Association of Physician Orders for Life-Sustaining Treatment With Inpatient Antimicrobial Use at End of Life in Patients With Cancer

Olivia S. Kates,[1,2] Elizabeth M. Krantz,[2] Juhye Lee,[3] John Klaassen,[4] Jessica Morris,[2] Irina Mezheritsky,[4] Ania Sweet,[2,4] Frank Tverdek,[2,4] Elizabeth T. Loggers,[4,5,6] Steven A. Pergam,[1,2,4] and Catherine Liu[1,2,4]

[1]Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington, USA, [2]Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA, [3]Department of Basic Sciences and Computational Biology Program, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA, [4]Seattle Cancer Care Alliance, Seattle, Washington, USA, [5]Division of Oncology, University of Washington, Seattle, Washington, USA, and [6]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Background. Antimicrobial utilization at end of life is common, but whether advance directives correlate with usage is unknown. We sought to determine whether Washington State Physician Orders for Life Sustaining Treatment (POLST) form completion or antimicrobial preferences documented therein correlate with subsequent inpatient antimicrobial prescribing at end of life.

Methods. This was a single-center, retrospective cohort study of adult patients at a cancer center who died between January 1, 2016, and June 30, 2019. We used negative binomial models adjusted for age, sex, and malignancy type to test the relationship between POLST form completion ≥30 days before death, antimicrobial preferences, and antimicrobial days of therapy (DOT) per 1000 inpatient-days in the last 30 days of life.

Results. Among 1295 eligible decedents with ≥1 inpatient-day during the last 30 days of life, 318 (24.6%) completed a POLST form. Of 318, 120 (37.7%) were completed ≥30 days before death, 35/120 (29.2%) specified limited antimicrobials, 55/120 (45.8%) specified full antimicrobial use, and 30/120 (25%) omitted antimicrobial preference. Eighty-three percent (1070/1295) received ≥1 inpatient antimicrobial. The median total and intravenous (IV) antimicrobial DOT/1000 inpatient-days were 1077 and 667. Patients specifying limited antimicrobials had significantly lower total antimicrobial DOT (adjusted incidence rate ratio [IRR], 0.68; 95% CI, 0.49–0.95; *P* = .02) and IV antimicrobial DOT (IRR, 0.57; 95% CI, 0.38–0.86; *P* = .008) compared with those without a POLST.

Conclusions. Indicating a preference for limited antimicrobials on a POLST form ≥30 days before death may lead to less inpatient antimicrobial use in the last 30 days of life.

Keywords. advance directives; antimicrobial stewardship; cancer; end-of-life care, oncology.

Infections are common terminal events for patients with chronic diseases in the United States [1]. Previous reports indicate that 17% to 90% of patients receive antimicrobials near the end of life, with wide variability due to differences in patient populations, study setting (inpatient vs outpatient; hospice vs acute care), and period of assessment before death [2–13]. Antimicrobial use at end of life tends to be higher among patients with cancer (58%–87%) [14–19]. Patients with cancer experience a high rate of infectious complications and often experience symptoms of malignancy, such

as fever, pain, or dyspnea, that can be mistaken for infection. Among patients with cancer, antibiotic therapy is frequently continued after transition to comfort care and discontinued <1 day before death [16]. Many patients receive antimicrobials at the end of life despite uncertain palliative benefits, risk of adverse events including *Clostridioides difficile* colitis, increased antimicrobial resistance, and excess costs [2–5, 14–19].

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommend that antimicrobial stewardship programs offer guidance for care at the end of life, with goals of decreasing antimicrobial toxicities and costs and slowing the development of antimicrobial resistance [20]. However, there are limited data on strategies to guide antibiotic decision-making at the end of life. The decision to initiate antibiotic therapy among cancer patients at end of life is often made by clinicians without discussion with the patient or family [21]. Treatment-limiting advance directives have been shown to decrease utilization of life-sustaining therapies including

intensive care unit (ICU) admission [22]. However, the same impact has not been consistently demonstrated for antimicrobials [5–8, 23], leading to exclusion of antimicrobial use preferences from the National Physician Orders for Life Sustaining Treatment (POLST) form, and from POLST forms in a majority of states [24].

Before April 2021, the Washington State POLST form included an antimicrobial use preferences section [25]. We sought to determine the association between a POLST form completed ≥30 days before death and subsequent antimicrobial utilization among cancer patients during the last 30 days of life, as well as whether specification of antimicrobial preferences was associated with antimicrobial prescribing.

