


The impact of palliative care consultation on reducing antibiotic overuse in hospitalized patients with terminal cancer at the end of life: a propensity score-weighting study

Jeong-Han Kim¹, Shin Hye Yoo ^{2*}, Bhumsuk Keam ^{2,3} and Dae Seog Heo⁴

¹Division of Infectious Diseases, Department of Internal Medicine, Ewha Woman University College of Medicine, Seoul Hospital, Seoul, Republic of Korea; ²Center for Palliative Care and Clinical Ethics, Seoul National University Hospital, Seoul, Republic of Korea; ³Division of Medical Oncology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; ⁴Patient-Centered Clinical Research Coordinating Center, National Evidence-based Healthcare Collaborating Agency, Seoul, Republic of Korea

*Corresponding author. E-mail: ifi1024@gmail.com

Received 2 July 2022; accepted 8 November 2022

Objectives: A substantial number of hospitalized patients with terminal cancer at the end-of-life phase receive antibiotics, even with imminent death. We evaluated the impact of palliative care consultation on antibiotic use in hospitalized patients with terminal cancer during the end-of-life phase.

Methods: We identified adult patients with metastatic solid cancer who died at a tertiary medical centre in Seoul, Republic of Korea, following at least 4 days of hospitalization (January 2018–December 2020). Patients were divided into palliative and non-palliative care consultation groups. Propensity score-weighted, multivariable logistic regression analysis was used to compare the proportion of patients receiving antibiotics within 3 days before death between the two groups.

Results: Among 1143 patients analysed, 940 (82.2%) received antibiotics within 3 days before death. The proportion of patients receiving antibiotics was significantly lower (propensity score-weighted $P < 0.001$) in the palliative care consultation group (344/468; 73.5%) than in the non-palliative care consultation group (596/675; 88.3%). The decrease in the proportion of patients receiving antibiotics in the palliative care consultation group was significant for a carbapenem (42.4% versus 22.4%; $P < 0.001$), a glycopeptide (23.3% versus 11.1%; $P < 0.001$) and a quinolone (30.5% versus 19.4%; $P = 0.012$). In the multivariable logistic regression analysis, receiving palliative care consultation (adjusted OR 0.46, 95% CI 0.33–0.65; $P < 0.001$) was independently associated with reduced antibiotic use during the end-of-life phase.

Conclusions: Palliative care consultation may reduce aggressive antibiotic use in hospitalized patients with terminal cancer during the end-of-life phase.

Introduction

Hospitalized patients with terminal cancer are highly susceptible to bacterial infection because of lethargy, impaired host defences, malnutrition, disease and anti-cancer chemotherapy-induced immunosuppression, and various vascular/drainage catheters.^{1,2} Also, these patients often present infection-like signs and symptoms induced by their disease progression, which is not easy to distinguish from bacterial infection. Thus, antibiotics are commonly administered in hospitalized patients with terminal cancer and, in many cases, administered until death.³

However, many studies have suggested that antibiotics are currently overused, with an uncertainty of substantial benefits in hospice and palliative care settings.^{4–8} Negligent use of

antibiotics in patients with terminal cancer at the end of life can increase the risk of adverse drug reactions by interacting with other comfort medication and can lead to side effects including nausea, antibiotic-associated diarrhoea or phlebitis, which can deteriorate the quality of end-of-life care.^{3,7,9–11} Furthermore, concerning public health and antimicrobial stewardship, these patients may represent reservoirs of MDR organisms that can be transmitted to other patients in hospital settings.¹² This issue has been internationally recognized and there is a need to balance antibiotic-related decision-making at the end of life.^{13–16}

In the Republic of Korea, the Act on Decisions on Life-sustaining Treatment for Patients in Hospice and Palliative Care or at the End of Life (Life-sustaining Treatment Decision

Act) was enacted in February 2018 to ensure that the patient's self-determination in the end-of-life care processes could be respected. Although the decision-making framework for end-of-life care under the Life-sustaining Treatment Decision Act did not specifically mention antibiotic treatment, comprehensive palliative care planning with patients, family caregivers and attending physicians were introduced and may affect perceptions and decision-making regarding antibiotic use during end-of-life care.^{17–19} To our knowledge, there is insufficient information regarding the effects of palliative care consultation on antibiotic use in hospitalized patients with terminal cancer during the end-of-life phase. Our primary aim was to determine whether palliative care consultation could reduce the proportion of patients with terminal cancer receiving antibiotic treatment in a state of imminent death.

