

Perceptions and Reality of Antimicrobial Prescribing During the Transition to Comfort Measures Only at an Academic Medical Center

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Background. Little is known about antimicrobial prescribing when patient care is transitioned to comfort measures only (CMO). We used a multidisciplinary survey and retrospective cohort study to gain insight into antimicrobial prescribing in this population at an academic medical center to inform future antimicrobial stewardship interventions.

Methods. A survey focusing on antimicrobial prescribing during the transition to CMO was electronically distributed to providers in medical subspecialties and responses were compared across specialties. A retrospective chart review was performed of patients admitted to an academic medical center in 2020 who were on antimicrobials in the 48 hours prior to CMO. We investigated the percentage of patients who remained on antimicrobials after the transition to CMO and rationale for continuing antimicrobials.

Results. We received 113 survey responses (35% response rate). Forty-one percent of respondents indicated that they “sometimes” or “often” continued antimicrobials during the transition to CMO. Patient/family preference and symptom palliation were the most common factors cited by respondents when deciding whether to continue antimicrobials in this population. Of the 546 patient charts reviewed, 140 (26%) patients were alive 48 hours after CMO order, and 19 (14%) of those patients remained on antimicrobials. Five of 19 (26%) patients had documentation that antimicrobials were continued due to patient/family preference and 5 of 19 (26%) patients had documentation that antimicrobials were continued for palliation of symptoms.

Conclusions. Patient/family preference and symptom palliation are important factors in prescribing antimicrobials when patient care is transitioned to CMO. More evidence is needed regarding palliative benefits of antibiotics to inform provider discussions of benefits and harms of antimicrobial use in this setting.

Keywords. antimicrobial stewardship; comfort measures only; end of life; palliative care.

Antibiotics are often a part of end-of-life (EOL) care [1], including patients who are transitioned to comfort measures only (CMO) [2–4]. Prior survey studies have also shown that some physicians favor prescribing antibiotics to patients receiving comfort care when they have an infection [5–7], and no difference was found between medicine subspecialties when asked about withholding antimicrobials when patient care is transitioned to CMO [7].

Though antimicrobials are sometimes utilized in patients receiving comfort-focused care, the evidence for their

effectiveness when used in a palliative capacity is mixed. A systematic review on the effectiveness of antimicrobials for symptom management in patients receiving palliative or hospice care was unable to draw conclusions due to limitations in the included observational data [8]. A more recent retrospective study of hospitalized patients in the last 14 days of life found that antibiotics were prescribed for symptom relief in 44.1% of patients, but only helped achieve symptom relief in 22.8% of cases [9]. In contrast, another observational study of patients receiving home or skilled nursing facility hospice care found that 60% of antimicrobial prescriptions that met a minimum use criteria led to symptom resolution [10]. Older, observational studies have suggested that antibiotics may be more helpful at alleviating symptoms caused by urinary tract infections (UTIs) compared with other infections at EOL [11–13].

Antimicrobial use at EOL, particularly for patients on CMO, also exposes patients to unwelcome medication side effects such as nausea and diarrhea (including *Clostridioides difficile* infection) [2, 14–16], as well as more indirect harms such as discomfort associated with peripheral line insertion [17].

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Moreover, there are additional potential harms of antimicrobials to consider; for example, a recent study showed that antimicrobial use was associated with increased length of stay in patients with advanced cancer who were transitioned to CMO [18]. Antibiotic use at EOL also has been associated with the development of antimicrobial resistance [19], and their use contributes to the significant costs of healthcare at EOL [16].

In the setting of the uncertain benefits and potential harms associated with antimicrobial use at EOL, relatively little is known about the rationale for prescribing antimicrobials in this population. A retrospective study of antimicrobials prescribed for patients discharged to hospice found that only a small minority were prescribed for palliative reasons, and antimicrobials were more commonly prescribed to cure, suppress, or prevent an infection [20]. However, in prior survey studies, the desire to palliate symptoms and patient and family preference have emerged as important factors in continuing antimicrobials at EOL [6, 7].