METHODS

Design, Setting, and Participants
We performed a single-center retrospective cohort study of adult patients at the Seattle Cancer Care Alliance (SCCA) who died between January 1, 2016, and June 30, 2019. The SCCA provides inpatient and outpatient cancer care and is affiliated with the University of Washington Medical Center. Together, these institutions comprise 677 inpatient beds. Study subjects were identified retrospectively through the electronic health record (EHR). Patients were eligible for inclusion in the study if they had 3 or more SCCA encounters (any inpatient, outpatient, or telemedicine visit) within 1 year before death, including at least 1 inpatient encounter within 30 days before death, or had a cancer-related diagnosis and died during an inpatient stay in either the SCCA Hospital or the affiliated University Hospital. The study and waiver of informed consent were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Data Collection
Patient demographics, malignancy type (determined from International Statistical Classification of Diseases and Related Health Problems [ICD], 10th version, diagnosis codes), presence or absence of POLST at the time of death, antimicrobial administrations, and hospitalization data were extracted from the EHR.

Antimicrobials
Inpatient and emergency department antimicrobial drug administrations during the last 30 days of life were extracted electronically. Antimicrobials with a topical, ophthalmic, otic, or vaginal route of administration were excluded. Medications used to manage chronic diseases (antiretrovirals for HIV, entecavir for hepatitis B infection, and rifaximin for hepatic encephalopathy) were excluded. Fidaxomicin and enteral vancomycin were excluded to avoid measuring a potential

antimicrobial toxicity—*C. difficile* infection—as a part of the outcome measure.

POLST
The Washington State POLST is a paper document that is scanned into the EHR and is recognized as a medical care order in both outpatient and inpatient settings. According to the Washington State Medical Association, the POLST form is intended for patients with "serious chronic or acute illness nearing its end stages or likely to progress to a life-threatening state suddenly," although the form can be completed by any patient at any time [22]. On the Washington State POLST in use before April 2021, in section D, "Non-emergency medical treatment preferences," patients can specify "Use antibiotics for prolongation of life" (hereafter "full use") or "Do not use antibiotics except when needed for symptom management" (hereafter "limited use") [25].

POLST completion date, POLST signatories (the patient or their representative and the provider), and treatment preferences including medical interventions and antimicrobial use preferences were abstracted by manual chart review by 1 individual (J.L.), who was blinded to study outcomes, and reviewed for accuracy by a second individual (O.K.). POLST forms completed ≥30 days before death were used as the main exposure for the primary analysis.

Outcomes
The primary outcome was inpatient antimicrobial use as measured by total antimicrobial days of therapy (DOT) per 1000 inpatient-days. Secondary outcomes were antimicrobial DOT per 1000 inpatient-days for intravenous antibiotics, antimicrobials with activity against methicillin-resistant *Staphylococcus aureus* (MRSA), nonfluoroquinolone antipseudomonals, carbapenems, fluoroquinolones, and antifungals (Supplementary Table 1). Categories were selected based on clinical importance at the end of life (treatment burden or challenges with transition to outpatient care) or importance for antimicrobial resistance.

Statistical Analysis
To test for an association between POLST completion ≥30 days before death and antimicrobial use in the last 30 days of life, we used negative binomial models with inpatient antimicrobial days of therapy as the dependent variable, and the natural logarithm of the total number of inpatient-days in the 30 days before death was included as an offset. For our primary exposure, POLST completion, we examined 2 different parameterizations; both used patients with no POLST as the reference group. First, we compared patients with any POLST completed ≥30 days before death with the reference group. Next, we divided patients with a POLST completed ≥30 days before death into categories

based on POLST antimicrobial specification and used indicator variables to compare each of the following categories with the reference group: patients specifying limited antimicrobial use, patients specifying full antimicrobial use, and patients with no antimicrobial preference indicated. Similar categories were created for patients with a POLST completed <30 days before death to compare with the reference group, though our primary analysis focused on POLST completed ≥30 days before death to ensure that the exposure occurred before the outcome assessment period. We present both unadjusted models and models adjusted for age at death, sex, race, and malignancy type (hematologic malignancies/transplant vs solid tumor). Model estimates are presented as incidence rate ratios (IRRs) with 95% confidence intervals. Similar models were used to evaluate secondary outcomes.