Material and methods

Study design and inclusion criteria

This retrospective cohort study was conducted at Seoul National University Hospital, a tertiary medical centre in Seoul, Republic of Korea, between January 2018 and December 2020. After a literature review of the definition of imminent death in cancer patients,^{20,21} we defined the imminent dying phase as 3 days before death. Patients aged ≥ 19 years, admitted for over 3 days for malignancy treatment and/or supportive care for complications associated with malignancy, and who died during hospitalization, were screened. Among these, we included patients with metastatic solid tumours. The included patients were divided into two groups for analysis: (1) a palliative care consultation group comprising patients who received palliative care consultation more than 3 days before death; and (2) a non-palliative care consultation group comprising patients who received palliative care consultation within 3 days before death or did not receive it. The study protocol was approved by the Institutional Review Board (number H-2203-120-1308) of Seoul National University Hospital, which waived the need for written informed consent from patients.

Process of palliative care consultation

Seoul National University Hospital is a referral hospital with 1761 beds, staffed by 1947 doctors working in acute and specialized care. It does not retain inpatient hospice palliative wards. The palliative care service of Seoul National University Hospital has mainly operated as hospice consultation for inpatients since 2005. After 2018, i.e. the year of enforcement of the Life-sustaining Treatment Decision Act, the service has acted as a consultation-based palliative care team, which is specialized in palliative care.²² The team comprises medical oncologists, palliative care nurses and medical social workers with sufficient clinical experience in palliative care. Palliative care consultation was conducted at outpatient or inpatient settings, when primary attending physicians (consisted of professor of admitting department, clinical fellows and/or a resident) determined it was necessary according to the course of the patient's diseases and made a request. During consultation, the team met patients and family caregivers and performed a comprehensive and holistic assessment of palliative care needs, including physical, psychosocial and spiritual distress. During a series of thorough interviews, discussion for goals of care and advance care planning at the end-of-life phase were necessarily included in palliative consultation by assessing the patient/family's wishes, preferences and core values, and helping them weigh the risks and benefits of the relevant treatment options. Furthermore, to facilitate communication between the primary attending physicians and the patient/family, the team delivered the interview contents to the primary care team along with recommendations for care planning.

Because the Life-sustaining Treatment Decision Act did not specifically mention withholding or withdrawing antibiotic treatment, the routine antimicrobial stewardship programme performed by infectious diseases specialists was not involved in this consultation process. The primary attending physicians continued to make decisions regarding medical procedures, such as the prescription and discontinuation of antibiotics, after palliative care consultations, just as they did with the non-palliative care consultation group.

Outcomes

The primary outcome was the proportion of patients receiving IV and/or oral antibiotic treatment within 3 days before death. The proportion of patients who received antibiotics on the day of death was also compared. The administration of at least one dose of antibiotics on these calendar days was considered an outcome measure. Additionally, specific antibiotic use (including quinolones, third-generation cephalosporins, piperacillin/tazobactam, carbapenems and glycopeptides) during this period were compared concerning the proportion of patients receiving antibiotics and days of therapy (DOT) per 1000 patient-days.²³ These outcome measures were compared in a sensitivity analysis, excluding patients with positive test results from blood cultures within 2 weeks of death.

Covariates of interest

We extracted clinical data that might have influenced antibiotic use within 3 days before death from electronic medical records. These variables included demographics, presence of physician orders for life-sustaining treatment (POLST), history of receiving anti-cancer chemotherapy within 1 month of death, admission duration, the year when the patients died, comorbidities represented as Charlson comorbidity score excluding cancer status, route of admission (via outpatient clinic or emergency department), admission department (medical, surgical or emergency), death in ICU, presence of fever ($\geq 37.5^\circ\text{C}$ measured at the axilla) within 2 weeks of death, presence of leucocytosis (WBC count $> 10\,000$ cells/ mm^3), or neutropenia (absolute neutrophil count < 500 cells/ mm^3) within 2 weeks of death, presence of abnormal C-reactive protein value (> 0.5 mg/dL) within 2 weeks of death, and positive results for blood culture suggesting bacteraemia within 2 weeks of death.

Statistical analysis

Continuous variables are expressed as medians with IQR and are compared using the Wilcoxon rank-sum test. Categorical variables are expressed as numbers with percentages and are compared using the chi-squared test. Because group allocation was not randomized in this retrospective cohort study, we applied propensity score weighting to minimize confounding using two-step multivariable regression models.²⁴ To identify variables that influenced the propensity to undergo palliative care consultation, we conducted univariate analysis for each variable, as appropriate. Multivariable logistic regression was used to estimate the propensity score for receiving palliative care consultations. Variables were considered in multivariable logistic regression model if the *P* value of a univariate association with palliative care consultation was < 0.10 . Goodness of fit of the multivariable logistic regression modelling of the propensity to receive palliative care consultation was assessed using the Hosmer–Lemeshow test. To perform the inverse probability of treatment weighting method, weights were constructed as the inverse of the probability of receiving palliative care consultation ($1/\text{propensity score}$) among those in the consultation group and as the inverse of the probability of not receiving palliative care consultation ($1/1 - \text{propensity score}$) among those in the non-consultation group. Balances between groups were evaluated by the covariates of standard difference. We considered standard difference in excess of 10% as imbalance in covariates