The aim of this study was to characterize antimicrobial use and rationale for antimicrobial prescribing when patient care was transitioned to CMO at an academic medical center and to use these data to inform future antimicrobial stewardship approaches and interventions in this population.

METHODS

We first conducted a cross-sectional survey at a single tertiary-care academic medical center. Respondents included attending physicians, advanced practice providers, and fellows in the internal medicine subspecialties that we believed would be most involved in antimicrobial decision making when patient care was transitioned to CMO. These specialties included infectious disease, hematology/oncology, palliative care, pulmonary/critical care, and hospital medicine.

A “faculty champion” from each specialty was identified who provided email listservs of providers from their respective specialty. The survey was administered using Research Electronic Data Capture (REDCap). Participation was voluntary and anonymous, and no financial incentive was provided.

The survey was created by the authors and included questions about the practices and attitudes of prescribing antimicrobials during the transition to CMO. Responses were graded using 4- to 5-point Likert scales and there was also an open-ended question for respondents to share other thoughts regarding antimicrobial prescribing in this population. Respondents were also asked for their training level and specialty. The survey was pilot tested on individuals outside of the authors’ institutions in the represented medicine subspecialties to obtain feedback, and the final 42-item survey was distributed on 31 January 2022 via email. Differences among specialties were compared using Kruskal-Wallis tests in

Stata/BE 17.0, and responses to the open-ended question were reviewed for representative comments.

A retrospective chart review was then performed for patients admitted to Beth Israel Deaconess Medical Center (BIDMC) from 1 January 2020 to 31 December 2020 who had an order for CMO placed during a hospitalization and who had at least 1 active antimicrobial order in the 48 hours prior to CMO order. Patients were subsequently excluded if their initial CMO order was reversed. Information extracted from the electronic medical record (EMR) included demographic information, comorbidities, antimicrobial orders, and antimicrobial indication. The authors (J. L. and L. B.) who performed manual extraction from clinician documentation in the EMR used a shared extraction tool. The extraction tool was piloted on 10 sample charts. Overall, 118 of the 130 items (91%) were rated concordantly by the reviewers. Cohen kappa statistic was 0.73–1 for individual variables. The authors involved in chart review used this pilot to address remaining areas of disagreement to further improve concordance.

We investigated patient and antimicrobial status 48 hours after CMO order placement. For patients who were still alive and remained on antimicrobials 48 hours after CMO order, we noted if antimicrobials were prescribed for symptom relief or patient/family preference. Data and descriptive statistics were tabulated and analyzed using Microsoft Excel. The BIDMC institutional review board deemed this study exempt from review.

RESULTS

Behaviors Around Antimicrobials and CMO Transition

One hundred thirteen of the invited 326 providers in infectious disease, palliative care, hematology/oncology, pulmonary/critical care, and hospital medicine completed the survey for a response rate of 35%. Two of the 113 did not indicate a specialty and thus were excluded from further analysis.

Hospital medicine had the most respondents (32/111 [29%]), followed by hematology/oncology (30/111 [27%]), infectious disease (20/111 [18%]), pulmonary/critical care (18/111 [16%]), and palliative care (11/111 [10%]). The majority of respondents were attending physicians (83/111 [75%]); a smaller proportion were fellows (21/111 [19%]), and advance practice providers (5/111 [5%]). Two respondents did not specify a practice level.

Overall, 96 of 111 (86%) respondents reported being at least sometimes involved in the care of patients when care was transitioned to CMO. A similar number of respondents (91/111 [82%]) specified that they at least sometimes discussed antimicrobial decision making with patients, family members, or primary teams when care was transitioned to CMO. There was no statistical difference between specialties ($P = .1564$). Forty-six of 111 (41%) respondents reported they at least sometimes continued or recommended continuing antimicrobials when

patient care was transitioned to CMO. There was a statistically significant difference between specialties ($P = .0135$), with the median response of hematology/oncology providers indicating they more often continued antimicrobials in this population.

