

# Burden and Management of Multidrug-Resistant Organisms in Palliative Care

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**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

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## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3–5</sup> It is unclear whether treatment of these infections with antimicrobials provides symptomatic relief.<sup>5–10</sup> The complexities of managing infection in the palliative care setting have been increasingly recognized.<sup>11,12</sup> 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.<sup>13,14</sup> Clinically significant MDRO include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant

enterococci (VRE), and extended-spectrum  $\beta$ -lactamase (ESBL) producing gram-negative bacilli such as *Escherichia coli* and *Klebsiella pneumoniae*.<sup>14</sup> These pathogens are highly transmissible, cause invasive disease, and are associated with increased morbidity and mortality.<sup>14–17</sup>

### *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.<sup>18</sup> 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.<sup>19,20</sup> As a result, accurate assessments of colonization versus infection are impeded by decreased verbalization of



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.<sup>21,22</sup>

## 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%.<sup>23,24</sup> These estimates appear stable across geographic locales, with comparable findings reported in both Europe and Saudi Arabia.<sup>25</sup> In hospice units, MRSA prevalence may be lower with reports suggesting that 4% to 8% of patients harbor MRSA.<sup>26,27</sup>

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.<sup>28–31</sup> 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.<sup>25,27</sup> 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%).<sup>25,26,28,31</sup>

### *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.<sup>32</sup> Nevertheless, a high burden can be inferred on the basis on 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.<sup>33–35</sup> Other common risk factors include advanced age, dialysis, bedsores, and extended exposure to antimicrobial therapy.<sup>36</sup> Given that palliative care populations share many of these clinical features, VRE prevalence may be as high as 10% to 33%.<sup>34,37,38</sup>

### *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 cancer

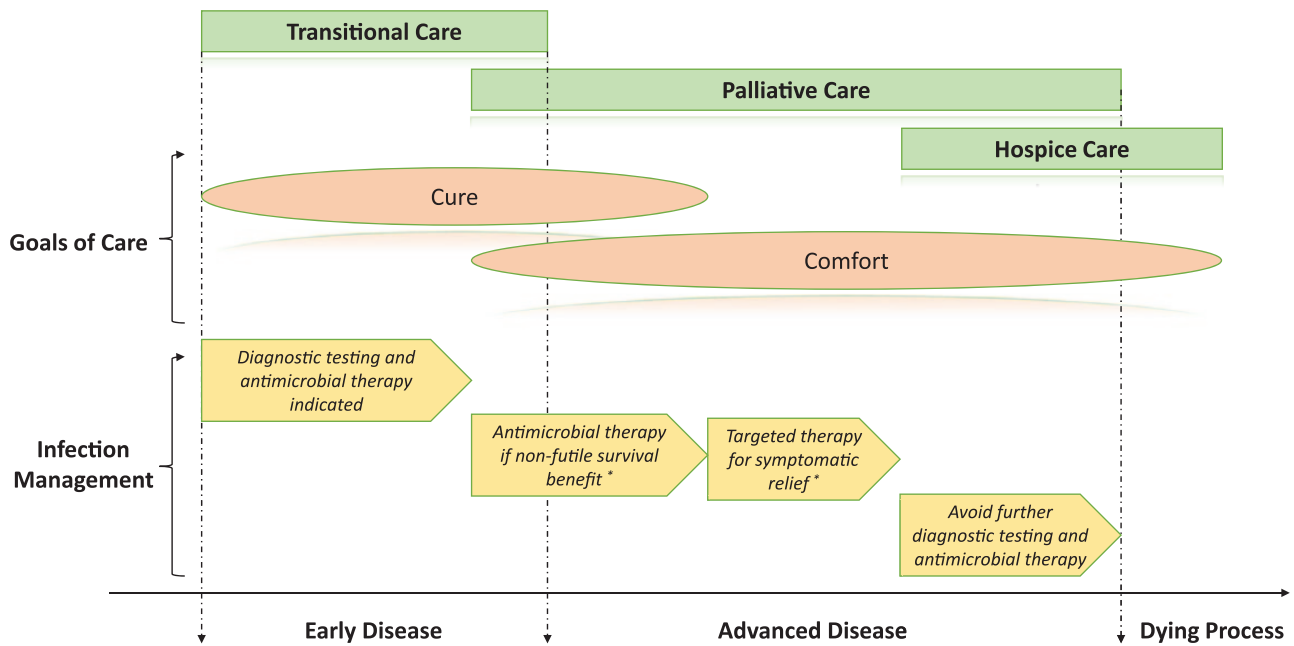
patients, among the subset of 79 patients treated with antimicrobials, only 41 patients had positive microbiological cultures, of which 2 revealed ESBL-producing *E. coli*.<sup>39</sup> Nevertheless, it is well known that nursing home residents and ICU patients frequently harbor ESBL-producing gram-negative organisms. Approximately 20% of nursing home residents have been shown to be colonized with ESBL-producing *Enterobacteriaceae*.<sup>40,41</sup> In ICUs, similar estimates have been reported.<sup>42</sup> 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.<sup>43</sup> 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.<sup>44</sup> 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.<sup>45</sup> 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.<sup>26</sup> More recent data from a qualitative survey revealed the effects of MRSA and multidrug-resistant gram-negative bacteria colonization on family caregivers.<sup>46</sup> Among 62 caregivers of 52 patients at the end of life, an MDRO diagnosis was associated with feelings of dismay, grief, and sorrow.<sup>46</sup> Contact precautions and isolation measures were additionally associated with astonishment and uncertainty among caregivers and shown to complicate the bereavement process among family members.<sup>46</sup>