Table 1. Baseline characteristics of study population

Characteristics	Non-consult (n=675)	Consult (n=468)	Standard difference unweighted	Standard difference weighted ^a	Weighted P value ^b
Age, median (IQR)	66 (59–73)	64 (56–72)	–0.205	0.008	0.930
Male sex, n (%)	430 (63.7)	273 (58.3)	–0.110	–0.008	0.913
Year, n/N (%)			0.252	–0.004	0.924
2018	272/401 (67.8)	129/401 (32.2)			
2019	224/405 (55.3)	181/405 (44.7)			
2020	179/337 (53.1)	158/337 (46.9)			
Charlson comorbidity index ^c , median (IQR)	0 (0–1)	0 (0–1)	–0.192	–0.007	0.938
0	412 (61.0)	324 (69.2)			0.766
>0	263 (39.0)	144 (30.8)			
Admission route, n (%)			–0.031	0.017	0.705
Outpatient clinic	298 (44.2)	214 (45.7)			
Emergency department	377 (55.8)	254 (54.3)			
Admission duration, median (IQR)	14 (8–26)	20 (12–34.5)	0.261	–0.013	0.675
Admitting department, n (%)			–0.191	–0.032	0.761
Medical	575 (85.2)	423 (90.4)			
Surgical	56 (8.3)	33 (7.1)			
Emergency	44 (6.5)	12 (2.5)			
Fever, n (%)	471 (69.8)	288 (61.5)	–0.174	0.010	0.848
Hypotension, n (%)	415 (61.5)	246 (52.6)	–0.181	–0.022	0.791
Leucocytosis or neutropenia, n (%)	475 (70.4)	287 (61.3)	–0.191	–0.025	0.708
Abnormal C-reactive protein, n (%)	528 (78.2)	315 (67.3)	–0.247	–0.004	0.936
Positive blood culture, n (%)	142 (21.0)	76 (16.2)	–0.123	–0.023	0.924
Anti-cancer chemotherapy, n (%)	246 (36.4)	118 (25.2)	–0.244	–0.022	0.828
POLST, n (%)	237 (35.1)	250 (53.4)	0.375	0.013	0.798
Death site, n (%)			–0.409	–0.019	0.874
General ward	529 (78.4)	433 (92.5)			
ICU	146 (21.6)	35 (7.5)			

^aAfter applying inverse probability of treatment weighting.

^bP value of the coefficient of palliative care consultation and covariate are presented.

^cExcept cancer status.

between groups.²⁵ After applying the inverse probability of treatment weighting, the predictive probabilities of outcomes were compared.

The second multivariable logistic regression analysis was used to calculate the OR with a 95% CI for the primary outcome. All factors clinically relevant to the outcome were evaluated using univariate analysis; variables with $P < 0.10$ were included in the multivariate analysis to adjust for the effect of palliative care consultation. The inverse probability of treatment weighting was also applied in the multivariate model to adjust for the propensity to receive palliative care consultation. To assess homogeneity, we repeated these analyses for different populations: age (≤ 50 , > 50 and ≤ 70 , > 70 years), year (2018, 2019, 2020), receiving anti-cancer chemotherapy within 1 month of death (yes, no), presence of POLST (yes, no) and admission duration (≤ 14 days, > 14 days).

All reported P values were two-tailed, and those < 0.05 were considered statistically significant. All statistical analyses were performed using STATA, version 15.0 (StataCorp LP, College Station, TX, USA).

Results

During the study period, 1689 patients with malignancy died in the hospital. Of these deceased patients, 546 patients with non-metastatic solid tumour or haematological malignancies were

excluded from the analysis. Finally, the study population included a non-palliative care consultation group ($n = 675$) and a palliative care consultation group ($n = 468$). Median time from receiving palliative care consultation to death was 12 days (IQR 7 to 24.5 days). The majority of patients (391/468; 83.5%) received palliative care consultation after admission. Overall, hepatobiliary-pancreatic cancer was the most common type of cancer ($n = 423$; 37.0%), followed by lung and intrathoracic cancers ($n = 257$; 22.5%), gastrointestinal cancer ($n = 168$; 14.7%), breast cancer ($n = 86$; 7.5%), bone and soft tissue cancers ($n = 49$; 4.3%), genitourinary cancer ($n = 46$; 4.0%), gynaecological cancer ($n = 44$; 3.8%) and other cancers ($n = 70$; 6.2%). These frequencies were similar in the two groups.

