AMA Journal of Ethics®
June 2024, Volume 26, Number 6: E456-462

CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

When Should Patients at the End of Life Get Antimicrobials?

Noah Boton, MD and Jeffrey Larnard, MD

Abstract

Although antimicrobial medications are commonly prescribed to patients at the end of life (EOL), clinicians might not discuss the benefits and harms of antimicrobials with their patients in the advance care planning process. This commentary on a case discusses challenges and strategies in antimicrobial decision making for patients at the EOL. As antimicrobial use can harm some patients, and as antimicrobial resistance remains an urgent public health issue, this article advocates for ethical reasoning to guide antimicrobial decision making for patients at the EOL.

Case

LK is a 75-year-old woman with metastatic lung cancer who is admitted for pneumonia. She is administered broad-spectrum intravenous antibiotics with subsequent improvement of her fever and hypoxia. Imaging of the chest reveals a tumor obstructing the right lower lobe bronchus. Due to the extent of metastatic disease, frequent infections, and generalized weakness, LK is not a candidate for additional surgery or other cancer-directed therapies. The decision is made to focus on comfort, and LK discusses her treatment preferences during transition to hospice care. While many of her preferences were previously outlined when completing her advance directive, she has not yet discussed the use of antimicrobials. LK asks if she should continue taking antibiotics when she returns home.

Commentary

End of life (EOL) is a term used in health care to describe the final days, weeks, or months of a patient's life. During this time, patients make many important decisions about their medical care. Often absent from goals-of-care discussions is the use of antimicrobials, which are administered to a significant proportion of patients at the EOL.[1,2] In particular, high rates of antimicrobial use have been reported in patients transitioning to comfort-focused care or enrolling in hospice services.[3,4,5,6] Patients at the EOL are predisposed to infection due to foreign bodies, disruption of host barriers, immobility, and malnutrition,[7,8,9] all of which likely contribute to the high rate of antimicrobial use. However, antibiotics are also prescribed at the EOL in the absence of confirmed infection.[6,10] In addition, antimicrobial use at the EOL can be influenced by the desire to palliate symptoms, as well as by patient or family preferences.[11,12,13]

As LK transitions to hospice care, she is faced with several important decisions regarding her medical care, including current and future use of antimicrobials. To guide LK, clinicians need to elicit her values, goals, and preferences, while ensuring that the potential benefits and harms of continued antimicrobial therapy are presented accurately to her. In LK's case, the use of antimicrobials alone without an intervention to relieve the obstruction in her lungs might not cure her infection. However, antimicrobials could suppress the infection and potentially improve her comfort. Clinicians might also be concerned that ongoing antimicrobial use in the presence of her persistent nidus of infection would promote development of antimicrobial resistance. Determining the appropriateness of antimicrobials for patients like LK involves a nuanced approach, especially given the lack of clear guidelines and limited evidence for patients at the EOL. This article, written from the perspective of infectious disease physicians, explores strategies based on the principles of beneficence, nonmaleficence, autonomy, and justice that clinicians can use to navigate these difficult clinical scenarios.

Weighing Benefits and Harms

When contemplating antimicrobial prescribing at the EOL, clinicians should use a patient-centered approach that balances beneficence and nonmaleficence. When patients at the EOL are suffering from an infection and there is reasonable confidence that antimicrobial treatment will alleviate their symptoms, prescribing a trial of antimicrobials aligns with the principle of beneficence.[14] While this approach is simple in theory, clinical practice is not often straightforward. Observational studies have shown varied success rates in symptom improvement with antimicrobials for patients at the EOL.[15] Older observational studies suggested that antimicrobials might be more effective at palliating symptoms of urinary tract infections than other infections at the EOL.[16,17,18] However, a more recent study that retrospectively applied an appropriate use tool to antibiotic prescriptions found that the rate of symptom improvement for urinary tract infections was similar to that for other infections.[10] Moreover, symptom improvement was only seen in about 60% of patients.[10] Observational studies have also indicated that antimicrobials might be less effective in palliating symptoms in the final weeks of life.[19,20] Overall, there remain significant limitations in the available data, and clinicians need to rely on their judgment to assess potential benefits of antimicrobials on a case-by-case basis.

