Burden and Management of Multidrug-Resistant Organisms in Palliative Care

Rupak Datta and Manisha Juthani-Mehta

Section of Infectious Diseases, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA.

ABSTRACT: Palliative care includes comprehensive strategies to optimize quality of life for patients and families confronting terminal illness. Infections are a common complication in terminal illness, and infections due to multidrug-resistant organisms (MDROs) are particularly challenging to manage in palliative care. Limited data suggest that palliative care patients often harbor MDRO. When MDROs are present, distinguishing colonization from infection is challenging due to cognitive impairment or metastatic disease limiting symptom assessment and the lack of common signs of infection. Multidrug-resistant organisms also add psychological burden through infection prevention measures including patient isolation and contact precautions which conflict with the goals of palliation. Moreover, if antimicrobial therapy is indicated per goals of care discussions, available treatment options are often limited, invasive, expensive, or associated with adverse effects that burden patients and families. These issues raise important ethical considerations for managing and containing MDROs in the palliative care setting.

KEYWORDS: MDRO, palliative care, antimicrobial therapy

Palliative Care

According to the World Health Organization, palliative care refers to a comprehensive approach to enhance quality of life for patients and families facing advanced disease.1 Key aspects of palliative care include an emphasis on symptom relief and the use of interdisciplinary support systems to address the physical, emotional, and spiritual needs of patients and families coping with disease and death. Importantly, palliative care may be offered in conjunction with curative therapies. Within the spectrum of palliative care lies hospice care. Hospice care refers to the subset of palliative care that provides multidimensional care for patients with expected survival less than 6 months and their families.2 Hospice care includes bereavement services in addition to symptom management.

Infection Management

One major challenge in palliative care is infection management. Suspected infections are a common complication in palliative care. Studies suggest that bacterial infection occurs in more than one-third of patients with advanced cancer or terminal illness and are associated with significant mortality.3-5 It is unclear whether treatment of these infections with antimicrobials provides symptomatic relief.5-10 The complexities of managing infection in the palliative care setting have been increasingly recognized.11,12 Importantly, multidrug-resistant organisms (MDROs) further complicate infection management in palliative care. Multidrug-resistant organisms refer to organisms resistant to one or more classes of antimicrobials, and these bacteria are often resistant to most available antimicrobial agents.13,14 Clinically significant MDRO include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β-lactamase (ESBL) producing gram-negative bacilli such as Escherichia coli and Klebsiella pneumoniae.14 These pathogens are highly transmissible, cause invasive disease, and are associated with increased morbidity and mortality.14-17

Distinguishing colonization from infection

With respect to MDRO management, the distinction between colonization and infection is critical. For example, MRSA or VRE detected from nonsterile sites such as wound or sputum specimens may represent colonization that do not warrant antimicrobial therapy. Similarly, ESBL-producing K. pneumoniae or E. coli isolated from the urine may signify asymptomatic bacteriuria rather than symptomatic urinary tract infection. For MDROs, in particular, differentiating colonization from infection is imperative as antimicrobial therapy for MDRO infections may be invasive, expensive, associated with adverse effects, and ultimately incompatible with goals of care.

Nevertheless, distinguishing colonization from infection is challenging. Common signs of infection such as fever and leukocytosis may be absent.18 When present, these markers may be attributable to alternative causes such as neoplastic fever, thrombus, and drug-induced fever. Noninfectious causes of fever are frequent in palliative care populations due to the high prevalence of hematologic malignancies and metastatic tumors. An additional diagnostic challenge is symptom assessment. Cognitive impairment is common in patients with dementia and terminal cancer.19,20 As a result, accurate assessments of colonization versus infection are impeded by decreased verbalization of symptoms and difficulty in symptom recognition.
symptoms. In patients with cognitive impairment, the use of objective parameters alone for diagnosis may additionally cause harm. For example, in patients unable to express symptoms, the use of bacteriuria and pyuria as the sole criteria for diagnosis of urinary tract infection leads to overtreatment of asymptomatic bacteriuria.21,22

Burden of MDROs

Methicillin-resistant Staphylococcus aureus

There are limited data regarding MDRO colonization rates in palliative care settings. Most published studies have focused on MRSA. In palliative care units, MRSA prevalence has been shown to range from 9% to 12%,23,24 These estimates appear stable across geographic locales, with comparable findings reported in both Europe and Saudi Arabia.25 In hospice units, MRSA prevalence may be lower with reports suggesting that 4% to 8% of patients harbor MRSA.26,27