Decisions about continuing antimicrobials in patients transitioned to CMO varied based on the type of infection being treated. While 24%–30% of respondents indicated they would be likely or very likely to continue antimicrobials for skin/soft tissue infection, UTI, pneumonia, gastrointestinal infections, and meningitis/central nervous system infections, only 19% and 16% of respondents would be likely or very likely to continue antimicrobials for musculoskeletal infections and bacteremia, respectively. There was a statistically significant difference between specialties for all infections, with pulmonary/critical care respondents notably having a median response of “very unlikely” to continue antimicrobials for all infections.

Perception of Palliative and Adverse Effects of Antimicrobials

For all specified symptoms, respondents thought antimicrobials were less likely to be helpful if patients were already being treated with symptom-directed medications (ie, acetaminophen for fevers, narcotics for pain or dyspnea, guaifenesin for cough). There was a significant minority (29%–47% depending on the symptom) of the total respondents who felt antimicrobials would be at least somewhat helpful for treating the queried symptoms (Table 1). There was a statistically significant difference between specialties only for fever ($P = .0089$), with infectious disease and hematology/oncology having a median response that antimicrobials would be “somewhat helpful” compared with other specialties having a median response of “not helpful.”

Respondents also expressed concern about side effects or toxicities of antimicrobials, though the level of concern varied somewhat by side effect and provider group. Diarrhea and nausea were of greatest concern overall, though there were

significant differences in the level of concern between specialties. Most respondents were also at least somewhat concerned about antimicrobial resistance, length of stay, and cost of antimicrobials, though there were no statistically significant differences between specialties (Table 2).

Factors Influencing Antimicrobial Prescribing at CMO

As seen in Figure 1, when asked about factors that contributed to continuing antimicrobials when patient care is transitioned to CMO, patient/family preference was specified by the most respondents (86/111 [77%]), followed by providing palliation of a symptom (69/111 [62%]). Ninety-five of 111 (86%) respondents indicated that antimicrobial decision making during the transition to CMO should be shared between patient and provider, while 10 of 111 (9%) indicated that decision making should be patient-directed and 6 of 111 (5%) indicated that decision making should be provider-directed. There was not a statistically significant difference between specialties ($P = .3680$). Participant responses to survey open-ended questions also suggested patient/family preference and symptom palliation were important drivers behind decisions to continue antimicrobials in this setting (Table 3).

Retrospective Chart Review

A total of 558 patient charts were initially identified; 12 were subsequently excluded as their initial CMO order was reversed. Demographic information and baseline characteristics of the cohort can be seen in Table 4. The use of broad-spectrum antimicrobials providing methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* coverage were common in the cohort prior to CMO order placement. Intravenous vancomycin was the most prescribed antibiotic in the cohort (324/546 patients [59%]), followed by intravenous cefepime (238/546 patients [44%]), intravenous/oral metronidazole (140/546 patients [26%]), intravenous ceftriaxone (98/546 patients [18%]), and intravenous piperacillin-tazobactam (93/546 patients [17%]). Seventy-two patients (13%) had an active intravenous carbapenem order in the 48 hours prior to CMO. Miconazole was the most common antifungal prescribed, with 42 patients (8%) having an active order prior to CMO order placement.