RESULTS

Patient Characteristics and POLST Completion

We identified 1295 eligible patients with at least 1 inpatient encounter within the 30 days before death (Figure 1). The median age was 64 years, and 769/1295 (59.4%) were male. Nearly two-thirds (800/1295, 61.8%) of decedents had a solid tumor diagnosis; 117/1295 (9.0%) had a bone marrow transplant (Table 1). At the time of death, 318/1295 patients (24.6%) had a POLST on file. Of 318, 120 (37.7%) were completed at least 30 days before death, including 35/120 (29.2%) that specified limited antimicrobial use and 55/120 (45.8%) that specified full antimicrobial use. In 30/120 (25%), the antimicrobial preferences section was not completed. A small number of POLST forms had internally inconsistent selections. Three of 120 patients requested comfort-directed care in general treatment preferences,
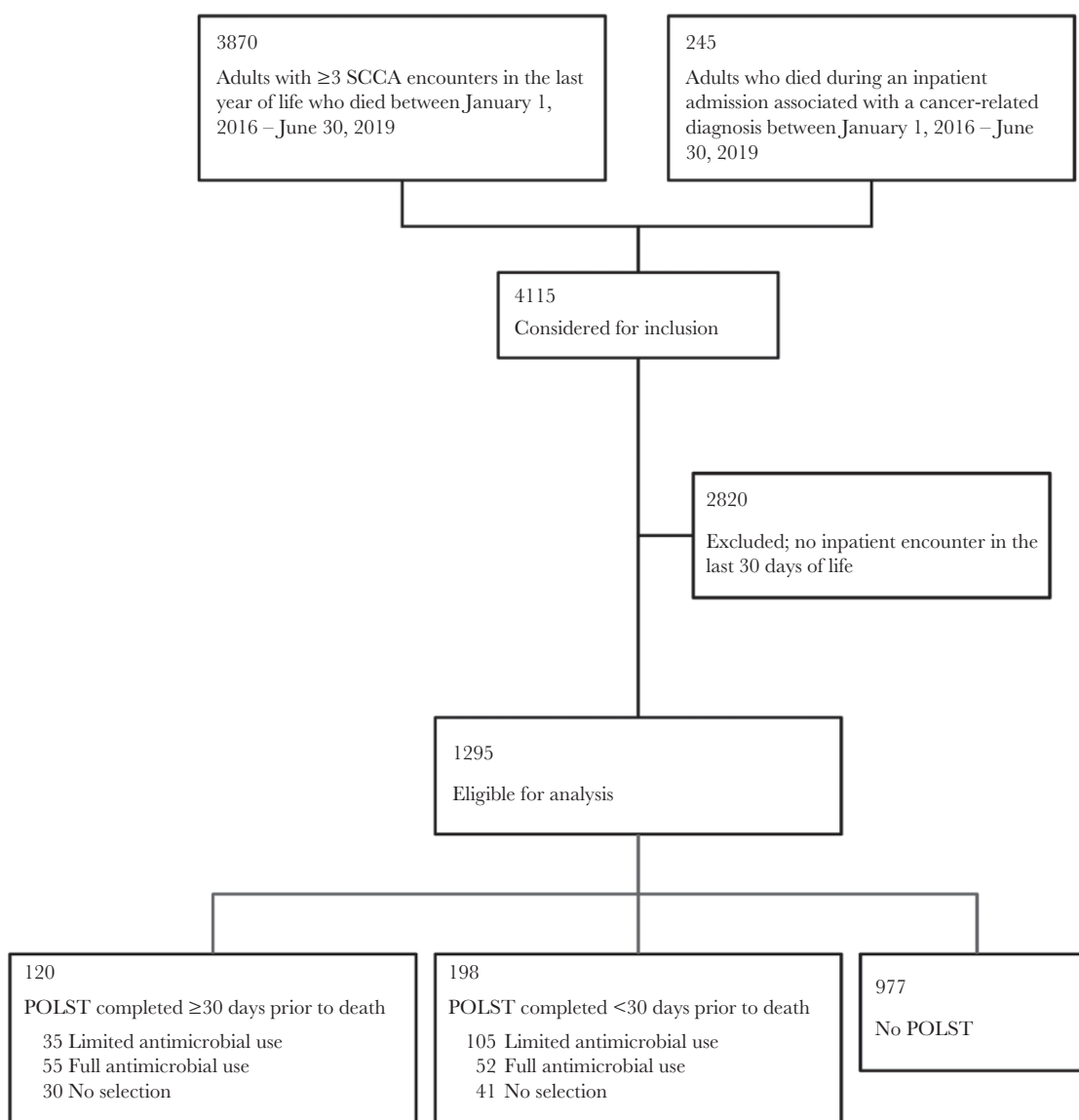
Figure 1. Study population. Abbreviations: POLST, Physician Orders for Life Sustaining Treatment; SCCA, Seattle Cancer Care Alliance.