Of note, the burden of MRSA among hospitalized patients and nursing home residents appears greater than the burden of MRSA among patients receiving palliative care. For example, 20% of intensive care unit (ICU) patients and up to 50% nursing home residents carry MRSA.28-31 This discrepancy in MRSA burden may be due to selection bias in palliative care studies whereby participation is limited due to death or patient preference. For example, only 79% of eligible patients were screened for MRSA in one palliative care study, and frailty and patient refusal were barriers to screening in another study.25,27 An additional factor may be the lack of active surveillance for MRSA in end-of-life care settings. The ICU patients and nursing home residents who transition to hospice have higher documented rates of MRSA colonization (20%-50%) as compared with palliative care and hospice patients (4%-12%).25,26,28,31

Vancomycin-resistant enterococci

In contrast to MRSA, the burden of VRE in patients receiving palliative care has not been examined. Some reports of VRE prevalence have even preferentially excluded palliative care patients from study participation.22 Nevertheless, a high burden can be inferred on the basis of known risk factors for VRE colonization. For example, the most significant risk factors for VRE colonization and infection include the presence of solid tumors, hematologic malignancies, solid organ transplants, and prolonged length of stay.33-35 Other common risk factors include advanced age, dialysis, bedsores, and extended exposure to antimicrobial therapy.36 Given that palliative care populations share many of these clinical features, VRE prevalence may be as high as 10% to 33%.34,37,38

ESBL-producing gram-negative bacilli

Similar to VRE, there is also a paucity of data regarding the burden of ESBL-producing gram-negative bacilli in the palliative care setting. In one study of deceased palliative care patients, among the subset of 79 patients treated with antimicrobials, only 41 patients had positive microbiological cultures, of which 2 revealed ESBL-producing E. coli.39 Nevertheless, it is well known that nursing home residents and ICU patients frequently harbor ESBL-producing gram-negative organisms. Approximately 20% of nursing home residents have been shown to be colonized with ESBL-producing Enterobacteriaceae.40,41 In ICUs, similar estimates have been reported.42 Although these limited data preclude broad generalizations, it may not be unreasonable to estimate the prevalence of ESBL-producing gram-negative bacilli in palliative care settings to be on the order of 15% to 20%.

Differential burden of MDRO infection

It is well known that MDRO infections are associated with significant morbidity and mortality. The differential burden of MDRO with respect to mortality is most apparent with endovascular infections. A meta-analysis of 31 cohort studies showed that MRSA bacteremia is associated with significantly higher mortality than methicillin-sensitive S. aureus bacteremia.43 More recently, a meta-analysis of 13 cohort and case-control studies indicates that VRE bacteremia confers markedly increased risks of in-hospital mortality when compared with vancomycin-sensitive Enterococcus bacteremia.44 Similarly, for bacteremia due to ESBL-producing gram-negative organisms, evidence suggests that ESBL production is associated with higher attributable mortality among E. coli, Klebsiella, and Proteus species.45 In the palliative care setting, the increased risk of mortality attributable to MDRO infection has important implications for goals of care with respect to antimicrobial therapy.

Psychological burden

MDRO colonization has been shown to have an adverse psychological impact on palliative care patients, family members, and caregivers. This stems from the need for infection prevention strategies to reduce the transmission of MDROs within health care facilities. Importantly, the implementation of infection prevention interventions, such as patient isolation and contact precautions, is discordant with the principles of palliative care. Previous data highlighted the distress and dysphoria experienced by family members and patients, respectively, as a result of MRSA isolation precautions.26 More recent data from a qualitative survey revealed the effects of MRSA and multidrug-resistant gram-negative bacteria colonization on family caregivers.46 Among 62 caregivers of 52 patients at the end of life, an MDRO diagnosis was associated with feelings of dismay, grief, and sorrow.46 Contact precautions and isolation measures were additionally associated with astonishment and uncertainty among caregivers and shown to Complicate the bereavement process among family members.46
Despite the adverse impact on comfort and quality of life, the use of isolation precautions for MDROs may be widespread in palliative care settings. An inpatient survey of all palliative care units and hospices in Germany revealed that more than 90% of responding institutions employed MRSA containment protocols. In this study, palliative care units more frequently isolated MRSA patients and restricted patients’ activities when compared with hospice facilities.47 More recently, there has been a shift away from contact precautions. A growing body of evidence has highlighted the unintended and adverse effects of contact precautions across all hospitalized patients.48–52 One large study involving survey, literature review, and hospital data found no high-quality evidence supporting the use of contact precautions for endemic MDROs.53 These findings have led some authors to argue for the removal of legal mandates for contact precautions for MRSA and VRE.54 Based on these data and the focus of palliative care, infection prevention groups should consider the removal of contact precautions from palliative care settings all together.