The baseline characteristics of the two groups are highlighted in Table 1. Among 487 patients who completed the POLST documentation, 72 (14.8%) did it before the admission. Except for the admission route, all other remaining baseline characteristics showed significant differences between the two groups and were associated with the propensity to receive palliative care consultation in univariate analysis [Table 1, Table S1 (available as [Supplementary data](#) at JAC Online)]. Multivariate logistic regression analysis

Table 2. Comparison of antibiotic use before and after propensity score weighting

	Non-consult (n=675)	Consult (n=468)	Crude P value ^a	Weighted P value ^b
Antibiotic use within 3 days before death, n (%)	596 (88.3)	344 (73.5)	<0.001	<0.001
Antibiotic use on death date, n (%)	455 (67.4)	236 (50.4)	<0.001	<0.001
Carbapenems				
Proportion, n (%)	286 (42.4)	105 (22.4)	<0.001	<0.001
DOT per 1000 patient-days	307.0	160.3	<0.001	0.004
Glycopeptides				
Proportion, n (%)	157 (23.3)	52 (11.1)	<0.001	<0.001
DOT per 1000 patient-days	148.5	73.2	0.028	0.025
Piperacillin/tazobactam				
Proportion, n (%)	241 (35.7)	136 (29.1)	0.019	0.149
DOT per 1000 patient-days	251.5	228.6	0.329	0.461
Third-generation cephalosporins				
Proportion, n (%)	117 (17.3)	66 (14.1)	0.144	0.506
DOT per 1000 patient-days	110.0	98.3	0.093	0.052
Quinolones				
Proportion, n (%)	206 (30.5)	91 (19.4)	<0.001	0.012
DOT per 1000 patient-days	232.2	144.8	<0.001	0.008

^aChi-squared test or Wilcoxon rank-sum test, as appropriate.

^bAfter applying inverse probability of treatment weighting.

Table 3. Univariate and multivariate analysis for probability of receiving antibiotics within 3 days before death

	No antibiotic use (n=203)	Antibiotic use (n=940)	Univariate, OR (95% CI)	P value	Multivariate, OR (95% CI)	P value
Age (years), median (IQR)	65 (57–73)	65 (58.5–73)	1.00 (0.99–1.02)	0.625	0.99 (0.98–1.01)	0.503
Male sex, n (%)	114 (56.2)	589 (62.7)	1.31 (0.96–1.78)	0.085	1.31 (0.90–1.90)	0.154
Year, n (%)			0.80 (0.67–0.97)	0.024	0.81 (0.65–1.01)	0.067
2018 (n=401)	58 (14.5)	343 (85.5)	reference			
2019 (n=405)	75 (18.5)	330 (81.5)				
2020 (n=337)	70 (20.7)	267 (79.3)				
Charlson comorbidity score, median (IQR)	0 (0–1)	0 (0–1)	0.99 (0.87–1.12)	0.846		
Admission via emergency visit, n (%)	92 (45.3)	539 (57.3)	1.62 (1.20–2.20)	0.002	1.17 (0.80–1.70)	0.420
Admission duration (days), median (IQR)	23 (10–40)	16 (9–27)	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
Admitting department			1.96 (1.26–3.06)	0.003	1.24 (0.67–2.28)	0.498
Medical (n=998)	188 (18.8)	810 (81.2)	reference			
Surgical (n=89)	14 (15.7)	75 (84.3)				
Emergency (n=56)	1 (0.2)	55 (99.8)				
Leucocytosis or neutropenia, n (%)	105 (51.7)	657 (69.9)	2.17 (1.59–2.95)	<0.001	0.68 (0.32–1.44)	0.314
Abnormal C-reactive protein, n (%)	113 (55.7)	730 (77.7)	2.77 (2.02–3.80)	<0.001	1.49 (0.54–4.07)	0.441
Positive blood culture, n (%)	17 (8.4)	201 (21.4)	2.98 (1.77–5.01)	<0.001	3.05 (1.65–5.64)	<0.001
Fever, n (%)	92 (45.3)	667 (71.0)	2.95 (2.16–4.02)	<0.001	2.19 (1.21–3.95)	0.009
Hypotension, n (%)	92 (45.2)	569 (60.5)	1.85 (1.36–2.51)	<0.001	0.77 (0.44–1.33)	0.343
Receipt of anti-cancer chemotherapy, n (%)	59 (29.1)	305 (32.5)	1.17 (0.84–1.63)	0.348		
POLST, n (%)	90 (44.3)	397 (42.2)	0.92 (0.68–1.25)	0.583		
Death in ICU, n (%)	10 (4.9)	171 (18.2)	4.29 (2.23–8.28)	<0.001	4.19 (1.71–10.26)	0.002
Palliative care consultation, n (%)	124 (61.1)	344 (36.6)	0.37 (0.27–0.50)	<0.001	0.46 (0.33–0.65)	<0.001

revealed that age, years, Charlson comorbidity score, admission duration, positive blood culture, anti-cancer chemotherapy, POLST and death in the ICU were independently associated with the

propensity to receive palliative care consultation (Table S1). After the inverse probability of treatment weighting was applied, the variables of the two groups were balanced (Table 1).

