

Antimicrobial Use at the End of Life



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KEYWORDS

• Antimicrobials • Antibiotics • End of life • Palliative care

KEY POINTS

- Antimicrobials are overused in the final weeks of life.
- Common goals of antimicrobial use at the end of life are prolongation of survival and relief of symptoms.
- End-of-life patients are a heterogeneous population. Antimicrobials are more likely to achieve specific goals within some subgroups than others.
- Decisions regarding antimicrobial use at the end of life should incorporate the patients' goals and the likelihood of achieving those goals.

INTRODUCTION

Health care providers of patients at the end of life (EOL) have the responsibility of reevaluating an evolving balance between potential benefits and harms of a variety of otherwise common medical interventions. Medicine is failing at this task across many medical specialties. Recent data suggest that 33% to 38% of patients at the EOL receive interventions that they are unlikely to benefit from, and 22.4% to 42% of patients die in the intensive care unit (ICU).^{1,2} These statistics include antimicrobial use, which tends to be one of the last interventions withdrawn or withheld, with 27% to 88% of patients receiving antimicrobials during the final weeks of life.^{3–7} In EOL patients with documentation of a suspected infection, antimicrobials are withheld in a small number of cases.⁸ For example, as many as 92% to 100% of patients with cancer receiving hospice and palliative care are treated with antimicrobials in this setting.⁸ This high rate of antimicrobial use may be because providers view antimicrobials differently from invasive interventions, such as mechanical ventilation and cardiopulmonary resuscitation. Many providers may believe that antimicrobials carry a lower potential for harm.

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Although there is a high utilization of antimicrobials at the EOL, data suggest that much of this use is in the absence of a documented infection. One study found that 15.6% of patients who transitioned to a comfort care protocol remained on antimicrobials, and 31% of those on antimicrobials did not have a documented infectious diagnosis.⁹ Another study found that among hospice patients who received antibiotics in the last 7 days of life, only 15% had a documented infectious diagnosis.³ These high rates of antimicrobial use delineate the importance of clearly defining the goals of these therapies in patients at the EOL. To date, most available data on antimicrobial use at the EOL are retrospective.¹⁰ Not only are prospective studies uncommon but ethical considerations also limit the feasibility of randomized controlled trials.^{11,12} Consensus guidelines were previously unavailable. However, newly published antimicrobial stewardship guidelines by the Infectious Diseases Society of America have broached the subject of antimicrobials at the EOL by suggesting that antimicrobial stewardship programs should provide support to clinicians in decisions related to antibiotic use.¹³

PATIENT POPULATIONS AND POPULATION-SPECIFIC CONSIDERATIONS

For this review, EOL is defined as the final weeks before death. The most commonly studied patient populations are those with advanced dementia, those with advanced malignancies, and those enrolled in hospice programs. Studies in palliative care units and hospice programs often include mixed populations. Because data on antimicrobial use at the EOL are limited, studies from one patient population may guide others. However, it is important to keep patient-specific nuances in mind.

A study by Ahronheim and colleagues⁶ compared management of patients with metastatic solid tumors to those with advanced dementia before their deaths at a tertiary care hospital. These 2 groups of patients had similar rates of nonpalliative invasive treatments (eg, hemodialysis, enteral tube feeding) and cardiopulmonary resuscitation attempts. Patients with cancer were more likely to receive invasive (eg, lumbar puncture, bronchoscopy) and noninvasive (eg, blood work, radiographs) diagnostic testing, much of which was for suspected infection. The overall rate of antibiotic administration in the 2 groups was high at 88%, most of which was empiric, particularly for patients with cancer.

Patients with cancer at the EOL have been found to receive antibiotics more often than advanced dementia patients, frequently in the absence of a documented infection.^{3,14} These results highlight not only overall similarities but also subtle differences in health care providers' approaches to these 2 EOL populations. Some of these differences may reflect the tempo of the underlying disease process. In advanced dementia patients in whom deterioration typically occurs over a longer period of time, patients, families, and providers may alter their approach to medical management decisions by favoring less aggressive measures with each stepwise decline in overall health. In advanced cancer where a more acute deterioration can occur, patients, families, and providers may be attached to the goal for cure or prolongation of life, thereby favoring more aggressive diagnostic and treatment strategies.