Table 1. Baseline Demographic and Clinical Characteristics

	All Patients (n = 1295)	POLST Completed ≥30 Days Before Death[a]			POLST <30 Days Before Death (n = 198)	No POLST (n = 977)
		Limited Antimicrobial Use (n = 35)	Full Antimicrobial Use (n = 55)	No Antimicrobial Selection (n = 30)		
Age at death, median (IQR), y	64 (54–71)	68 (64–75)	69 (57–77)	68 (54–75)	65 (55–71)	63 (54–71)
Race, No. (%)						
Native American	20 (1.5)	1 (2.9)	0 (0)	1 (3.3)	6 (3.0)	12 (1.2)
Native Hawaiian	19 (1.5)	0 (0)	1 (1.8)	0 (0)	3 (1.5)	15 (1.5)
Asian	125 (9.7)	2 (5.7)	5 (9.1)	1 (3.3)	21 (10.6)	96 (9.8)
Black or African	71 (5.5)	2 (5.7)	2 (3.6)	3 (10)	16 (8.1)	48 (4.9)
White	1034 (79.9)	30 (85.7)	47 (85.5)	24 (80.0)	149 (75.3)	784 (2.3)
Unknown	26 (2.0)	0 (0)	0 (0)	1 (3.3)	3 (1.5)	22 (3.8)
Sex, No. (%)						
Female	526 (40.6)	14 (40.0)	27 (49.1)	16 (53.3)	76 (38.4)	393 (40.2)
Male	769 (59.4)	21 (60.0)	28 (50.9)	14 (46.7)	122 (61.6)	584 (59.8)
Oncology diagnosis,[b] No. (%)						
Heme/BMT	495 (38.2)	9 (25.7)	17 (30.9)	11 (36.7)	42 (21.2)	416 (42.5)
Acute leukemia	190 (14.7)	7 (20.0)	10 (18.2)	6 (20.0)	9 (4.6)	158 (16.2)
Lymphoma	109 (8.4)	2 (5.7)	3 (5.5)	2 (6.7)	17 (8.6)	85 (8.7)
Myeloid neoplasm	32 (2.5)	0 (0)	2 (3.6)	0 (0)	2 (1.0)	28 (2.9)
Plasma cell disorders	41 (3.2)	0 (0)	1 (1.8)	1 (3.3)	7 (3.5)	32 (3.3)
Bone marrow transplant	117 (9.0)	0 (0)	1 (1.8)	2 (6.7)	7 (3.5)	107 (11.0)
Other hematology	6 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0.6)
Solid tumor	800 (61.8)	26 (74.29)	38 (69.1)	19 (63.3)	156 (78.8)	561 (574)
Breast	58 (4.5)	3 (8.6)	5 (9.1)	3 (10.0)	9 (4.6)	38 (3.9)
Endocrine	14 (1.1)	0 (0)	1 (1.8)	1 (3.3)	2 (1.0)	10 (1.0)
Gastrointestinal	281 (21.7)	9 (25.7)	13 (23.6)	3 (10.0)	50 (25.3)	206 (21.1)
Genitourinary	96 (7.4)	3 (8.6)	6 (10.9)	1 (3.3)	22 (11.1)	64 (6.6)
Gynecological	43 (3.3)	1 (2.9)	3 (5.5)	1 (3.3)	9 (4.6)	29 (3.0)
Head and neck	41 (3.2)	1 (2.9)	1 (1.8)	2 (6.7)	12 (6.1)	25 (2.6)
Melanoma	21 (1.6)	0 (0)	2 (3.6)	0 (0)	2 (1.0)	17 (1.7)
Nervous system	23 (1.8)	1 (2.9)	0 (0)	2 (6.7)	4 (2.0)	16 (1.6)
Sarcoma	45 (3.5)	1 (2.9)	3 (5.5)	0 (0)	7 (3.5)	34 (3.5)
Thoracic	139 (10.7)	5 (14.3)	3 (5.5)	3 (10)	35 (177)	93 (9.5)
Other solid oncology	39 (3.0)	2 (5.7)	1 (1.8)	3 (0)	4 (2.0)	29 (3.0)
Inpatient-days during the 30 d before death among hospitalized patients, median (IQR)	11 (5–19)	6 (3–14)	7 (5–12)	10.5 (5–16)	10 (6–17)	11 (5–20)
Any ICU stay during the 30 d before death, No. (%)	600 (46.3)	5 (14.3)	21 (38.2)	13 (43.3)	57 (28.8)	504 (51.6)

Abbreviations: BMT, bone marrow transplant; ICU, intensive care unit; IQR, interquartile range; POLST, Physician Orders for Life Sustaining Treatment.

[a]Full antibiotic use refers to the selection "Use antibiotics for prolongation of life." Limited antibiotic use refers to the selection "Do not use antibiotics except when needed for symptom management."

[b]Oncologic diagnosis refers to the most recent primary oncologic diagnosis associated with a patient encounter.

Table 2. Antimicrobial Use in the 30 Days Before Death for all Patients and by Advance Directive Group

	All Patients (n = 1295), No. (%)	POLST Completed ≥30 Days Before Death[a]			POLST <30 Days Before Death (n = 198), No. (%)	No POLST (n = 977), No. (%)
		Limited Antimicrobial Use (n = 35), No. (%)	Full Antimicrobial Use (n = 55), No. (%)	No Antimicrobial Selection (n = 30), No. (%)		
Any inpatient antimicrobial use	1070 (83)	20 (57)	43 (78)	24 (80)	146 (74)	837 (86)
Any inpatient IV antimicrobial use	996 (77)	16 (46)	42 (76)	22 (73)	127 (64)	789 (81)
Any inpatient anti-MRSA antibiotic[b] use	715 (55)	10 (29)	32 (58)	16 (53)	78 (39)	579 (59)
Any inpatient nonfluoroquinolone antipseudomonal antibiotic[c] use	807 (62)	11 (31)	36 (65)	18 (60)	94 (47)	648 (66)
Any inpatient carbapenem use	240 (19)	2 (6)	7 (13)	5 (17)	20 (10)	206 (21)
Any inpatient fluoroquinolone use	455 (35)	8 (24)	19 (35)	11 (37)	57 (29)	360 (37)
Any inpatient antifungal use	436 (34)	6 (17)	17 (31)	5 (17)	31 (16)	377 (39)

Abbreviations: IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; POLST, Physician Orders for Life-Sustaining Treatment.