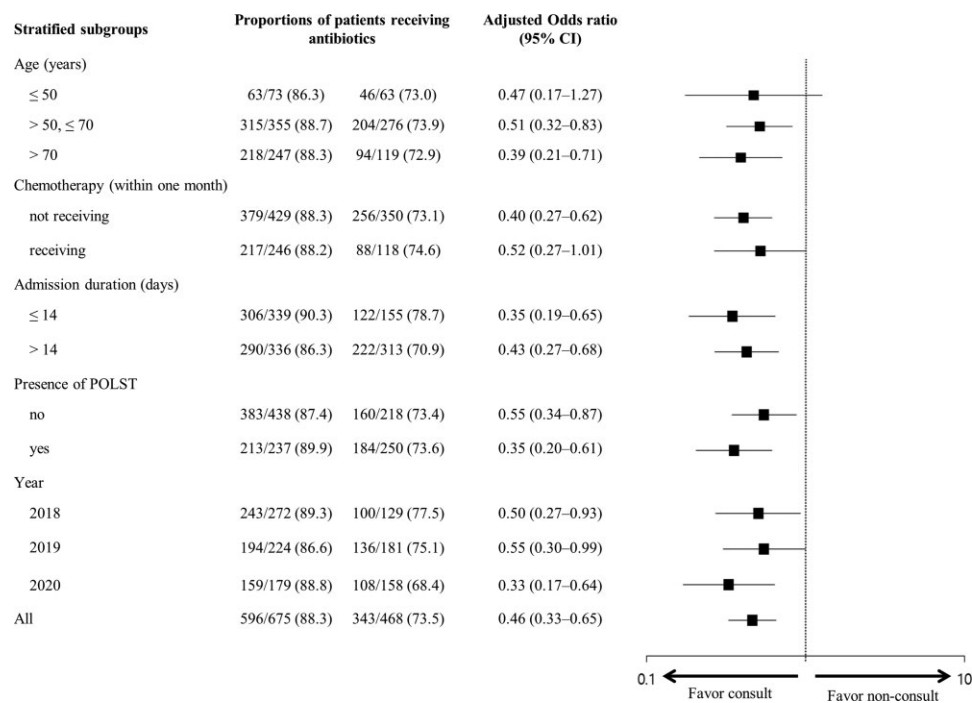


Figure 1. The probability of receiving antibiotics within 3 days before death as per stratified group analysis.

Outcomes

Among 1143 patients, 940 (82.2%) received antibiotics within 3 days before death. After adjusting for the propensity to receive palliative care consultation, the proportion of patients receiving antibiotics was significantly lower ($P < 0.001$) in the palliative care consultation group (344/468; 73.5%) than in the non-palliative care consultation group (596/675; 88.3%) (Table 2). Additionally, the proportion of patients receiving antibiotics on the day of death was significantly lower ($P < 0.001$) in the palliative care consultation group (236/468; 50.4%) than in the non-palliative care consultation group (455/675; 67.4%). The results were consistent even after excluding patients with positive results for blood cultures (Table S2).

The decrease in the proportion of patients receiving antibiotics in the palliative care consultation group, compared with the non-palliative care consultation group, was significant for carbapenems ($P < 0.001$), glycopeptides ($P < 0.001$) and quinolones ($P = 0.012$). Additionally, carbapenem ($P = 0.004$), glycopeptide ($P = 0.025$) and quinolone ($P = 0.008$) consumption were significantly lower in the palliative care group than in the non-palliative care consultation group.

Analyses for probability of receiving antibiotics within 3 days before death

The univariate and multivariable analysis of the probability of receiving antibiotic treatment is presented in Table 3. Receiving palliative care consultation was significantly associated with lower odds of antibiotic administration 3 days before death (crude OR 0.37; 95% CI 0.27–0.50; $P < 0.001$). Age, sex and statistically significant factors (all $P < 0.100$) were included in multivariate

analysis to adjust for the effect of palliative care consultation. In the multivariate analyses, receiving palliative care consultation [OR 0.46 (95% CI 0.33–0.65); $P < 0.001$], death in the ICU [OR 4.19 (95% CI 1.71–10.26); $P = 0.002$], admission duration [OR 0.98 (95% CI 0.97–0.99); $P < 0.001$], fever [OR 2.19 (95% CI 1.21–3.95); $P = 0.009$] and positive results for blood cultures within 2 weeks of death [OR 3.05 (95% CI 1.65–5.64); $P < 0.001$] were independently associated with receiving antibiotics during this period. Receiving palliative care consultation generally remained an independent factor associated with reduced antibiotic use in stratified analysis of different populations (Figure 1).