Although clinicians might be familiar with many of the potential harms associated with antimicrobial use, when the goals of care are focused on palliation, particular attention should be paid to nonmaleficence. Potential harms of antimicrobial use include symptoms of intolerance, such as gastrointestinal distress, as well as allergic reactions. Specific toxicities are associated with certain antimicrobials, such as encephalopathy with beta-lactam use.[21] The frequency of these events can be significant, including for patients at the EOL. For example, of patients with advanced cancer receiving palliative chemotherapy who were exposed to an antimicrobial during their hospital stay, 35% developed an adverse drug event.[22] Furthermore, antimicrobial use is a risk factor for acquisition of *Clostridioides difficile* infection, including at the EOL.[3,23] The use of intravenous antimicrobials can additionally lead to indirect harms such as pain, infections, and thrombi at intravenous sites,[24,25] and antibiotic use in acute care settings at the EOL has been associated with increased length of stay.[26] In light of these risks, ethical prescribing at the EOL requires carefully balancing the potential benefits (ie, symptom relief or extended duration of life) and the likelihood of adverse effects.

Due to the heterogenous nature of the EOL population and differing goals of care, antimicrobial prescribing must be tailored to each patient's unique situation and care objectives. If the goal of antimicrobials is symptom palliation, clinicians should first consider carefully whether a bacterial infection is present and whether that infection is leading to bothersome symptoms. Additionally, clinicians should ask whether antimicrobials could realistically lead to symptom improvement and whether it would be more or less than what could be expected from a non-antimicrobial medication, such as acetaminophen. These considerations need to be weighed against the risk of direct harms from antimicrobials, which depend on the specific agent used. As an example, the need for central venous access and intensive lab monitoring involved in prescribing intravenous vancomycin exposes patients to more potential harms than prescribing oral amoxicillin. Finally, and perhaps most importantly, realistic expectations of benefits and harms should be presented clearly to the patient and family.

Clinical Decision Making

The implications of antimicrobial prescribing for patients at the EOL extend beyond individual patients. Antimicrobial use promotes the development of antimicrobial resistance in health care facilities and in the community.[27,28] The downstream effects of antimicrobial resistance, including increased patient mortality and rising health care costs, are urgent global problems.[29,30] A significant contributing factor is the prevalence of unnecessary or inappropriate antimicrobial prescriptions, estimated in 2013 to be as high as 50%.[31] These unnecessary prescribing practices extend to patients at the EOL. For example, one nationwide analysis showed that only 15% of patients receiving antibiotics during the last week of life had a documented infectious diagnosis.[6] This issue highlights the principle of justice, which necessitates a fair distribution of health care resources, giving consideration to the needs of both individual patients and society.[14] In the context of rising antimicrobial resistance, this principle necessitates preserving the effectiveness of antimicrobials for society now and in the future.

Applying the principle of justice to antimicrobial prescribing at the EOL presents significant challenges for clinicians. One critical issue is the limited evidence of which specific antimicrobial prescribing practices do the most to promote resistance among this patient population. Observational data suggest that antimicrobial use for patients receiving EOL care in intensive care units is associated with increased resistance.[32] However, the broader impact of antimicrobial use for EOL patients in health care facilities and in the community is not well elucidated. Another challenge is the complex microbiologic landscape of antimicrobial resistance. There are many different pathways to resistance depending on the specific pathogen-antimicrobial interaction. For example, while the emergence of resistance to vancomycin in enterococci is not likely to occur during therapy, bacteria such as *Pseudomonas aeruginosa* can rapidly develop resistance during treatment when exposed to multiple classes of antimicrobials.[33]

Recognizing these challenges, clinicians can apply the principle of justice, as exemplified by LK's case. For example, if LK's respiratory cultures reveal an infection caused by an extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*, antimicrobial options are limited to the use of broad-spectrum agents, such as fluoroquinolones or carbapenems. However, given the obstruction in LK's lungs, which might prevent complete resolution of her infection, clinicians must answer an important question: Will antimicrobials actually benefit her? If clinical judgment suggests limited or no benefit, then the ethical implications of continuing antibiotics could extend beyond LK's individual care. Continued use of broad-spectrum agents can contribute to higher

levels of antimicrobial resistance, potentially affecting other patients through transmission of resistant organisms. When prescribing antimicrobials at the EOL, we believe clinicians have an obligation to incorporate the risk of antimicrobial resistance in their decision making, particularly when antimicrobials are suspected to have little benefit. Moreover, care should be taken to review the available microbiology data and local antimicrobial resistance patterns to avoid prescribing antimicrobials with unnecessary broad-spectrum activity.