**Risks of diagnostic testing and antimicrobial therapy**

The decision to initiate antimicrobial therapy for MDROs in the palliative care setting is often complicated by the collection and interpretation of diagnostic data. For example, in the presence of fever, empiric antimicrobials are often administered pending further evaluation with diagnostic testing. However, this approach may not be applicable to patients at the end of life whose goal is palliation, and diagnostic data are often difficult to obtain and interpret. Blood and sputum cultures may be contraindicated by patient preferences and stated goals of comfort. Viral polymerase chain reaction studies may be overly expensive. Urine cultures are perhaps the most frequently collected microbiological specimen. Yet, positive urine cultures may represent asymptomatic bacteriuria rather than infection. Consequently, provider and family members are often left with uncertainty regarding the most appropriate next step in management.
Recently, there has been increasing recognition regarding the importance of diagnostic stewardship, an interdisciplinary approach by which infection management is improved through a modified process of ordering, performing and reporting diagnostic tests. This concept emerged from the desire to improve clinical care and reduce overdiagnosis and unnecessary testing. In the palliative care setting, diagnostic stewardship is particularly relevant to the focus on comfort. Clinicians should incorporate the principles of diagnostic stewardship into palliative care decision making and be prepared to address findings from diagnostic testing. Oftentimes, it may be more appropriate to avoid sending microbiological specimens all together and instead revisit goals of care with patients and family members.

When diagnostic testing reveals an MDRO infection rather than colonization, and antimicrobial therapy is indicated per goals of care discussions, parenteral or combination therapy is often required. Limited treatment options are available for multidrug-resistant gram-negative infections, particularly carbapenem-resistant Enterobacteriaceae (CRE). Most evidence supports the use of combination therapy with agents such as tigecycline, polymyxins, and aminoglycosides in addition to a carbapenem for CRE infections. However, these agents are not benign. For example, a substantial fraction of patients receiving tigecycline experience nausea, and colistin has been associated with renal insufficiency and neurotoxicity. These common side effects are discordant with the goals of improving comfort and quality of life in the palliative care setting.

In addition to the adverse effects associated with antimicrobials for CRE, their administration is also burdensome. For example, current regimens for multidrug-resistant gram-negative infections include antimicrobials such as ceftazidime-avibactam 2.5 g intravenous every 8 hours, cefotolozene-tazobactam 1.5 g intravenous every 8 hours, and polymyxin B 1.25 mg/kg intravenous every 12 hours. Such frequent dosing regimens may be taxing for both patients and caregivers in palliative care settings. Other agents that require loading doses, such as tigecycline (100 mg intravenous loading dose followed by 50 mg intravenous every 12 hours thereafter), are also onerous.

Similar to CRE, therapeutic options for VRE are challenging. Typical agents include linezolid and daptomycin. However, the former is associated with peripheral and ocular neuropathy as well as hematologic abnormalities that may require transfusion support. Another complication of linezolid is the potential development of serotonin syndrome when administered with serotonin agonists. This syndrome is characterized by mental status changes, autonomic hyperactivity, and neuromuscular abnormalities and may be lethal. Given that serotonin agonists are widely used in palliative care, this drug interaction should be considered carefully prior to linezolid use. Similar to linezolid, daptomycin also has important drug toxicities that are relevant to palliative care patients. The most pertinent adverse effects are myopathy and rhabdomyolysis. Monitoring for these toxicities requires routine diagnostic testing, which may cause further discomfort.

Beyond antimicrobial-specific adverse effects and drug interactions, there are additional considerations related to antimicrobials, in general, and the route of drug administration, in particular. Clostridium difficile infection is a well-known complication of antimicrobial therapy and accounts for approximately 25% of cases of antibiotic-associated diarrhea. With respect to the route of drug administration, parenteral antimicrobials confer risks of infectious and noninfectious complications. These include phlebitis, local skin and soft tissue infections, secondary bacteremia, hematoma, thrombosis, and air embolism. The insertion of central or peripheral venous access catheters may also cause pain and require mechanical restraints in patients with delirium or dementia. These outcomes directly conflict with the goals of palliation.