Noninfectious fever is an important reason for overuse of antimicrobials and may occur at different rates in patients with malignancies and dementia. When fever occurs without other localizing signs of infection, alternative causes of an elevated temperature such as drug-induced, venous thromboembolism and neoplastic fever should be considered. Although patients both with dementia and with cancer can develop noninfectious fever, this diagnosis is particularly relevant to patients with advanced malignancies. The finding that antimicrobials are used empirically more often in patients

with cancer may be related to the fact that malignancies can be the direct cause of fever, with cancer identified as the underlying cause of fever of unknown origin in 7% to 19% of cases.^{15–18} The incidence of neoplastic fever is increased in patients with hematologic malignancies and metastatic tumors, although it has been described with a wide variety of cancers. Fevers caused by malignancy are associated with fewer symptoms than those resulting from infection,¹⁹ a greater antipyretic response to nonsteroidal anti-inflammatory drugs than acetaminophen,^{19–21} and a low procalcitonin.^{22–24} Typically, neoplastic fever is a diagnosis of exclusion, and empiric antimicrobials are administered while undertaking further evaluation. However, this approach may not be universally appropriate for patients with advanced cancer at the EOL, for whom the primary goal is palliation, particularly if fever is the only sign of potential infection and symptoms are minimal.

For patients with advanced dementia, nursing homes are the most common site of death.²⁵ Consequentially, care of nursing home residents is complicated by close living quarters and the risk of nosocomial infectious outbreaks. Given the progressive cognitive decline present in these patients, many EOL decisions must be made by health care proxies. Decreased verbalization of symptoms presents a barrier to accurate diagnosis of infections in this patient population. For example, using bacteriuria and pyuria as the sole criteria for diagnosis of urinary tract infection in patients who cannot express symptoms leads to overtreatment of asymptomatic bacteriuria.^{26,27}

GOALS OF ANTIMICROBIAL THERAPY

Increased patient survival is a common goal of antimicrobial use. In patients near the EOL, a determination as to whether the goal of prolonged survival is congruent with the overall goals of care should be made. Antimicrobials are unable to alter the natural history of the underlying disease in most patients at the EOL, and hence, this goal of prolonging life should be weighed against the risk of prolonging suffering.²⁸ Furthermore, data regarding prolongation of life with antimicrobial use in the final weeks of life are mixed. One study evaluated survival in patients who chose either “full use” of antimicrobials, to avoid antimicrobials entirely, or to accept antimicrobials only when there were symptoms attributed to an infection. They did not find a survival difference between these groups.²⁹ Another survey of inpatients in a palliative care unit did not find a statistically significant difference in survival for patients with an identified bacterial infection.³⁰ In contrast, prospective data suggest that survival may be increased in EOL patients with pneumonia who receive antimicrobials.¹²

Rather than focusing on extending survival in EOL patients, a goal of palliation is often deemed appropriate by patients and health care providers. An important aspect of this paradigm shift toward symptom relief and minimization of suffering is individualization of care. Antimicrobials likely increase comfort in specific patient populations and infections (eg, urinary tract infections). In one study, antimicrobials administered to patients with advanced cancer with identified infections in the last several weeks of life led to symptomatic relief in only 33% of patients. This benefit was seen in an even smaller minority of those patients (9.2%) in their last week of life.³¹ The same study also reported that patients receiving potentially painful invasive measures, such as indwelling catheters and surgical procedures, were less likely to have a perceived symptomatic benefit from antimicrobial therapy in the setting of a suspected infection. These findings suggest that the palliative benefit from anti-infective therapy is not universal, but may have a role for some patients with certain infections.

The Choices, Attitudes, and Strategies for Care of Advanced Dementia at the End-of-Life study conducted by Givens and colleagues¹² is one of the few prospective

studies of antimicrobial therapy at the EOL. In this study, the efficacy of antimicrobial therapy on the outcomes of both survival and palliation in nursing home residents with advanced dementia and pneumonia was evaluated. A survival benefit was seen in patients who received antimicrobials for suspected pneumonia. This benefit was present regardless of the route of drug administration. In contrast, lower comfort levels were observed in patients who received antimicrobials. These findings suggest a tradeoff between the goals of prolonging survival and reducing symptoms. They are also in contrast with previously published reports of a possible role for antimicrobials in palliation of EOL patients with pneumonia.^{32,33} These discrepancies may reflect the challenges of symptom assessment in patients with advanced dementia.