Advance Care Planning

In LK's case, it might not be clear if antimicrobials will improve the symptoms of her pneumonia as she transitions to hospice care. After discussing the benefits and risks of ongoing antimicrobials and making a recommendation, her clinicians have a responsibility to respect her right to make a decision. LK is in a position to make an informed choice. However, many terminally ill patients might not have the capacity to fully engage in these conversations. For these patients, incorporating discussions about antimicrobial use in advance care planning (ACP) is one strategy that can improve patient autonomy by aligning future prescribing practices with patients' goals of care.

However, discussion of antimicrobial use in ACP is not yet widely adopted.[1,34] Clinicians have cited several reasons for not discussing antimicrobials in ACP processes, including concerns about overwhelming patients or families and about having insufficient training to discuss antimicrobials at the EOL.[34] Other topics commonly included in ACP, such as the use of life support interventions and identifying a health care surrogate, already involve complex discussions, so discussing antimicrobial use during this process may seem arduous for clinicians, patients, and families.

Despite these concerns, we believe that antimicrobial use deserves a place in ACP, given the frequency with which antimicrobials are used at the EOL and their potential for significant benefit and harm. Integrating discussions of antimicrobial use into ACP facilitates more informed choices and provides patients and families more time to understand potential impacts of these treatments. Importantly, the objective of these discussions should not be to convince patients to avoid antimicrobials at the EOL but rather to ensure antimicrobial prescribing practices align with patients' values and preferences. Research suggests that this strategy can be practical and impactful, as completing a Physician Orders for Life Sustaining Treatment (POLST) form with a preference for limited antimicrobial use was shown to reduce use of antimicrobials in the last 30 days of life.[1] However, it should be noted that not all state POLST forms include a section to indicate antimicrobial preferences.[1]

Conclusion

Prescribing antimicrobials at the EOL is rarely straightforward, and clinicians need to weigh multiple ethical considerations. Clinicians must consider the patient's individual values, goals of care, underlying disease, and current infectious process when deciding if antimicrobials would be beneficial. Moreover, clinicians need to consider the potential harms of antimicrobials to the patient and the broader effects of antimicrobial overuse on society. In states that include antimicrobial preferences on POLST forms, ACP can be an impactful tool to guide prescribing.[1] Clinicians should take particular care at the EOL to assess the potential benefits and harms of antimicrobials in the context of patients' specific goals of care and clinical scenarios and then communicate those benefits and harms clearly to patients and families. If clinicians believe antimicrobials will not be

helpful in realizing their patients' known wishes—and could instead be detrimental—a recommendation to withhold or stop antibiotics can be given.

References

1. Kates OS, Krantz EM, Lee J, et al. Association of Physician Orders for Life-Sustaining Treatment with inpatient antimicrobial use at end of life in patients with cancer. *Open Forum Infect Dis*. 2021;8(8):ofab361.
2. Marra AR, Puig-Asensio M, Balkenende E, Livorsi DJ, Goto M, Perencevich EN. Antibiotic use during end-of-life care: a systematic literature review and meta-analysis. *Infect Control Hosp Epidemiol.* 2021;42(5):523-529.
3. Thompson AJ, Silveira MJ, Vitale CA, Malani PN. Antimicrobial use at the end of life among hospitalized patients with advanced cancer. *Am J Hosp Palliat Care.* 2012;29(8):599-603.
4. Merel SE, Meier CA, McKinney CM, Pottinger PS. Antimicrobial use in patients on a comfort care protocol: a retrospective cohort study. *J Palliat Med*. 2016;19(11):1210-1214.
5. Furuno JP, Noble BN, Horne KN, et al. Frequency of outpatient antibiotic prescription on discharge to hospice care. *Antimicrob Agents Chemother.* 2014;58(9):5473-5477.
6. Albrecht JS, McGregor JC, Fromme EK, Bearden DT, Furuno JP. A nationwide analysis of antibiotic use in hospice care in the final week of life. *J Pain Symptom Manage*. 2013;46(4):483-490.
7. Vitetta L, Kenner D, Sali A. Bacterial infections in terminally ill hospice patients. *J Pain Symptom Manage.* 2000;20(5):326-334.
8. Pereira J, Watanabe S, Wolch G. A retrospective review of the frequency of infections and patterns of antibiotic utilization on a palliative care unit. *J Pain Symptom Manage.* 1998;16(6):374-381.
9. Chen JH, Lamberg JL, Chen YC, et al. Occurrence and treatment of suspected pneumonia in long-term care residents dying with advanced dementia. *J Am Geriatr Soc.* 2006;54(2):290-295.
10. Clark MD, Halford Z, Herndon C, Middendorf E. Evaluation of antibiotic initiation tools in end-of-life care. *Am J Hosp Palliat Care*. 2022;39(3):274-281.
11. Servid SA, Noble BN, Fromme EK, Furuno JP. Clinical intentions of antibiotics prescribed upon discharge to hospice care. *J Am Geriatr Soc*. 2018;66(3):565-569.
12. Gaw CE, Hamilton KW, Gerber JS, Szymczak JE. Physician perceptions regarding antimicrobial use in end-of-life care. *Infect Control Hosp Epidemiol*. 2018;39(4):383-390.
13. Larnard J, Blackshear L, Lee MSL, Buss MK, Stead W. Perceptions and reality of antimicrobial prescribing during the transition to comfort measures only at an academic medical center. *Open Forum Infect Dis.* 2022;10(1):ofac692.
14. Beauchamp T, Childress J. *Principles of Biomedical Ethics*. 8th ed. Oxford University Press; 2019.
15. 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(12):1568-1574.
16. White PH, Kuhlenschmidt HL, Vancura BG, Navari RM. Antimicrobial use in patients with advanced cancer receiving hospice care. *J Pain Symptom Manage*. 2003;25(5):438-443.