**Figure 1.** Proposed infection management considerations according to strata of disease progression and goals of care.

\*Antimicrobial therapy may be indicated if perceived benefits outweigh the risks of antimicrobial therapy which include, among others, antibiotic-associated diarrhea, *Clostridium difficile* infection, nausea and vomiting, local skin and soft tissue irritation associated with peripheral intravenous lines, myelosuppression, neurotoxicity, and drug-drug interactions. Adapted from Hui et al.<sup>2</sup>

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.<sup>47</sup>

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.<sup>48–52</sup> One large study involving survey, literature review, and hospital data found no high-quality evidence supporting the use of contact precautions for endemic MDROs.<sup>53</sup> These findings have led some authors to argue for the removal of legal mandates for contact precautions for MRSA and VRE.<sup>54</sup> 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.

## Management of MDROs in Palliative Care

### Goals of care

Management of infection in the palliative care setting must be consistent with patient and family goals of care. Given the spectrum of palliative care that includes both curative therapies and hospice care, antimicrobial therapy may be appropriate when prolongation of life is desired. In contrast, when comfort and quality of life are desired, such as with hospice care,

antimicrobial therapy may be inappropriate or only selectively appropriate for symptom relief (Figure 1). The middle ground between life-prolonging and comfort-achieving interventions is often the most challenging for infection management. The high mortality associated with bacterial infection at the end of life and unclear impact of antimicrobial therapy on symptom relief add further complexity to this issue. Algorithms for antimicrobial use at the end of life have been proposed to guide clinical decision making during this period.<sup>12</sup> Comprehensive patient-centered goals of care discussions with family members, providers, and caregivers remain of utmost importance.

### 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.<sup>55</sup> 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).<sup>56</sup> Most evidence supports the use of combination therapy with agents such as tigecycline, polymyxins, and aminoglycosides in addition to a carbapenem for CRE infections.<sup>56,57</sup> 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.<sup>58–61</sup> 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, ceftolozone-tazobactam 1.5 g intravenous every 8 hours, and polymyxin B 1.25 mg/kg intravenous every 12 hours.<sup>62</sup> 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.<sup>63</sup> Another complication of linezolid is the potential development of serotonin syndrome when administered with serotonin agonists.<sup>64</sup> This syndrome is characterized by mental status changes, autonomic hyperactivity, and neuromuscular abnormalities and may be lethal.<sup>65</sup> Given that serotonin agonists are widely used in palliative care, this drug interaction should be considered carefully prior to linezolid use.<sup>66</sup> 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.<sup>67</sup>

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.<sup>68</sup> 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.<sup>69</sup> 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.<sup>70</sup> 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.<sup>71</sup> 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,<sup>72</sup> 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,<sup>73</sup> 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.<sup>74</sup> 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.<sup>75</sup> 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.

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