Forty-eight hours after CMO order placement, 140 of the 546 patients in the cohort remained alive (26%). Of those 140, 19 (14%) remained on antimicrobials. Among CMO patients alive on antimicrobials at 48 hours, 7 of 19 (37%) patients were discharged from the hospital on at least 1 antimicrobial in the 48 hours after CMO order, and 12 of 19 (63%) patients remained in the hospital on at least 1 antimicrobial. Baseline characteristics of these 19 patients are shown in Table 4 and characterization of their infections and antimicrobials are shown in Table 5. Of note, 5 of 19 (26%) had documentation that antibiotics were prescribed to palliate symptoms and 5 of

Table 1. Number and Percentage of Responses Indicating Antimicrobials Were at Least Somewhat Helpful for Specified Symptoms in Patients Already on Symptom-Directed Medications

Specialty	Fever	Pain	Cough	Dyspnea	Dysuria
Total (N = 111)	52 (47)	38 (34)	32 (29)	35 (32)	48 (43)
Hematology/oncology (n = 30)	19 (63)	13 (43)	13 (43)	15 (50)	16 (53)
Infectious disease (n = 20)	11 (55)	5 (25)	6 (30)	5 (25)	10 (50)
Palliative care (n = 11)	1 (9)	5 (45)	4 (36)	>4 (36)	6 (55)
Hospital medicine (n = 32)	14 (44)	13 (41)	6 (19)	7 (22)	12 (38)
Pulmonary/critical care (n = 18)	7 (39)	2 (11)	3 (17)	4 (22)	4 (22)
P value	.0089	.1447	.1454	.0570	.1039

Data are presented as No. (%) unless otherwise indicated. Specialties compared using Kruskal-Wallis test; $P < .05$ indicates significant difference between specialties.

Table 2. Number and Percentage of Responses Indicating Respondents Who Were at Least Somewhat Concerned About Antimicrobials Causing Specified Symptoms

Specialty	Altered Mental Status	Diarrhea	Nausea	Rash	Antibiotic Resistance	Length of Stay	Cost
Total (N = 111)	57 (51)	100 (90)	84 (76)	60 (54)	68 (61)	55 (50)	70 (63)
Hematology/oncology (n = 30)	15 (50)	27 (90)	23 (77)	15 (50)	15 (50)	19 (63)	20 (67)
Infectious disease (n = 20)	13 (65)	20 (100)	18 (90)	14 (70)	13 (65)	11 (55)	16 (80)
Palliative care (n = 11)	7 (64)	11 (100)	11 (100)	9 (82)	10 (91)	5 (45)	8 (73)
Hospital medicine (n = 32)	14 (44)	29 (91)	25 (78)	16 (50)	21 (66)	13 (41)	16 (50)
Pulmonary/critical care (n = 18)	8 (44)	13 (72)	7 (39)	6 (33)	9 (50)	7 (39)	10 (56)
<i>P</i> value	.3909	.0448	.0055	.1155	.1368	.3241	.2024

Data are presented as No. (%) unless otherwise indicated. Specialties compared using Kruskal-Wallis Test; *P* < .05 indicates significant difference between specialties.

19 (26%) also had documentation that antimicrobials were prescribed at least in part because of patient/family preference.

DISCUSSION

We found that decision making about antimicrobials is an important consideration for clinicians caring for hospitalized patients at the end of life, and almost half of survey respondents indicated that they at least sometimes continued antimicrobials when patient care is transitioned to CMO. However, we found that only 14% of patients who were alive 48 hours after CMO order placement remained on antimicrobials. This discrepancy may be in part due to survey participants recalling prescribing antimicrobials at EOL, but not necessarily those who have formal CMO orders. Our findings were similar to a retrospective cohort study performed at 2 academic centers in the United

States where 16.5% of patients who were alive 48 hours after CMO initiation remained on antimicrobials [3]. There was a statistically significant difference between medicine subspecialties when asked how often antimicrobials are continued when patient care is transitioned to CMO with hematology/oncology having the highest median response, indicating more frequent antimicrobial continuation. Solid malignancy was also the most common comorbidity among patients who were alive with active antimicrobial orders 48 hours after CMO order placement.

Patient and family preference emerged as an important factor in antimicrobial decision making during the transition to CMO in our survey, which was also seen in previous survey studies about antimicrobial prescribing at EOL [6, 7]. The overwhelming majority of survey respondents also thought that antimicrobial decision making during the transition to CMO

Which of the following factored into your decision making when deciding whether to continue antimicrobials when patient care is transitioned to CMO?