Despite evidence of significant antimicrobial use described thus far, most patients may have preferences in stark contrast with these practices. A survey of patients with advanced cancer in community-based hospice programs found that 79.2% preferred to either avoid antimicrobials altogether or to use antimicrobials with the goal of symptomatic relief only.²⁹ Patients and health care proxies may not have the opportunity to address these wishes with health care providers. In a cohort of patients with advanced dementia, despite 94.8% of health care proxies stating that comfort was their primary objective, 72.4% of suspected infections were treated with antimicrobials. Only 45.3% of patients or health care proxies were asked about their preferences for antimicrobial use, and fewer received counseling on this issue.³⁴ Similarly, another study found that the health care proxies of patients with advanced dementia were aware of suspected infections in 39% of cases, and only 57% of those who were aware of a suspected infection participated in the decision-making process.³⁵

POTENTIAL BENEFITS OF ANTIMICROBIAL THERAPY

Although antimicrobial use in EOL patients does not universally result in positive survival and symptomatic outcomes, these patient populations are heterogeneous. There may be subgroups of patients with greater potential for benefit. As outlined above, antimicrobial use for pneumonia at the EOL does not consistently demonstrate an improvement in survival or symptomatic relief in patients with advanced dementia. Beyond these findings, some studies have suggested that antimicrobial therapy for urinary tract infections in EOL patients is more likely to result in resolution of symptoms than therapy for other sites of infection, with the least symptomatic benefit seen in bloodstream infections.^{29,36,37} In addition, treatment of symptomatic infections may contribute to improvement in psychological distress.³⁰ Intuitively, individual patients with painful symptoms directly attributable to particular infections, such as herpes simplex virus, varicella zoster virus, or oral candidiasis, should be treated with antimicrobials with a goal of palliation. Treatment of these infections should not impact mortality, but may provide symptom relief, which is the primary goal of palliative care.

POTENTIAL HARMS OF ANTIMICROBIAL THERAPY

One potential for harm secondary to antimicrobial use relates to the route of drug administration. The use of intravenous devices for parenteral antibiotics carries the risk of phlebitis, local skin and soft tissue infections, and secondary bacteremia. Furthermore, insertion of either central or peripheral venous access catheters is painful and may necessitate mechanical restraints in delirious or demented patients, which are outcomes in direct opposition to a goal of palliation. Despite these risks, as many as 82% of patients with terminal cancer receive parenteral antibiotics.³¹ Patients in hospice units are more likely to receive oral antimicrobials, accounting for up to 83% of antimicrobial use in this setting, compared with patients in acute care settings

or tertiary palliative care units. In these inpatient settings, intravenous therapy is more frequent, and alternative invasive routes such as intramuscular administration are also reported.³⁸ A potential explanation for the increased use of parenteral antimicrobials in a tertiary palliative care setting is that many patients in such units have pain that requires intravenous opiates. In addition, some patients may have difficulty with oral medications because of odynophagia related to thrush, mucositis, or their underlying condition, making parenteral therapy the less painful route.

Health care providers should weigh the risk of adverse drug side effects and immunologically mediated allergic reactions against the drug's potential benefit to patients when they prescribe antimicrobials. Undesirable drug reactions may be more clinically significant in EOL patients because of underlying frailty and polypharmacy. Antibiotic-associated diarrhea is one such example. A large prospective study compared rates of antibiotic-associated diarrhea across multiple medical settings and found the highest rate (7.1%) in the geriatrics unit. Half of the patients tested were positive for *Clostridium difficile*.³⁹ As another example, an association between beta-lactam antibiotics and seizures has been described. The risk of seizure with beta-lactam use is likely higher in patients with underlying central nervous system structural abnormalities and encephalopathy and hence may disproportionately affect patients in their final weeks of life.⁴⁰ It is important to consider these adverse effects when using antimicrobials in EOL patients, because antibiotics administered in nonbeneficial scenarios can have devastating consequences for patients and their families.

In addition to adverse patient outcomes, societal costs of nonbeneficial treatments are significant. As mentioned previously, one-fifth to almost one-half of patients die during a hospitalization with an ICU admission. The average cost of a terminal ICU admission is between \$24,541 and \$39,315, with drugs accounting for 4.1% of these costs.^{2,41} Terminal non-ICU admissions cost an average of \$8548.² A recent comparison between EOL expenditures in 7 countries found that although a lower percentage of patients in the United States die in the hospital compared with several western European countries and Canada, the United States had the highest percentage of ICU admissions in the final 180 days of life.⁴² Avoidance of interventions that are not beneficial to patients at the EOL, including antimicrobials in many instances, is a crucial step in reducing these costs.