Discussion

The rationales that should decrease antibiotic overuse in hospitalized patients with terminal cancer during the end-of-life phase are as follows: to reduce antibiotic-associated adverse events for each patient; to mitigate antibiotic selection pressure; and to prevent the emergence of MDR organisms for public health.^{14,26} We observed that palliative care consultation reduced antibiotic use in hospitalized patients with terminal cancer during the end-of-life phase. Moreover, exposure to broad-spectrum antibiotics, including carbapenems and glycopeptides, decreased by nearly half in the palliative care consultation group. To our knowledge, the present study is the first comparative study to evaluate the effect of palliative care consultation on antibiotic use in hospitalized patients with terminal cancer during the end-of-life phase.

In our study, a high proportion of patients received antibiotics at the end of life (81.6%), which is a result similar to that reported in other studies.^{3,7,27} In the real world, withholding or withdrawing

antibiotics at the end-of-life phase is one of the most complicated medical decisions due to multidimensional facets with ethical dilemma, including difficulties of distinguishing between infection and cancer-related inflammation, the effectiveness of antibiotic treatment (to prolong life or control infection-related symptoms), difficulties in estimating cancer-related prognosis, and the relationship with other life-sustaining treatment.²⁸ Additionally, this medical decision may be affected by the physician's medical paternalism, which is based on technology-oriented medicine that overlooks distinct characteristics of the end-of-life situation.²⁹ Physicians may feel guilty discontinuing the antibiotics when patients present signs of inflammation^{8,30} and believe that the benefits of continuing antibiotic treatment outweigh the risks of possibility for clinical deterioration which can occur after stopping antibiotic administration, even if there is insufficient evidence of patients having a definitive infection.

The finding that palliative care consultation was associated with reduced antibiotic use near death can be explained by two aspects of core components: goals of care discussion with patients/family caregivers and facilitation of end-of-life communication between stakeholders. Regarding the appropriateness of antibiotic use in end-of-life care, we should consider medical indications and ethical concerns such as whether the use is goal-concordant with the patient's wishes.³¹ During goals-of-care discussion, the palliative care team helps patients and/or their surrogate decision-makers explore and clarify the core value and preferences (i.e. 'what do you want during the end-of-life care in the hospital?').³² In addition, the team can help attending physicians maintain high-quality communication with patients/family caregivers regarding end-of-life care through consultation content and palliative care education. The close interaction of specialized palliative care teams with primary attending physicians in our study may have contributed to reducing antibiotic use and de-prescribing broad-spectrum antibiotics in patients at the end-of-life phase.³³ Similarly, there is literature on the positive effect of palliative care consultation on de-prescribing unnecessary medications.³⁴ Douglas et al.¹⁷ reported that physicians without formal education in palliative care are more likely to use antibiotics in this setting.

Even though patients received palliative care consultations, a significant proportion of patients (73.5%) were still prescribed antibiotics during the imminent death period. This may reflect the Korean trend of aggressive cancer care near the end of life due to family-centred culture and regarding death as a taboo.³⁵ But also, there are several clinical implications for improving antibiotic overuse among end-of-life patients with terminal cancer. First, this study was based in an acute-care hospital, not at a hospice facility, which would explain why the high proportion of patients receiving palliative care consultation were still given antibiotics near death. Current literature on antibiotic use for end-of-life care has focused on hospice facilities; therefore, this study may provide valuable data on reducing antibiotic overuse among terminal cancer patients in a different setting. Second, consultation-based palliative care does not include antimicrobial stewardship performed by infectious disease specialists and pharmacists. As palliative care consultation can reduce antibiotic use, recent data suggest that antimicrobial stewardship programmes can also reduce antibiotic use in terminal cancer patients without unfavourable outcomes.³⁶ Third, the effect of palliative care

consultation on antibiotics became prominent over time after the enforcement of the Life-Sustaining Treatment Decision Act, as shown in the stratified analysis; therefore, it is thought that the legal foundation is more settled and may influence the effect.

The primary limitation of this study was its retrospective design, which prevented a better understanding of the intention to prescribe antibiotics for end-of-life care. Specifically, whether antibiotic use was intended to treat a confirmed infection to prolong life or used empirically to relieve infection/cancer-mediated inflammation-induced symptoms was unclear. Therefore, this observational study could not show a causal sequence between not administering antibiotics and associated outcomes and could not provide a rationale for what proportion of antibiotics used in end-of-life phase patients should be reduced. Second, since our study only focused on regarding antibiotic use before 3 days of death, it was difficult to evaluate the effect of palliative care consultation on reducing antibiotic use during other periods. Third, despite adjustment for many potential confounders and propensity to receive palliative care consultation, the impact of residual confounding by indication may have persisted in the retrospective, observational design. Lastly, it was a single-centre study, which could reduce the applicability of study findings to other hospital settings.

