to hospice. We describe 3 patients with terminal cancer with methicillin-resistant *Staphylococcus aureus*, *Streptococcus gallolyticus*, and *Granulicatella adiacens* bacteremia who were managed with the long-acting lipoglycopeptide oritavancin to facilitate discharge to hospice.

**Keywords.** antimicrobials; end-of-life; oritavancin; palliative care.

There are limited data on antimicrobial use in hospice care [1, 2]. Available studies suggest that one-third of advanced cancer patients entering hospice remain on antimicrobials, of which two-thirds receive antimicrobials until the day of death [3–5]. Most antimicrobial use in hospice is intended to treat infection-related symptoms, but only 15% to 37% of patients achieve symptom relief with antimicrobials [4–6]. Furthermore, once patients are initiated on antimicrobials, withdrawing therapy may be difficult [7].

Several factors complicate antimicrobial use in hospice care. First, antimicrobials are inconsistently addressed across states in advance care planning. Second, administering and monitoring intravenous antimicrobials with catheters and blood draws may burden patients in whom the goals of care emphasize comfort. Third, the route of administration may be impacted by hospice facilities as many prohibit intravenous antimicrobials [8]. Additionally, evaluating infection may be challenging as fever and leukocytosis may be absent or due to alternative causes and symptom assessment may be limited by cognitive impairment or delirium.

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Finally, the indication for antimicrobials may be ill defined. For many functional and cognitively intact patients, antimicrobials may be prescribed empirically though occasionally inappropriately (eg, asymptomatic bacteriuria). For obtunded patients, even with documented infection, intravenous antimicrobials may be inappropriate as they may impede transition to hospice. However, select patients may nevertheless benefit from antimicrobials. Managing infection in such patients without oral therapeutic alternatives may be challenging as continued intravenous antimicrobial therapy may delay transition to hospice. We report 3 cases of Gram-positive bacteremia managed with the long-acting lipoglycopeptide oritavancin to facilitate timely transition to hospice care.

### CASE REPORT 1

A 64 year-old gentleman with poorly controlled diabetes and previously treated hepatitis C virus infection was admitted with fatigue, anorexia, and unintentional 20-pound weight loss. His initial exam was notable for a cachectic appearance and I/VI systolic ejection murmur. Laboratory data revealed an elevated alkaline phosphatase with mild transaminitis and serum alpha fetoprotein of >200 000 ng/mL. A presumptive diagnosis of metastatic hepatocellular carcinoma was made in the setting of an occlusive portal vein thrombus, multifocal hepatic lesions, and extensive destructive lesions of the thoracic spine noted on imaging. On hospital day 7, he developed a new fever secondary to methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. Tagged white blood cell scan revealed uptake in the lungs only, and the patient declined transesophageal echocardiogram. Despite therapeutic levels of vancomycin, the patient remained bacteremic for 7 days, and his course was complicated by acute kidney injury. His bacteremia ultimately cleared following the administration of telavancin, after which the patient opted to pursue hospice care. As hospice placement was precluded by the cost of telavancin, and further nonanalgesic intravenous medications were discordant with goals of care, he received a single dose of oritavancin, which has been shown to be active against MRSA (minimum inhibitory concentration [MIC] 50 of 0.003 µg/mL) [9]. Following oritavancin administration on the day of discharge to hospice, he experienced continued pain requiring increasing patient-controlled analgesia without fever recurrence. The patient died 15 days after receiving oritavancin.

### CASE REPORT 2

A 72 year-old lady with non-small cell lung cancer, initially treated with right lower lobe lobectomy and radiation therapy, with recurrence to the left deltoid and right chest wall who was

actively receiving palliative radiation therapy was admitted with confusion and acute-onset dyspnea. Physical exam was notable for tachycardia, hypoxia with 72% oxygen saturation on room air, diffuse wheezing, and a large, nontender mass on the right chest wall. Chest computed tomography revealed a 11 × 10-cm right anterior chest wall necrotic mass with invasion of the right pectoral muscle with left upper lobe pulmonary emboli. She developed a fever on hospital day 3 and was found to have penicillin-intermediate *Streptococcus gallolyticus* bacteremia. Transthoracic echocardiogram findings were limited by patient delirium with motion artifact. Her bacteremia cleared after 3 days of ceftriaxone therapy. Following family discussions, she opted to pursue hospice care. At that time, the patient had received 2 weeks of a planned 6-week course of antimicrobial therapy. Due to intermediate penicillin resistance, she was given 1 dose of oritavancin, which has activity against *S. bovis* (MIC 50 of 0.03 mg/mL) [10] to facilitate discharge to hospice. Following oritavancin administration, she was treated symptomatically with hydromorphone and lorazepam and remained afebrile. She died in hospice care 2 weeks after receiving oritavancin.

### CASE REPORT 3

A 69 year-old lady with stage IV non-small cell lung cancer with brain metastases treated with left lower lobe lobectomy following neoadjuvant chemotherapy with radiation gamma knife therapy was admitted with confusion, malaise, and falls. Initial physical exam revealed temporal wasting, II/VI ejection murmur, and diffuse upper and lower extremity weakness. She was unable to follow commands. Brain magnetic resonance imaging revealed interval progression of a right occipital lobe mass and left lateral ventricle mass involving the choroid plexus with large adjacent edema. Subsequently, she developed fever and hypotension and was found to have *Granulicatella adiacens* bacteremia. She was started on vancomycin, and surveillance blood cultures were negative. Transthoracic echocardiogram revealed no valvular vegetations. To accommodate the patient's desire to treat infection and promote comfort without prolonged antimicrobials, a single dose of oritavancin was administered that has activity against viridans group *Streptococci* (MIC 50 of 0.008 mg/mL) [10], from which Clinical and Laboratory Standards Institute interpretative criteria for *Granulicatella* are derived. Following oritavancin administration, she was discharged home with hospice care and remained alert without recurrent falls. She died 5 weeks after receipt of oritavancin.