17. 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(2):175-182.
18. Clayton J, Fardell B, Hutton-Potts J, Webb D, Chye R. Parenteral antibiotics in a palliative care unit: prospective analysis of current practice. *Palliat Med*. 2003;17(1):44-48.
19. 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(5):535-540.
20. Tagashira Y, Kawahara K, Takamatsu A, Honda H. Antimicrobial prescribing in patients with advanced-stage illness in the antimicrobial stewardship era. *Infect Control Hosp Epidemiol*. 2018;39(9):1023-1029.
21. Snavely SR, Hodges GR. The neurotoxicity of antibacterial agents. *Ann Intern Med.* 1984;101(1):92-104.
22. Datta R, Han L, Doyle M, et al. Antibiotic therapy is associated with adverse drug events among older adults with advanced cancer: a cohort study. *Palliat Med.* 2023;37(5):793-798.
23. Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. *N Engl J Med*. 1994;330(4):257-262.
24. Larnard J, Stead W, Branch-Elliman W. Considering patient, family, and provider goals and expectations in a rapidly changing clinical context: a framework for antimicrobial stewardship at the end of life. *Infect Dis Clin North Am*. 2023;37(1):139-151.
25. Morrison RS, Ahronheim JC, Morrison GR, et al. Pain and discomfort associated with common hospital procedures and experiences. *J Pain Symptom Manage*. 1998;15(2):91-101.
26. Datta R, Zhu M, Han L, Allore H, Quagliarello V, Juthani-Mehta M. Increased length of stay associated with antibiotic use in older adults with advanced cancer transitioned to comfort measures. *Am J Hosp Palliat Care*. 2020;37(1):27-33.
27. Baghban A, Juthani-Mehta M. Antimicrobial use at the end of life. *Infect Dis Clin North Am*. 2017;31(4):639-647.
28. Cizman M. The use and resistance to antibiotics in the community. *Int J Antimicrob Agents*. 2003;21(4):297-307.
29. Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2019*. US Department of Health and Human Services; 2019. Accessed January 19, 2024. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
30. Antimicrobial resistance. World Health Organization. November 21, 2023. Accessed January 19, 2024. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
31. Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2013.* US Department of Health and Human Services; 2013. Accessed January 19, 2024. https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
32. Levin PD, Simor AE, Moses AE, Sprung CL. End-of-life treatment and bacterial antibiotic resistance: a potential association. *Chest*. 2010;138(3):588-594.
33. Rice LB. The Maxwell Finland Lecture: for the duration—rational antibiotic administration in an era of antimicrobial resistance and *Clostridium difficile*. *Clin Infect Dis.* 2008;46(4):491-496.

34. Datta R, Topal J, McManus D, et al. Education needed to improve antimicrobial use during end-of-life care of older adults with advanced cancer: a cross-sectional survey. *Palliat Med*. 2021;35(1):236-241.

Noah Boton, MD is a senior infectious disease fellow at Beth Israel Deaconess Medical Center in Boston, Massachusetts, who is planning a career in clinical infectious disease and antimicrobial stewardship.

Jeffrey Larnard, MD is an attending physician in the Division of Infectious Diseases at Beth Israel Deaconess Medical Center and an instructor of medicine at Harvard Medical School in Boston, Massachusetts.

Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2024;26(6):E456-462.

DOI

10.1001/amajethics.2024.456.

Conflict of Interest Disclosure

Authors disclosed no conflicts of interest.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

ISSN 2376-6980