[a]Full antibiotic use refers to the selection "Use antibiotics for prolongation of life." Limited antibiotic use refers to the selection "Do not use antibiotics except when needed for symptom management."

[b]Anti-MRSA antibiotics are vancomycin (excluding enteral administration), daptomycin, ceftaroline, and linezolid.

[c]Nonfluoroquinolone antipseudomonal antibiotics are aztreonam, piperacillin, ticarcillin, ceftazidime, cefepime, ceftolozane, imipenem, meropenem, colistin, tigecycline, amikacin, gentamicin, tobramycin, and derivatives/combinations of these agents.

but requested life-prolonging rather than comfort-directed antimicrobials. Another 5 patients requested comfort-directed antimicrobials, but requested full use of other treatments to prolong life, including 2 who requested cardiopulmonary resuscitation.

Antimicrobial Utilization

Among the 1295 patients, 1070 (83%) received at least 1 inpatient antimicrobial, including 715/1295 (55%) who received antimicrobials with activity against MRSA, 807/1295 (62%) who received nonfluoroquinolone antipseudomonal antibiotics, and 240/1295 (19%) who received a carbapenem. The median overall antimicrobial DOT (range) was 1077 (0–7167) per 1000 inpatient-days, and the median intravenous antimicrobial DOT (range) was 667 (0–4379) per 1000 inpatient-days. Additional summaries of antimicrobial use overall and for subgroups defined by POLST completion are shown in Table 2, Figure 2, and Supplementary Figure 1.

Association of POLST Completion ≥30 Days Before Death With Inpatient Antimicrobial Use

Antimicrobials were administered to 87 of 120 (73%) inpatients with POLST completed at least 30 days before death and to 837 of 977 (86%) inpatients with no POLST. In univariable analysis, compared with those with no POLST, those with a POLST completed ≥30 days before death had significantly lower total antimicrobial DOT (IRR, 0.73; 95% CI, 0.59–0.90; $P = .003$) and IV antimicrobial DOT (IRR, 0.71; 95% CI, 0.57–0.89; $P = .003$); however, these differences were not significant in models adjusted for age, sex, race, and malignancy type (total antimicrobial DOT IRR, 0.86; 95% CI, 0.72–1.03; $P = .09$; IV antimicrobial DOT IRR, 0.81; 95% CI, 0.66–1.01; $P = .06$).

Association of Antimicrobial Preferences Among POLSTs Completed ≥30 Days Before Death With Inpatient Antimicrobial Use

Compared with those with no POLST, patients specifying limited antimicrobial use ≥30 days before death had significantly lower total antimicrobial DOT (adjusted IRR, 0.68; 95% CI, 0.49–0.95; $P = .02$) and IV antimicrobial DOT (adjusted IRR, 0.57; 95% CI, 0.38–0.86; $P = .008$) (Figure 3). These patients also had significantly lower antifungal DOT compared with those with no POLST (adjusted IRR, 0.45; 95% CI, 0.21–0.97; $P = .04$) (Supplementary Figure 2). No significant differences in anti-MRSA, fluoroquinolone, nonfluoroquinolone antipseudomonal, or carbapenem DOTs were observed for patients with a POLST completed at least 30 days before death, regardless of antimicrobial preferences, when compared with patients with no POLST (Supplementary Figure 2).