In conclusion, this study demonstrated that palliative care consultation would reduce aggressive antibiotic use in hospitalized patients with terminal cancer during the end-of-life phase. Additionally, these data suggest that antibiotics may be administered due to various ethical issues rather than clinical indications of infectious disease in this patient group. The uncertainty of the benefits and harmful effects of antibiotic use in palliative care at the end of life instigates further prospective research to validate these data to clarify the role of antibiotic use in this setting.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 are available as [Supplementary data](#) at JAC Online.

- ## References
- Macedo F, Nunes C, Ladeira K et al. Antimicrobial therapy in palliative care: an overview. *Support Care Cancer* 2018; **26**: 1361–7. <https://doi.org/10.1007/s00520-018-4090-8>
 - Marcus EL, Clarfield AM, Moses AE. Ethical issues relating to the use of antimicrobial therapy in older adults. *Clin Infect Dis* 2001; **33**: 1697–705. <https://doi.org/10.1086/323757>
 - Thompson AJ, Silveira MJ, Vitale CA et al. Antimicrobial use at the end of life among hospitalized patients with advanced cancer. *Am J Hosp Palliat Care* 2012; **29**: 599–603. <https://doi.org/10.1177/1049909111432625>
 - Macedo F, Bonito N. Current opinion about antimicrobial therapy in palliative care: an update. *Curr Opin Oncol* 2019; **31**: 299–301. <https://doi.org/10.1097/CCO.0000000000000514>
 - Cardona-Morrell M, Kim J, Turner RM et al. Non-beneficial treatments in hospital at the end of life: a systematic review on extent of the problem.