### DISCUSSION

We present 3 patients with advanced cancer and Gram-positive bacteremia who were managed with a long-acting lipoglycopeptide at the end of life to overcome the challenges associated with standard intravenous antimicrobials. Intravenous antimicrobials confer risks of phlebitis, skin and soft tissue infection,

and bacteremia with central line devices. Peripheral catheters may also cause pain and necessitate mechanical restraints, particularly in patients with difficulty tolerating oral medications. In hospice patients, these risks associated with intravenous antimicrobials may conflict with the stated goals of comfort.

Consensus recommendations are lacking for antimicrobial use at the end of life. Infectious Diseases Society of America guidelines suggest that antimicrobial stewardship programs should provide support to clinicians in decisions related to antimicrobial use [11]. Patients with advanced cancer may represent an emerging population for stewardship intervention given that antimicrobial use may be driven by the high prevalence of noninfectious fever caused by neoplasm, thrombus, or medication and the desire to provide symptom relief. Additionally, continued intravenous antimicrobial therapy may delay timely transition to hospice care.

The use of long-acting lipoglycopeptides at the end of life may appeal to hospice patients. Oritavancin has been shown to be effective in the treatment of serious infections with Gram-positive bacteria including *Staphylococcus aureus* and *Enterococcus* spp [12]. With a terminal half-life of 393 hours, oritavancin can be administered as a single-dose regimen with therapeutic levels up to 4 weeks, which precludes the need for repeated intravenous doses [12]. Moreover, dose adjustment is frequently unnecessary by virtue of its clearance by the reticuloendothelial system rather than the kidney or liver. This agent has already been described in the treatment of a variety of Gram-positive bacteremias [13].

In the context of end-of-life care, oritavancin may confer many benefits. Repeated dosing or drug monitoring with blood tests is unnecessary. Continued hospitalization for intravenous antimicrobials becomes preventable, thereby facilitating timely transition to hospice care. Patients and families may feel reassured that infection is still being treated without the associated discomfort of intravenous injections. Collectively, this intervention may be desirable to patients and families. Although its wholesale price is high, oritavancin may reduce the length of inpatient care. Future studies should consider quantifying clinical outcomes including patient comfort and length of stay following administration of oritavancin versus usual care for the management of invasive Gram-positive infections at the end of life.

Other long-acting antimicrobials have also been described for the management of invasive Gram-positive infections. Dalbavancin is a lipoglycopeptide with a long half-life of 9–12 days. Dosing intervals of 1 week have been proposed to maintain minimum inhibitory concentrations above bactericidal concentrations for target pathogens. Dalbavancin has been used effectively in the treatment of catheter-related bloodstream infections [14]. Recent data also suggest that dalbavancin can be used in the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia secondary to septic phlebitis [15]. The pharmacokinetic properties of oritavancin and dalbavancin, as well as their broad spectrum of

**Table 1. Select Antibiotics Conducive to Palliative Infection Management at the End of Life**

Antimicrobial	Spectrum of Activity	Dosing	Half-Life, h	Dose Adjustment for Renal Dysfunction
Oritavancin [12]	Gram-positive organisms	1200 mg IV × 1	393	No
Dalbavancin [16]	Gram-positive organisms	1500 mg IV × 1	204	CrCl < 30 mL/min: 1125 mg IV × 1 No dose adjustments in hemodialysis
Gentamicin [17]	Gram-negative organisms	5–7 mg/kg IV every 24–72 h <sup>a</sup>	2–4	CrCl 40–59 mL/min: 7 mg/kg every 36 h CrCl 20–39 mL/min: 7 mg/kg every 48 h CrCl < 20 mL/min: 2 mg/kg × 1, re-dose per levels
Ertapenem [18]	Gram-negative, Gram-positive, and anaerobic organisms	1000 mg IV/IM <sup>b</sup> every 24 h	4	CrCl < 30 mL/min: 500 mg every 24 h
Ceftriaxone [19]	Gram-positive and Gram-negative organisms	1000 mg IV/IM <sup>b</sup> every 24 h	6–9	No

Abbreviations: CrCl, creatinine clearance; IM, intramuscular; IV, intravenous.

<sup>a</sup>Dependent on creatinine clearance (mL/min).

<sup>b</sup>Reconstitute with 1% lidocaine, per package insert.

activity, are conducive to the palliative management of infections at the end of life. Table 1 shows additional antimicrobials conducive to infection management at the end of life.

In summary, we provide cases of infection management at the end of life that attempt to merge best practices from infectious diseases and palliative care through the use of a long-acting lipoglycopeptide oritavancin. Long-acting lipoglycopeptides have broad Gram-positive coverage, avoid the risks and discomfort associated with repeated intravenous dosing and drug monitoring, and offer therapeutic benefit in patients unable to tolerate oral antimicrobials. These agents may circumvent potential limitations introduced by hospice agencies precluding intravenous antimicrobials and address the desire of patients to treat infection at the end of life. When antimicrobial therapy is indicated per goals-of-care discussions for hospice-eligible patients without oral alternatives, clinicians should consider the utility of long-acting lipoglycopeptides to facilitate transition to hospice.

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**Informed consent.** Given that these patients are deceased and their information has been de-identified, informed consent was not required as per the Yale Human Investigations Committee.

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