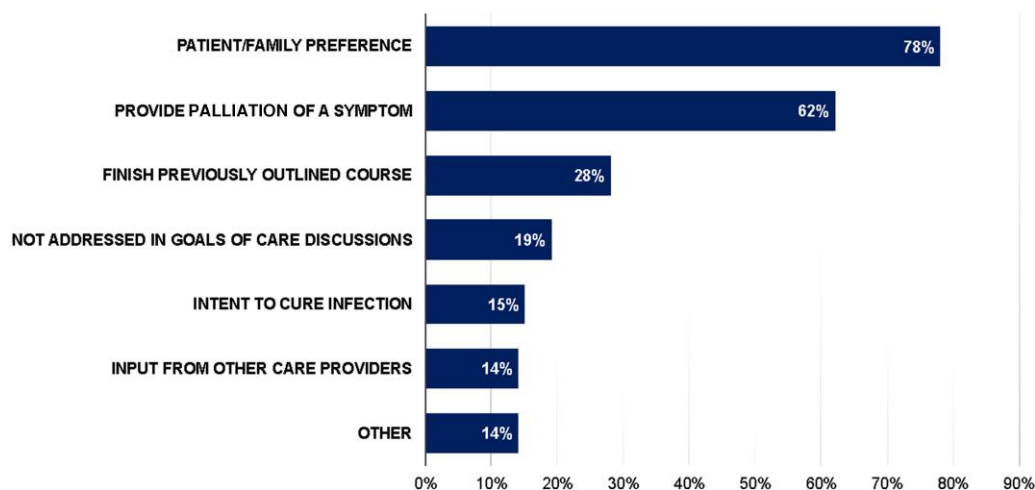


Figure 1. Percentage of respondents who indicated that the below items factored into decision making when deciding whether to continue antimicrobials during the transition to comfort measures only (CMO).

Table 3. Factors in Antimicrobial Prescribing During the Transition to Comfort Measures Only and Representative Comments Identified From Survey Open Response Question

Factors in Antimicrobial Prescribing at CMO	Representative Comments
Patients and family often influence antimicrobial decision making	<p>"The decision to continue abx is usually driven by families who are unwilling to fully withdraw all measures ... the attendings are aware of antimicrobial resistance and other associated issues, but feel that their hands are tied so long as there is shared decision making with patient's family."</p> <p>"It feels like it's basically 95% family preference ... I generally recommend against but have a low threshold to just go with family preference."</p> <p>"The emotional burden of removing interventions is already very heavy, and we are trying to spare the family the burden of yet another decision."</p> <p>"If a day of antibiotics allows us to otherwise move toward CMO, that is a reasonable tradeoff for the patient."</p> <p>"I advise drawbacks, but don't push back too hard ... They [families] will sometimes let the antibiotics go in a day or two."</p>
Antimicrobial prescribing with goal of symptom palliation	<p>"Is there data to indicate that administering antibiotics for XYZ infection helps palliate symptoms in general and/or at the end of life; alternatively, does cessation of antibiotics lead to an increase in symptoms?"</p> <p>"It would be helpful from an ID perspective to know if treatment of infection would improve QoL or symptoms and side effect risks."</p> <p>"For an infection that will require a prolonged course of IV antibiotics I am more likely to recommend stopping as the antibiotics would likely cause more harm than benefit. However, if a patient had dysuria from a UTI and could complete a 5-day course of PO antibiotics with improved symptoms, then I would typically offer this."</p>

Abbreviations: abx, antibiotics; CMO, comfort measures only; ID, infectious disease; IV, intravenous; PO, oral; QoL, quality of life; UTI, urinary tract infection.

should be shared between patient and provider. The survey responses also reflected practices at our institution; 26% of the patients who were alive and on antimicrobial therapy after CMO order had documentation that antimicrobials were prescribed at least in part because of patient/family preference. Prior literature had found that a similar percentage of patients received antimicrobials due to patient/family preference on discharge to hospice [20]. Free text survey responses also suggested that providers were often reluctant to withdraw antibiotics if patients and/or families favor continuing them, even if they were not convinced of their benefit.