- Int J Qual Health Care* 2016; **28**: 456–69. <https://doi.org/10.1093/intqhc/mzw060>
- 6** Peron EP, Hirsch AA, Jury LA *et al.* Another setting for stewardship: high rate of unnecessary antimicrobial use in a veterans affairs long-term care facility. *J Am Geriatr Soc* 2013; **61**: 289–90. <https://doi.org/10.1111/jgs.12099>
- 7** Oh DY, Kim JH, Kim DW *et al.* Antibiotic use during the last days of life in cancer patients. *Eur J Cancer Care (Engl)* 2006; **15**: 74–9. <https://doi.org/10.1111/j.1365-2354.2005.00603.x>
- 8** Rosenberg JH, Albrecht JS, Fromme EK *et al.* Antimicrobial use for symptom management in patients receiving hospice and palliative care: a systematic review. *J Palliat Med* 2013; **16**: 1568–74. <https://doi.org/10.1089/jpm.2013.0276>
- 9** Nakagawa S, Toya Y, Okamoto Y *et al.* Can anti-infective drugs improve the infection-related symptoms of patients with cancer during the terminal stages of their lives? *J Palliat Med* 2010; **13**: 535–40. <https://doi.org/10.1089/jpm.2009.0336>
- 10** Baghban A, Juthani-Mehta M. Antimicrobial use at the end of life. *Infect Dis Clin North Am* 2017; **31**: 639–47. <https://doi.org/10.1016/j.idc.2017.07.009>
- 11** Datta R, Zhu M, Han L *et al.* 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**: 27–33. <https://doi.org/10.1177/1049909119855617>
- 12** Levin PD, Simor AE, Moses AE *et al.* End-of-life treatment and bacterial antibiotic resistance: a potential association. *Chest* 2010; **138**: 588–94. <https://doi.org/10.1378/chest.09-2757>
- 13** Clark MD, Halford Z, Herndon C *et al.* Evaluation of antibiotic initiation tools in end-of-life care. *Am J Hosp Palliat Care* 2022; **39**: 274–81. <https://doi.org/10.1177/10499091211027806>
- 14** Seaton RA, Cooper L, Fairweather J *et al.* Antibiotic use towards the end of life: development of good practice recommendations. *BMJ Support Palliat Care* 2021; [bmjspcare-2020-002732](https://doi.org/10.1136/bmjspcare-2020-002732). <https://doi.org/10.1136/bmjspcare-2020-002732>
- 15** Ford PJ, Fraser TG, Davis MP *et al.* Anti-infective therapy at the end of life: ethical decision-making in hospice-eligible patients. *Bioethics* 2005; **19**: 379–92. <https://doi.org/10.1111/j.1467-8519.2005.00450.x>
- 16** Barlam TF, Cosgrove SE, Abbo LM *et al.* Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016; **62**: e51–77. <https://doi.org/10.1093/cid/ciw118>
- 17** Crispim DH, da Silva IO, de Carvalho RT *et al.* End-of-life use of antibiotics: a survey on how doctors decide. *Int J Infect Dis* 2022; **114**: 219–25. <https://doi.org/10.1016/j.ijid.2021.10.026>
- 18** Stiel S, Krumm N, Pestinger M *et al.* Antibiotics in palliative medicine—results from a prospective epidemiological investigation from the HOPE survey. *Support Care Cancer* 2012; **20**: 325–33. <https://doi.org/10.1007/s00520-011-1084-1>
- 19** Broom J, Broom A, Kirby E. The drivers of antimicrobial use across institutions, stakeholders and economic settings: a paradigm shift is required for effective optimization. *J Antimicrob Chemother* 2019; **74**: 2803–9. <https://doi.org/10.1093/jac/dkz233>
- 20** Hui D, dos Santos R, Chisholm G *et al.* Clinical signs of impending death in cancer patients. *Oncologist* 2014; **19**: 681–7. <https://doi.org/10.1634/theoncologist.2013-0457>
- 21** Hui D, Dos Santos R, Chisholm G *et al.* Bedside clinical signs associated with impending death in patients with advanced cancer: preliminary findings of a prospective, longitudinal cohort study. *Cancer* 2015; **121**: 960–7. <https://doi.org/10.1002/cncr.29048>
- 22** Hui D, Bruera E. Models of palliative care delivery for patients with cancer. *J Clin Oncol* 2020; **38**: 852–65. <https://doi.org/10.1200/JCO.18.02123>
- 23** Polk RE, Fox C, Mahoney A *et al.* Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. *Clin Infect Dis* 2007; **44**: 664–70. <https://doi.org/10.1086/511640>
- 24** Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ* 2019; **367**: l5657. <https://doi.org/10.1136/bmj.l5657>
- 25** Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015; **34**: 3661–79. <https://doi.org/10.1002/sim.6607>
- 26** Leibovici L, Paul M. Ethical dilemmas in antibiotic treatment: focus on the elderly. *Clin Microbiol Infect* 2015; **21**: 27–9. <https://doi.org/10.1016/j.cmi.2014.10.013>
- 27** Kwak YG, Moon C, Kim ES *et al.* Frequent prescription of antibiotics and high burden of antibiotic resistance among deceased patients in general medical wards of acute care hospitals in Korea. *PLoS One* 2016; **11**: e0146852. <https://doi.org/10.1371/journal.pone.0146852>
- 28** Broom J, Broom A, Good P *et al.* Why is optimisation of antimicrobial use difficult at the end of life? *Intern Med J* 2019; **49**: 269–71. <https://doi.org/10.1111/imj.14200>
- 29** Heo DS, Yoo SH, Keam B *et al.* Hospice-palliative medicine as a model of value-based healthcare. *J Korean Med Sci* 2022; **37**: e111. <https://doi.org/10.3346/jkms.2022.37.e111>
- 30** Abduh Al-Shaqi M, Alami AH, Zahrani AS *et al.* The pattern of antimicrobial use for palliative care in-patients during the last week of life. *Am J Hosp Palliat Care* 2012; **29**: 60–3. <https://doi.org/10.1177/1049909111406900>
- 31** Vaughan L, Duckett AA, Adler M *et al.* Ethical and clinical considerations in treating infections at the end of life. *J Hosp Palliat Nurs* 2019; **21**: 110–5. <https://doi.org/10.1097/NJH.0000000000000541>
- 32** You JJ, Fowler RA, Heyland DK *et al.* Just ask: discussing goals of care with patients in hospital with serious illness. *CMAJ* 2014; **186**: 425–32. <https://doi.org/10.1503/cmaj.121274>
- 33** van Buul LW, Sikkens JJ, van Agtmael MA *et al.* Participatory action research in antimicrobial stewardship: a novel approach to improving antimicrobial prescribing in hospitals and long-term care facilities. *J Antimicrob Chemother* 2014; **69**: 1734–41. <https://doi.org/10.1093/jac/dku068>
- 34** Marin H, Mayo P, Thai V *et al.* The impact of palliative care consults on deprescribing in palliative cancer patients. *Support Care Cancer* 2020; **28**: 4107–13. <https://doi.org/10.1007/s00520-019-05234-w>
- 35** Choi Y, Keam B, Kim TM *et al.* Cancer treatment near the end-of-life becomes more aggressive: changes in trend during 10 years at a single institute. *Cancer Res Treat* 2015; **47**: 555–63. <https://doi.org/10.4143/crt.2014.200>
- 36** Hung KC, Lee LW, Liew YX *et al.* Antibiotic stewardship program (ASP) in palliative care: antibiotics, to give or not to give. *Eur J Clin Microbiol Infect Dis* 2022; **41**: 29–36. <https://doi.org/10.1007/s10096-021-04325-z>