Impact of palliative care setting

Although MDROs frequently require parenteral therapy, the route of antimicrobial delivery may be affected by the palliative care setting. Data suggest that there is marked variability in route of antimicrobial administration among palliative care patients managed at acute care hospitals, tertiary palliative care units, and hospice centers. In a retrospective study of 150 patients observed across 3 different palliative care settings, parenteral antimicrobials were most frequently used in the acute and tertiary care settings, whereas oral antimicrobials were primarily used in the hospice setting. The route of medication delivery may also be affected by time from death. In one retrospective study of 208 patients at a Dutch palliative care center, 89% of prescription medications on admission were administered orally and 94% of medications on the day of death were administered via the subcutaneous route. These data suggest that the method of MDRO management may be dictated by the site of palliative care.

Ethical considerations

In the palliative care setting, it is important to ascertain whether antimicrobial therapy promotes comfort or prolongs suffering. This determination is particularly important in the context of MDRO management given the public health implications of treatment with last-line antimicrobials and MDRO transmission within a population. According to one review, the decision to give or withhold antimicrobials should be based on the principles of autonomy, beneficence, nonmaleficence, and justice. However, autonomy in the palliative care setting is undermined by the high prevalence of cognitive impairment. This point highlights the need for advance care planning and family member involvement. Yet, antimicrobial use is rarely discussed in advance care planning, and the optimal time over the course of clinical illness to discuss infection treatment and the appropriateness of oral versus parenteral agents remains unclear.
The principles of beneficence and nonmaleficence invoke the role of physicians to provide unbiased and understandable information regarding the risks and benefits of antimicrobial therapy. For MDRO infection, these risks are significant and include the potential for antimicrobial-associated diarrhea and drug toxicities, the discomfort associated with parenteral therapy, the improbability of cure, and the unclear impact on symptom relief. In addition, fairness and equality raise the difficult issue of balancing the rights of the individual palliative care patient against the rights of others. For example, the benefit of last-line or combination antimicrobial therapies in the individual palliative care patient must be weighed against the risk of breeding further antimicrobial resistance in a population.

Finally, social justice and stewardship of community resources warrant careful evaluation of the need for antimicrobial therapy for MDROs. Specifically, the administration of costly antimicrobial agents for MDROs, which are known to be significantly more costly than antimicrobial agents for non-MDROs, should be considered in palliative care patients with limited life expectancy in the setting of limited health care resources. In many cases, continuation of resource-intensive intravenous antimicrobials is a barrier to hospice care transition. Although oral alternatives may be considered in lieu of intravenous antimicrobials, these agents may lack therapeutic efficacy for MDROs. Long-acting lipoglycopeptides such as oritavancin represent one appealing alternative. This agent has a terminal half-life of 393 hours and broad spectrum of activity against multidrug-resistant gram-positive bacteria including MRSA and VRE. Although costly, this antimicrobial can be administered via one dose with therapeutic levels up to 4 weeks precluding the need for further medication administration or monitoring in the hospice setting. This single-dose regimen may facilitate transition to hospice and reassure patients and families that infection is still being treated without the discomfort of repeated intravenous injections.

Conclusions
Management of MDROs represents a major challenge in palliative care. Palliative care patients frequently harbor MDROs resulting in diagnostic and therapeutic challenges for clinicians and caregivers. Antimicrobial therapies and infection prevention methods for MDROs are complex, confer significant physiologic and psychosocial risks, and often conflict with the goals of palliation. The ethical aspects of managing MDROs in palliative care patients are also problematic. Further research is needed to quantify the burden of MDROs in palliative care settings and inform advance care planning interventions for patients and clinicians.

Author Contributions
RD and MJ-M contributed to the writing, interpretation of results, jointly developed the structure and arguments for the review, made critical revisions, and reviewed and approved the final manuscript.