After patient/family preference, the desire to palliate symptoms was the next most common factor seen in survey responses for continuing antimicrobials when patient care is transitioned to CMO. The importance of the perception of symptom relief in antimicrobial prescribing at EOL was also seen in a prior survey study [6]. Again, our survey data reflected actual practices at our institution; 26% of the patients who were alive and on antimicrobial therapy after CMO order had documentation that antimicrobials were prescribed at least in part for symptom palliation. Our survey also found that, when taking into account symptom-directed therapy, providers thought antibiotics would be most helpful with fever and dysuria and less helpful with cough and dyspnea. Interestingly, however, about the same percentage of respondents indicated they would be likely or very likely to continue antibiotics for either UTI or pneumonia when patients are transitioned to CMO. This finding may suggest that providers are more likely to continue antibiotics if a short or defined course of antibiotics can be established.

Despite evidence that the desire to palliate symptoms is an important driver of antimicrobial prescribing at EOL, there is a paucity of data to support this approach in the EOL

population [8]. The variability in symptom palliation with antimicrobials is likely driven both by the difficulty in diagnosing an acute bacterial infection at EOL as well as the heterogeneity of the EOL population. For example, for a patient with stage IV pancreatic cancer who is receiving home hospice and has an estimated prognosis of weeks to months, antimicrobials could feasibly help to relieve dysuria from a UTI. However, if that same patient developed hypoxic respiratory failure secondary to progression of metastatic pulmonary disease and has a prognosis of hours to days, antimicrobials are likely to be less effective at palliating symptoms from a postobstructive pneumonia. In general, we suspect that antimicrobials are less likely to be helpful when patients are closer to the active dying process, which was also seen in a prior observational study [21]. This is especially important to consider in the CMO population at our institution, as most patients died within 48 hours of CMO initiation.

Our findings have important implications for antimicrobial stewardship in the CMO population. In clinical scenarios in which providers do not think antimicrobials will realistically improve symptoms at EOL, especially in patients in the active dying process (ie, expected prognosis is hours to days), care should be taken to carefully frame the anticipated lack of benefits alongside the potential harms of antimicrobial use to patients, families, and other providers. Providers should keep in mind that patients and families may overestimate the potential benefits of antimicrobials at EOL [22], though providers themselves may not always be aware of the risks associated with antimicrobial therapy [7]. If no clinical benefit of antimicrobial use is suspected, it may be reasonable to strongly recommend discontinuation of antibiotics while reassuring patients and families that antimicrobials would be very unlikely to offer benefit and may, in fact, prolong suffering from their underlying

Table 4. Baseline Characteristics of All Patients in the Cohort and Patients Who Remained in Hospital or Discharged on Antimicrobials 48 Hours After Comfort Measures Only Order Placement

Characteristic	Total Cohort (N = 546)	Patients in Hospital/Discharged With Active Antimicrobial 48 h After CMO Order (n = 19)
Average age, y	72	75
Sex		
Male	305 (56)	12 (63)
Female	241 (44)	7 (37)
Race		
White	358 (66)	15 (79)
Non-White	>188 (34)	4 (21)
Ethnicity		
Hispanic	19 (3)	1 (5)
Non-Hispanic	527 (97)	18 (95)
Primary service		
ICU	406 (74)	4 (21)
Medicine	98 (18)	8 (42)
Solid oncology	23 (4)	6 (32)
Liquid oncology	12 (2)	0 (0)
Neurology	4 (1)	0 (0)
Surgery	1 (0)	1 (5)
Unknown/unclear	2 (0)	0 (0)
Comorbidities		
Heart failure	173 (32)	3 (16)
Solid malignancy	168 (31)	8 (42)
Cirrhosis	94 (17)	2 (11)
COPD	89 (16)	0 (0)
ESRD on dialysis	86 (16)	0 (0)
Dementia	64 (12)	3 (16)
Liquid malignancy	53 (10)	1 (5)
Bone marrow/solid organ transplant	10 (2)	1 (5)
COVID-19 infection during hospitalization	91 (17)	0 (0)
Active palliative care consult	129 (24)	14 (74)
Active ID consult	95 (17)	5 (26)

Data are presented as No. (%).