There were no significant differences in antimicrobial use (total, IV, or antimicrobial subclasses) when comparing those with a POLST ≥30 days before death who omitted the antimicrobial preferences section or those who specified full antimicrobials
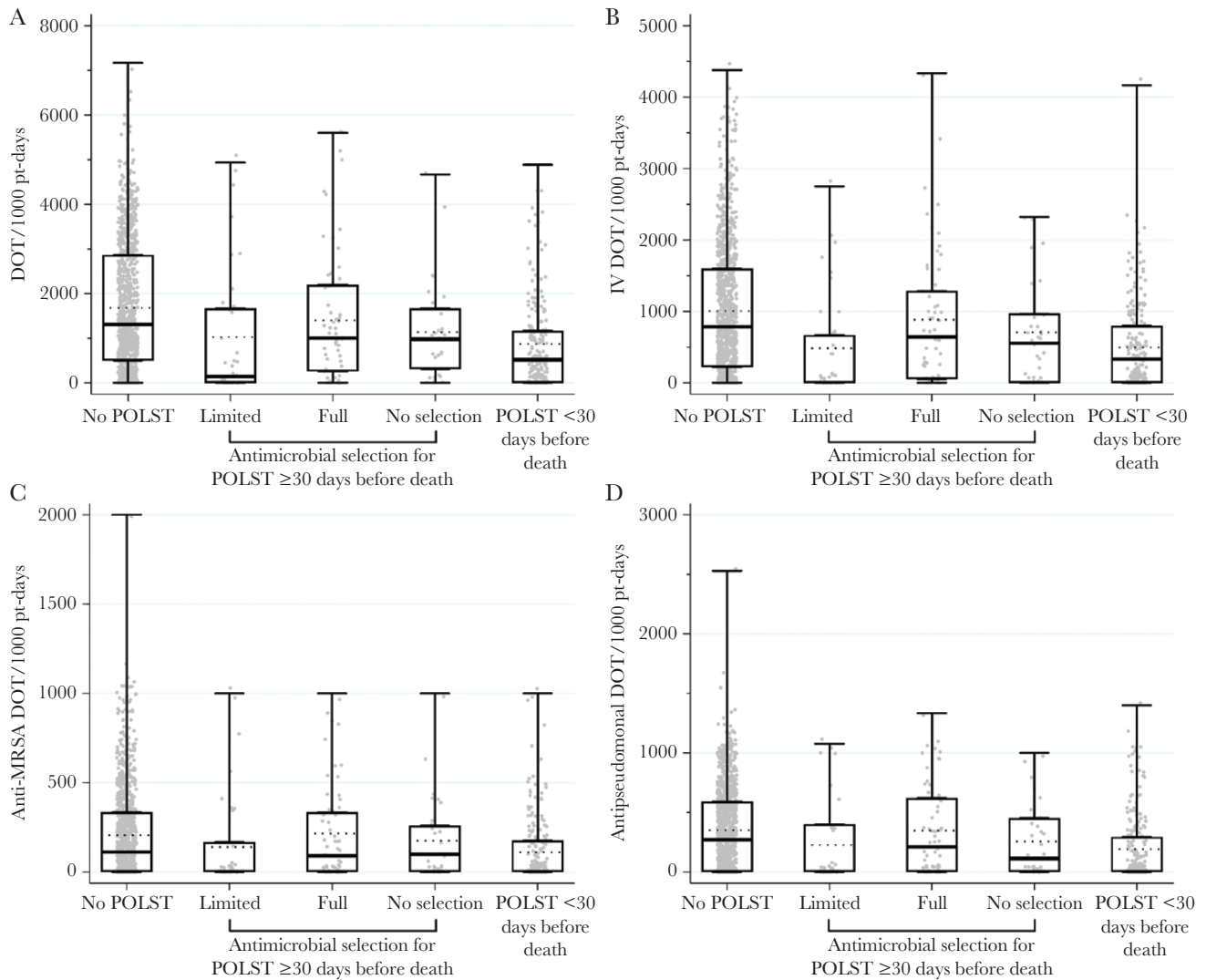
Figure 2. Antimicrobial use during the last 30 days of life by POLST group. Boxplots represent antimicrobial DOT per 1000 inpatient-days for patients with no POLST, for patients with POLST ≥30 days before death specifying limited antimicrobials, full antimicrobials, or omitting the antimicrobial preferences section, and for patients with POLST <30 days before death for all inpatient antimicrobials (A), inpatient IV antimicrobials (B), anti-MRSA antimicrobials (C), antipseudomonals (D). Boxes represent inter-quartile ranges, whiskers extend to the minimum and maximum values, and horizontal lines within the boxes represent the median (solid line) and mean (dotted line) values. Individual data points are shown as gray dots. Instances where no box is drawn indicate that the upper quartile was 0. Note that the scales of the y-axes differ by panel to accommodate the wide range of DOT values across panels. Abbreviations: DOT, days of therapy; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; POLST, Physician Orders for Life Sustaining Treatment.

with those with no POLST (Figure 3; Supplementary Figure 2). Additionally, antimicrobial use was not significantly different between patients who omitted the antimicrobial preferences section and those who specified full antimicrobials (total antimicrobial DOT adjusted models $P = .39$; IV antimicrobial DOT adjusted models $P = .46$).

Association of Antimicrobial Preferences Among POLSTs Completed <30 Days Before Death With Inpatient Antimicrobial Use

When compared with patients with no POLST, those who had a POLST completed <30 days before death had significantly lower inpatient total and IV antimicrobial DOT, regardless of antimicrobial preferences (Figure 3).