REFERENCES
1. WHO. WHO definition of palliative care. http://www.who.int/cancer/palliative/definition/en/. Accessed September 6, 2017.
2. Hui D, De La Cruz M, Mori M, et al. Concepts and definitions for “supportive care,” “best supportive care,” “palliative care,” and “hospice care” in the published literature, dictionaries, and textbooks. Support Care Cancer. 2013;21:659–685.
3. Homsy J, Walsh D, Panta R, Lagman R, Nelson KA, Longworth DL. Infectious complications of advanced cancer. Support Care Cancer. 2009;17:487–492.
4. Vittert L, Kenner D, Salis A. Bacterial infections in terminally ill hospice patients. J Pain Symptom Manage. 2000;20:326–334.
5. Reinbolt RE, Shenk AM, White PH, Navari RM. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2005;30:183–189.
6. Rosenberg JH, Albrecht JS, Fromme EK, et al. Antimicrobial use for symptom management in patients receiving hospice and palliative care: a systematic review. J Palliat Med. 2013;16:1568–1574.
7. Chen LK, Chou YC, Hsu PS, et al. Antibiotic prescription for fever episodes in hospice patients. Support Care Cancer. 2002;10:338–341.
8. Oh DY, Kim JH, Kim DW, et al. Antibiotic use during the last days of life in cancer patients. Eur J Cancer Care (Engl). 2006;15:74–79.
9. Stiel S, Krumm N, Pestinger M, et al. Antibiotics in palliative medicine—results from a prospective epidemiological investigation from the HOPE survey. Support Care Cancer. 2012;20:325–333.
10. Nakagawa S, Toya Y, Okamoto Y, et al. Can anti-infective drugs improve the infection-related symptoms of patients with cancer during the terminal stages of their lives? J Palliat Med. 2010;13:535–540.
11. Juthani-Mehta M, Malani PN, Mitchell SL. Antimicrobials at the end of life: an opportunity to improve palliative care and infection management. JAMA. 2015;314:2017–2018.
12. Bagban A, Juthani-Mehta M. Antimicrobial use at the end of life. Infect Dis Clin North Am. 2017;31:637–647.
13. Hidron AI, Edwards JR, Patel J, et al; National Healthcare Safety Network Team; Participating National Healthcare Safety Network Facilities. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2014. J Infect Control Hosp Epidemiol. 2015;36:966–1011.
14. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control. 2007;35:165–193.
15. Hanberger H, Walther S, Leone M, et al; EPIC II Group of Investigators. Increased mortality associated with methicillin-resistant Staphylococcus aureus (MRSA) infection in the intensive care unit: results from the EPIC II study. Int J Antimicrob Agents. 2011;38:331–335.
16. Qvi Å, Segal-Maurer S, Mariano N, et al. Increased mortality associated with a clonal outbreak of vancomycin-resistant Klebsiella pneumoniae: a case-control study. Infect Control Hosp Epidemiol. 2005;26:63–68.
17. Song X, Srinivasan A, Plaut D,Perl TM. Effect of nosocomial vancomycin-resistant enterococcal bacteremia on mortality, length of stay, and costs. Infect Control Hosp Epidemiol. 2003;24:251–256.
18. Wasserman M, Levinstein M, Keller E, Lee S, Yoshikawa TT. Utility of fever, white blood cells, and differential count in predicting bacterial infections in the elderly. J Am Geriatr Soc. 1989;37:537–543.
19. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer. 1997;79:835–842.
20. Parsons C, van der Steen JT. Antimicrobial use in patients with dementia: current concerns and future recommendations. CNS Drugs. 2017;31:433–438.
21. Mody L, Juthani-Mehta M. Urinary tract infections in older women: a clinical review. JAMA. 2014;311:844–854.
22. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40:643–654.
23. Schmalz O, Stratatsis T, Alefelder C, Grebe SO. Methicillin-resistant Staphylococcus aureus in palliative care: a prospective study of methicillin-resistant Staphylococcus aureus prevalence in a hospital-based palliative care unit. Palliat Med. 2016;30:703–706.
24. Gleeson A, Larkin P, Walsh C, O’Sullivan N. Methicillin-resistant Staphylococcus aureus: prevalence, incidence, risk factors, and effects on survival of patients in a specialist palliative care unit: a prospective observational study. Palliat Med. 2016;30:374–381.
25. Ghanem HM, Abou-Alia AM, Alisarafy SA. Prevalence of methicillin-resistant Staphylococcus aureus colonization and infection in hospitalized palliative care patients with cancer. Am J Hosp Palliat Care. 2013;30:377–381.
26. Prestince W, Dunlop R, Armes PJ, Cunningham DE, Lucas C, Todd J. Methicillin-resistant Staphylococcus aureus infection in palliative care. Palliat Med. 1998;12:443–449.
33. Patel R. Clinical impact of vancomycin-resistant enterococci. J Antimicrob Chemother. 2003;51:i13-i1121.