Abbreviations: CMO, comfort measures only; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; ICU, intensive care unit; ID, infectious disease.

disease. Moreover, there may be nonantimicrobial medications that may offer a better chance at symptom improvement. Patients and families understandably may not as be motivated by length of stay, antimicrobial resistance, and healthcare costs, but providers should also take these factors into account.

This study is the first to our knowledge to use a multidisciplinary survey to gain insight into antimicrobial prescribing when patient care is transitioned to CMO. We were also able to verify survey respondent perceptions of antimicrobial prescribing in patients on CMO by performing a comprehensive chart review of this patient group over 1 year. There are also several limitations to our study. Our findings are from a single academic tertiary care center in the United States, and may not be reflective of other medical institutions in the United States

Table 5. Characterization of Infections and Antimicrobials for Patients Who Remained in Hospital or Discharged on Antimicrobials 48 Hours After Comfort Measures Only Order Placement

Characteristic	Patients in Hospital or Discharged With Active Antimicrobial 48 h After CMO Order
Antimicrobial indication (n = 19)	
Active infection	18 (95)
Empiric for fever/sepsis	1 (5)
Other	0 (0)
Type of active infection (n = 18)	
Pneumonia	4 (22)
Multiple	4 (22)
Urinary tract	4 (22)
Bacteremia	3 (17)
Gastrointestinal	2 (11)
Soft/soft tissue	1 (6)
Antimicrobial used (n = 19)	
Amoxicillin-clavulanate (PO)	4 (21)
Cefepime (IV)	3 (16)
Metronidazole (PO/IV)	
Vancomycin (PO)	
Azithromycin (PO/IV)	2 (11)
Ceftriaxone (IV)	
Daptomycin (IV)	
Vancomycin (IV)	
Ceftaroline (IV)	1 (5)
Ciprofloxacin (PO)	
Doxycycline (PO)	
Levofloxacin (PO)	
Nitrofurantoin (PO)	
Piperacillin-tazobactam (IV)	
Trimethoprim-sulfamethoxazole (PO)	
Patient/family preference at least part of prescriber rationale	5 (26)
Palliation of symptoms at least part of prescriber rationale	5 (26)

Data are presented as No. (%).

Abbreviations: CMO, comfort measures only; IV, intravenous; PO, oral.

and elsewhere in the world. Our retrospective chart review was also limited by reliance on provider documentation, especially as documented preferences about life-sustaining treatments are not always documented in the medical record.

Overall, we found that a significant number of providers indicated that they at least sometimes continued or recommended continuing antimicrobials when patient care is transitioned to CMO, and 14% of patients in our cohort who were alive 48 hours after CMO order remained on antimicrobials. Patient and family preference and a desire to palliate symptoms emerged as important influences in antimicrobial decision making in this population. Given the limited evidence base supporting the efficacy of antimicrobials to palliate symptoms for many patients receiving comfort-focused care, providers should carefully frame the expected benefits alongside the potential risks of continued antimicrobial therapy with patients and families. Future studies are needed to establish whether

antimicrobials provide symptom palliation for specific infections in patients at EOL who are already receiving comfort-focused care. This information could help guide future antimicrobial stewardship interventions and, more importantly, prescribers and patients/families as they make these difficult management decisions together.

Notes

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Patient consent. The design of this work has been reviewed and determined exempt by the Beth Israel Deaconess Medical Center institutional review board.

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