DISCUSSION

We found a high rate of antimicrobial use during the last 30 days of life among a large cohort of patients with cancer. To our knowledge, this is the first study to show a significant relationship between specification of antimicrobial use preferences on the POLST and subsequent inpatient antimicrobial use at end of life. We found a 32% lower rate of total inpatient antimicrobial use and a 43% lower rate of inpatient IV antimicrobial use among patients who expressed a preference for limited antimicrobial use ≥30 days before death compared with patients without a POLST. This supports our hypothesis that completion of the antimicrobial preferences section of the
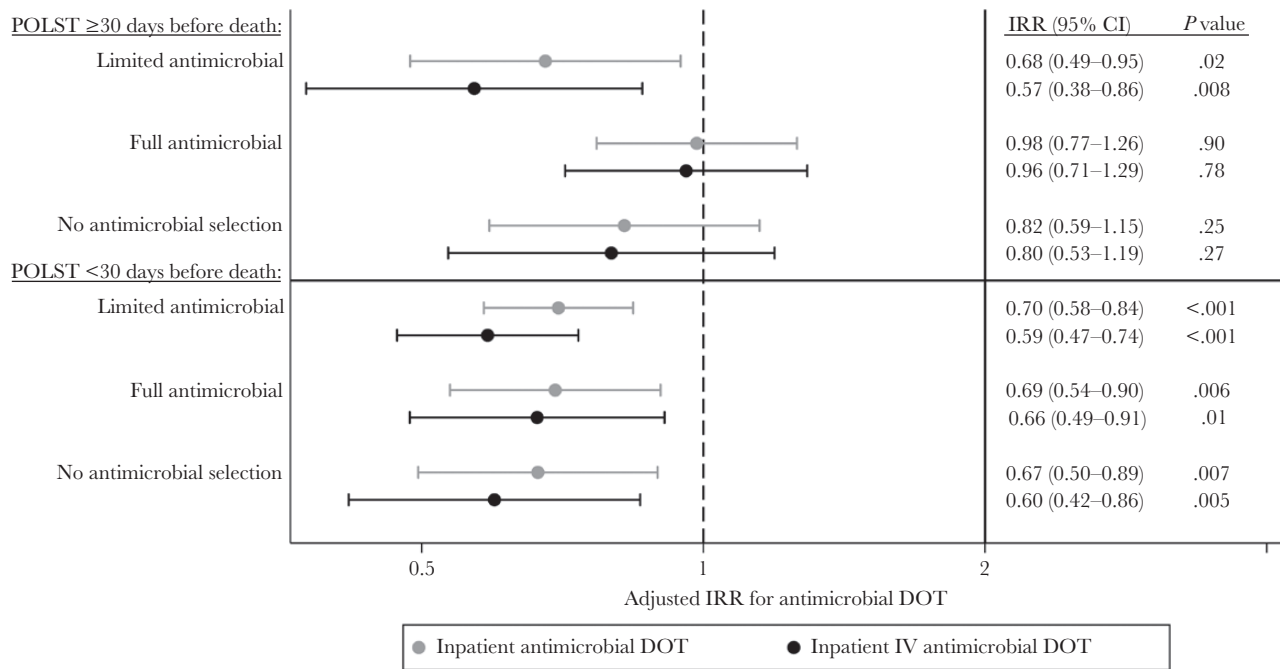
Figure 3. Associations between POLST antimicrobial preferences and antimicrobial use in the 30 days before death. Forest plot of model estimates, represented as IRRs with 95% CIs, for associations between POLST antimicrobial specifications completed ≥30 days before death or <30 days before death and inpatient antimicrobial DOT in the 30 days before death. Estimates represent comparisons between each POLST category and no POLST completed. Dots represent the IRRs, and brackets extend to the lower and upper limit of the 95% CIs. Light gray estimates are for the inpatient total antimicrobial DOT outcome, and dark gray estimates are for the inpatient IV antimicrobial DOT outcome. Abbreviations: DOT, days of therapy; IRR, incidence rate ratio; POLST, Physician Orders for Life Sustaining Treatment.

POLST form at an intermediate interval before death is associated with subsequent antimicrobial exposure in the 30 days before death.

Existing literature has described antimicrobial use for patients who choose to limit or withdraw life-sustaining care much closer to the moment of death, often in the final days or hours of life [9, 10, 14]. In contrast, our study considered completion of the antimicrobial section of the POLST at an earlier time point and evaluated the association with subsequent antimicrobial use extending to 30 days before death. When conversations about end-of-life antimicrobial use occur earlier relative to the moment of death, there may be more opportunity for patient and family participation, less emotional burden on patients, families, and clinicians, and more time for discussion and reflection [26]. Our data show that antimicrobial treatment preferences captured in these upstream conversations are associated with subsequent antimicrobial prescribing over a 30-day period before death. We are unable to draw conclusions based on findings in patients with a POLST completed <30 days before death in our study. These patients had consistently lower antimicrobial use than patients with no POLST; however, the timing of the exposure (POLST completion) relative to assessment of outcomes (antimicrobial use over the 30 days before death) is inconsistent in this group, leading to inherent problems with comparison.

A previous large study by Hickman et al. did not show a relationship between antimicrobial preferences documented on the POLST form and antimicrobial prescribing rates among 1711 long-term nursing facility residents [23]. However, the study was limited to treatments administered in long-term care facilities rather than in hospitals and did not focus on the final weeks of life. Furthermore, the rate of antimicrobial prescribing in that study was 35%, much lower than what was observed in our study, where 83% of inpatients received at least 1 antimicrobial.