34. Ford CD, Lopansri BK, Gazdik MA, et al. The clinical impact of vancomycin-resistant enterococcus colonization in hospital patients. Clin Infect Dis. 2008;46:1368-1373.

35. Reynolds C, Quan V, Kim D, et al. Methicillin-resistant Staphylococcus aureus (MRSA) carriage in 10 nursing homes in Orange County, California. Infect Control Hosp Epidemiol. 2011;32:91-93.

36. Karki S, Houston L, Land G, et al. Prevalence and risk factors for VRE colonization in a tertiary hospital in Melbourne, Australia: a cross sectional study. Antimicrob Resist Infect Control. 2012;1:31.

37. Ford CD, Lopansri BK, Haydoura S, et al. Frequency, risk factors, and outcomes of vancomycin-resistant Enterococcus colonization and infection in patients with newly diagnosed acute leukemia: different patterns in patients with acute myelogenous and acute lymphoblastic leukemia. Infect Control Hosp Epidemiol. 2015;36:47-53.

38. Weinstein JW, Roe M, Towns M, et al. Resistant enterococci: a prospective surveillance program. Triantif Infect Dis. 2015;17:688-694.

39. Helde-Frankling M, Bergqvist J, Bergman P, Björkhem-Bergman L. Antibiotic use in the ICU: a meta-analysis of published studies. PLoS ONE. 2013;8:e57658.

40. Calderwood M, Mauer A, Tolentino J, et al. Epidemiology of vancomycin-resistant enterococcal infections among patients on an adult stem cell transplant unit: observation from an active surveillance program. Infect Control Hosp Epidemiol. 2008;29:1019-1025.

41. Helde-Frankling M, Bergqvist J, Bergman P, Björkhem-Bergman L. Antibiotic treatment in end-of-life cancer patients-a retrospective observational study at a palliative care center in Sweden. Cancer. 2016;8;E84.

42. Razazi K, Derde LP, Verachten M, Legrand P, Lesprit P, Brun-Buisson C. Clinical impact and risk factors for endemic methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus. Infect Control Hosp Epidemiol. 2015;36:1163-1172.

43. Weinstein JW, Roe M, Towns M, et al. Effects of methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus. Infect Control Hosp Epidemiol. 2011;32:91-93.

44. Morgan DJ, Diekema DJ, Sepkowitz K, Perencevich EN. Adverse outcomes associated with contact precautions: a review of the literature. Am J Infect Control. 2009;37:85-93.

45. Morgan DJ, Murthy R, Munoz-Price LS, et al. Reconsidering contact precautions for endemic methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus. Infect Control Hosp Epidemiol. 2015;36:1163-1172.

46. Helm J, Rajagopalan A, Young J, et al. Cost of managing methicillin-resistant Staphylococcus aureus in long-term care facilities (LTCFs): a systematic review and meta-analysis. Int J Antimicrob Agents. 2017;50:649–656.

47. Waage AE, Mårtensson J, Svanström O, Sundzén M. Extended-spectrum β-lactamase-producing Enterobacteriaceae colonization in long-term care facilities (LTCFs): Systematic review and meta-analysis. Int J Antimicrob Agents. 2017;50:649–656.

48. Rafailidis PI, Falagas ME. Options for treating carbapenem-resistant Enterobacteriaceae. Curr Opin Infect Dis. 2014;27:479–483.

49. Feldman RA, Loo VG, Thrall JD, et al. Cost of care associated with health care-associated bloodstream infections due to multidrug-resistant Gram-negative pathogens: a population-based study. Perspect Biol Med. 2015;58:450–455.

50. Falagas ME, Vardakas KZ, Tsiveriotis KP, Triarides NA, Tansarli GS. Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections. Int J Antimicrob Agents. 2013;44:1-7.

51. Lauf L, Ozsvar Z, Mitha I, et al. Phase 3 study comparing tigecycline and erdapin in patients with diabetic foot infections with and without ostoemyelitis. Diag Microbial Infect Dis. 2014;78:460-480.