The increasing prevalence of multidrug-resistant organisms (MDROs) is an additional adverse societal outcome associated with antimicrobial overuse. MDROs are especially significant in nursing homes, where many patients with advanced dementia die. Colonization with any MDRO in a 12-month period can be as high as 66.9% of nursing home residents, and the 12-month incidence of acquisition of an MDRO is 47.9%.³⁴ A study of ICU patients identified EOL antimicrobial use as a risk factor for colonization with drug-resistant organisms and hypothesized that this patient population is a reservoir for MDROs in the ICU.⁴³ Antimicrobial stewardship programs limiting the inappropriate use of antimicrobials decrease the prevalence of MDROs in health care settings.^{13,44} Reducing the use of nonbeneficial antimicrobials in EOL patients may aid in combating this epidemic.

PROPOSED ALGORITHM FOR MANAGEMENT

The authors propose the following guidelines for management of patients at the EOL with suspected infections (**Fig. 1**). First, the use of antimicrobial agents should be included in a comprehensive goals-of-care discussion, ideally during routine care. This conversation should include the education of patients and health care proxies regarding the harms and benefits of diagnostic testing and antimicrobial therapy.

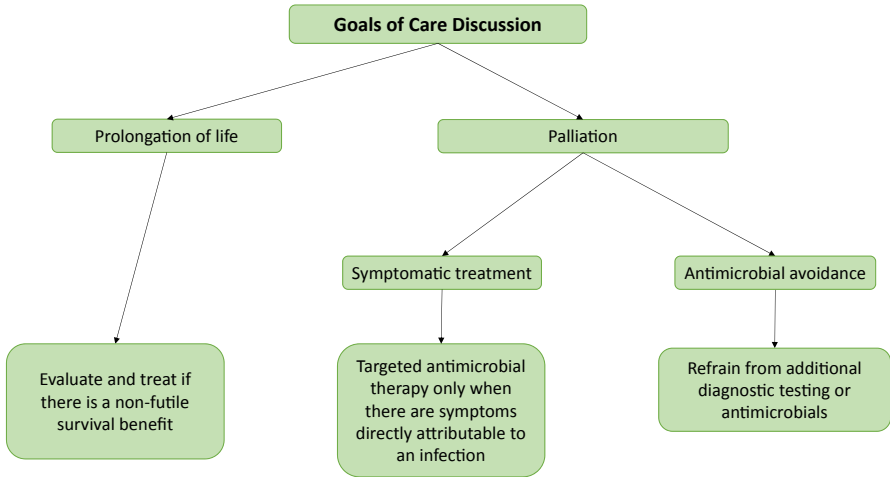


Fig. 1. A proposed algorithm for use of antimicrobial agents at the EOL that begins with discussing antimicrobial use during a comprehensive goals-of-care discussion.

Options, including the limitation of antimicrobials to palliative use and complete abstinence from antimicrobials, should be broached. Future decisions regarding antimicrobial use should take into account the educated wishes of the patient and their health care proxies. Second, when considering antimicrobial therapy for a suspected infection, the patient's life expectancy, symptoms, and the possibility of noninfectious fever should be considered. As discussed thus far, antimicrobials are unable to alter the progression of advanced dementia or cancer, may or may not affect survival time in some patient populations, and conversely may prolong suffering. If the patient has symptoms attributable to an infection (eg, dysuria, odynophagia), it is reasonable to consider treating a suspected infection, with urinary tract infections being the most likely to result in symptomatic improvement. Finally, nonparenteral routes of administration should be used, unless intravenous access is otherwise necessary for therapies such as pain medication or there is severe odynophagia related to their underlying condition.

SUMMARY

Health care providers across medical specialties continue to use societal resources for nonbeneficial treatments at the EOL, which at best will not help and at worst can harm their patients. Antimicrobials are not exempt from this problem. The authors have proposed an approach to management of suspected infections in patients at the EOL. Providers should carefully consider the appropriate goals of such therapy for individual patients and the likelihood of achieving such goals.

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