Several additional findings highlight opportunities to improve goal-concordant care including antimicrobial use at end of life. First, the proportion of patients with a completed POLST in our cohort was low. Approximately 1 in 4 patients had a POLST form on file at the time of death, and only 1 in 10 completed a POLST form 30 days or more before death, despite a median age of >60 and an oncologic diagnosis for patients in this cohort. Barriers to early discussion of prognosis and completion of advance directives have been identified in multiple previous studies [27, 28].

Second, 25% of completed POLST forms omitted the antimicrobial preferences section. These patients had similar antibiotic use when compared with patients who specified full antimicrobial use and patients with no POLST. We also observed a small number of patients whose documented antimicrobial preferences appeared to be inconsistent with their general treatment preferences. Reasons for omissions or discrepancies are

unknown. Practical, social, and ethical considerations may impact decisions about whether and how to address antimicrobial preferences as a part of advance care planning [26]. A recent survey of inpatient medical subspecialists found that antimicrobials were infrequently discussed as a part of advance care planning, with respondents citing concern about overwhelming patients and families, practical challenges, and insufficient training. Further research should identify patient, clinician, and contextual factors associated with completion of the section and should seek to elucidate barriers to completion. Antimicrobial stewardship programs can play a role by partnering with palliative care providers to develop education, communication simulation exercises, and other tools to facilitate effective conversations about antimicrobial use during advance care planning [29].

In our study, completion of a POLST in and of itself was not associated with a significant impact on antimicrobial use; only patients who specified limited antimicrobial use had significantly less antimicrobial exposure. While all states' POLSTs include an order either to perform or not perform cardiopulmonary resuscitation in the event of cardiac arrest, opportunities to specify more detailed treatment preferences (eg, dialysis, medically assisted nutrition, antimicrobial use, or others) and the language used to present and characterize these options vary by state. Thirty-two state POLST forms mention antibiotics at least once, typically under the full treatment section, but as of November 1, 2020, only 18 states included a separate antimicrobial section in their POLSTS (Supplementary Table 2) [30]. After the completion of our study, Washington State modified their POLST form to no longer include an antimicrobial preferences section, bringing this number down to 17 states [31]. National POLST, an organization promoting a standardized version of the form, does not include an antimicrobial section but instead mentions antimicrobials among other treatments (noninvasive mechanical ventilation, intravenous hydration) in the Initial Treatment Orders section [32]. National POLST guidance materials from 2018 indicate that a separate antimicrobial section was removed from the national form and many state forms following the study by Hickman et al. in 2010 [23]. More recently, the organization has questioned whether that study provides a sufficient basis to discourage the use of an antibiotic section [24]. Along with the rising threat of antimicrobial resistance, we believe that findings from this study support restoration of the antimicrobial section to the National POLST form and to state-created forms that do not address this important topic.

Our study has several strengths. For our large cohort, we report comprehensive advance directive data paired with subsequent, detailed antimicrobial use data, establishing a possible temporal sequence of events rather than concurrent or cross-sectional associations. We focus on clinically relevant antimicrobials by excluding topical antimicrobials and medications used for the treatment of chronic diseases.

However, we acknowledge several limitations. First, we report a single-center experience in patients with cancer, which may not be generalizable to other centers or subpopulations, including populations with high rates of end-of-life antimicrobial use such as patients with advanced dementia or patients with end-stage organ dysfunction. Second, our data collection methods may not have captured all antimicrobial use, such as inpatient antimicrobials administered at other centers including inpatient hospice centers, and we did not address outpatient antimicrobial use. The potential bias from missing data is minimized in our analyses, which are restricted to patients with at least 1 inpatient-day where we have complete antimicrobial data. Third, the small number of patients with POLST completed at least 30 days before death and specifically with POLST specifying limited antimicrobial use may have limited our ability to detect an effect of POLST antimicrobial use preferences on additional outcomes such as antimicrobial subcategories. Fourth, our data do not allow us to explore additional factors of interest, including antimicrobial indication. Because of this, we are not able to assess the appropriateness or goal concordance of antimicrobials prescribed to patients who indicated a preference for limited antimicrobial use on their POLST forms. Goal-discordant prescribing may be an additional unmeasured barrier to the full potential impact of documenting antimicrobial preferences with the POLST on subsequent antimicrobial utilization. Fifth, with this observational study design, we were unable to exclude a contribution from unmeasured confounding variables, although we adjusted for key variables including patient age, malignancy type, and sex.

This study demonstrates that advance care planning and addressing antimicrobials using the POLST form may lead to decreased antimicrobial use at the end of life. The fact that only a fraction of patients in our study completed a POLST form, and many patients did not complete the antimicrobial preferences section, presents an opportunity for institutional improvement. Because most states do not offer patients this choice and Washington State recently stopped offering this choice, there is also an opportunity for broader policy change. Advance care planning is a potential context for antimicrobial stewardship that is aligned with the individual patient's wishes and has favorable implications for public health. Early discussion of advance directives including POLST with specification of antimicrobial use preferences may promote more thoughtful use of antimicrobials near the end of life in an ethical and patient-centered way.

Supplementary Data

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