52. Lim LM, Ly N, Anderson D, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. Pharmacotherapy. 2010;30:1279-1291.

53. Kaye KS, Pogue JM. Infections caused by resistant gram-negative bacteria: epidemiology and management. Pharmacotherapy. 2015;35:949–962.

54. Visn D, Rubinstein E. Linezolid: a review of safety and tolerability. J Infect. 2009;59:59-77.

55. Quinn DK, Stern TA. Linezolid and vancomycin. Prim Care Companion J Clin Psychiatry. 2009;11:353–356.

56. Boyer EW, Shannon M. The vancomycin syndrome. N Engl J Med. 2005;352:1112-1120.

57. Bernard SA, Bruera E. Drug interactions in palliative care. J Clin Oncol. 2000;18:1780–1799.

58. Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. Clin Infect Dis. 2009;49:1351-1357.

59. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. Clin Infect Dis. 2008;46:812–818.

60. Oneschuk D, Fainsinger R, Demoissac D. Antibiotic use in the last week of life in three different palliative care settings. J Palliat Care. 2002;18:25–28.

61. Masman AD, van Dijk M, Tibboel D, Baar PP, Mathôt RA. Medication use during end-of-life care in a palliative care centre. Int J Clin Pharm. 2015;37:767-775.

62. Marcus EL, Clarfield AM, Moses AE. Ethical issues relating to the use of antimicrobial therapy in older adults. Clin Infect Dis. 2000;33:1697-1705.

63. Lacey D. End-of-life decision making for nursing home residents with dementia: a survey of nursing home social services staff. Health Soc Work. 2006;31:189–199.

64. Cartaxo Salgado FX, Carneiro Goncalves J, Monteiro De Souza C, Barbosa Da Silva N, Gavilanes Sanchez TE, Gomes de Oliveira Karnikowski M. Cost of antimicrobial treatment of patients infected with multidrug-resistant organisms in the Intensive Care Unit. Medicina. 2011;71:531–535.

65. Ford PJ, Fraser TG, Davis MP, Kodish E. Anti-infective therapy at end of life: a qualitative study. Palliat Med. 2013;27:84–90.

66. Buik J, Klein J, But L, et al. Methicillin-resistant Staphylococcus aureus (MRSA) management in palliative care units and hospices in Germany: a nationwide survey on patient isolation policies and quality of life. Palliat Med. 2013;27:84–90.

67. Mehrotra P, Croft L, Day HR, et al. Effects of contact precautions on patient perception of care and satisfaction: a prospective cohort study. Infect Control Hosp Epidemiol. 2013;34:1087-1093.

68. Day HR, Perencevich EN, Harris AD, et al. Depression, anxiety, and mood of hospitalized patients under contact precautions. Infect Control Hosp Epidemiol. 2013;34:251-258.

69. Morgan DJ, Pines L, Sharell M, et al. The effect of contact precautions on healthcare worker activity in acute care hospitals. Infect Control Hosp Epidemiol. 2011;32:273-281.

70. Day HR, Perencevich EN, Harris AD, et al. Association between contact precautions and delirium at a tertiary care center. Infect Control Hosp Epidemiol. 2012;33:34–39.

71. Morgan DJ, Diekema DJ, Sepkowitz K, Perencevich EN. Adverse outcomes associated with contact precautions: a review of the literature. Am J Infect Control. 2009;37:85-93.

72. Morgan DJ, Malani P, Diekema DJ. Diagnostic stewardship—leveraging the laboratory to improve antimicrobial use. JAMA. 2017;318:607–608.

73. Izadpanah M, Khalili H. Antibiotic regimes for treatment of infections due to multidrug-resistant Gram-negative pathogens: an evidence-based literature review. J Res Pharm Pract. 2015;4:105-114.

74. Prematunge C, MacDougall C, Johnstone J, et al. VRE and VSE bacteremia in three different palliative care settings. J Pain Symptom Manage. 2009;59:S59–S74.

75. Pelant M, Mühlenkamp I, Musher MD, et al. Use of VRE and VRE: time to retire legal mandates. JAMA. 2017;318:329-330.

76. Bina M, Bozym D, Verheijen J, et al. Cost of care associated with vancomycin-resistant enterococci infections: a systematic review. Curr Infect Dis Rep. 2016;18:379–392.

77. Tice A, Oritavancin: a new opportunity for outpatient therapy of serious infections. Clin Infect Dis. 2012;54:S229–S234.