A Nationwide Analysis of Antibiotic Use in Hospice Care in the Final Week of Life

Running Title: Antibiotic Use in Hospice Care

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Abstract

Context: Antibiotic prescribing in hospice patients is complicated by the focus on palliative rather than curative care and concerns regarding increasing antibiotic resistance.

Objective: To estimate antibiotic use in a national sample of hospice patients and identify facility and patient characteristics associated with antibiotic use in this population.

Methods: This was an analysis of data from the 2007 National Home and Hospice Care Survey, a nationally-representative sample of U.S. hospice agencies. We included data from 3,884 patients who died in hospice care. Our primary outcome measure was prevalence of antibiotic use in the last 7 days of life. Diagnoses, including potential infectious indications for antibiotic use, were defined using International Classification of Diseases, Ninth Revision (ICD-9) codes. Chi-square tests and t-tests were used to quantify associations of patient and facility characteristics with antibiotic use.

Results: During the last 7 days of life, 27% (95% confidence interval (CI); 24%, 30%) of patients received at least one antibiotic and 1.3% (95% CI; 0.7%, 2.0%) received $\geq$ 3 antibiotics. Among patients who received at least one antibiotic, 15% (95% CI; 10%, 20%) had a documented infectious diagnosis, compared with 9% (95% CI; 7%, 11%) who had an infectious diagnosis but received no antibiotics.

Conclusions: In this nationally-representative sample, 27% of hospice patients received an antibiotic during the last 7 days of life, most without a documented infectious diagnosis. Further research is needed to elucidate the role of antibiotics in this patient population to maintain palliative care goals while reducing unnecessary antibiotic use.

Introduction

Hospice is intended to provide palliative care for patients with a terminal diagnosis and offer support to them and their families. In the U.S., the number of patients utilizing hospice care has increased sharply. In 2009, an estimated 1.56 million patients received hospice care in the U.S., a 30% increase from 2005, and 41% of all U.S. deaths occurred in a hospice setting.(1) Furthermore, the aging of the U.S. population will no doubt continue to increase utilization of hospice services, especially among those aged 85 and older, who constitute the fastest growing group of hospice patients.(2)

Hospice patients are especially vulnerable to infection due to suppressed immune function following chemotherapeutic regimens in advanced cancer patients or due to multiple comorbid conditions, functional debility, and complex diseases which also compromise host resistance.(1, 3) Despite this increased risk, healthcare providers have little guidance regarding antibiotic use when caring for hospice patients.(4) Hospice care represents a change in focus from curative care to symptom management, thereby complicating the decision to use antibiotics.(5)

While Medicare hospice benefit guidelines explicitly define hospice care as 'palliative rather than curative,' in reality, many treatments do not clearly fit in one category of treatment goals.(6) Antibiotics are a case in point, since current evidence is divided regarding whether they improve symptoms.(7, 8) Furthermore, excess antibiotic use may unnecessarily increase patient and societal burdens in terms of side effects, use of invasive devices such as intravenous lines, and increasing healthcare costs as well as potentially increase selective pressure and for the development and spread of antimicrobial-resistant organisms.(4)

The frequency and determinants of antibiotic use in hospice patients have not been well described. A better understanding of prescribing patterns is essential for structuring guidelines for antibiotic use in this growing healthcare population. In this study, we used data from the 2007 National Home and Hospice Care Survey (NHHCS) to estimate antibiotic utilization in hospice care patients and identify potential infectious indications, and facility and patient characteristics associated with antibiotic use in this population.

Methods

The 2007 NHHCS was conducted by the Centers for Disease Control and Prevention and National Center for Health Statistics and is a nationally-representative sample of U.S. home health and hospice agencies which was designed to provide descriptive information on the agencies along with their staff, services, and patients. The survey design has been previously described in detail.(9) Briefly, the survey used a stratified two-stage probability sample design. In the first stage, 1,545 agencies were systematically and randomly sampled with probability proportional to agency size. The second stage consisted of randomly selecting up to 10 current home health patients per home health agency, up to 10 hospice discharges per hospice agency, and a combination of up to 10 current home health patients and hospice discharges per mixed agency. Hospice discharges were defined as patients who were discharged from the hospice agency during the 3-month period beginning 4 months before the agency interview.[9] For this study, we only included patients who were deceased at discharge.

Patient data were collected through in-person interviews with the hospice agency directors and designated staff in consultation with patients' medical records. Neither patients nor family members were interviewed. Patient data collected for NHHCS included demographic variables, as well as the current primary and secondary diagnoses at discharge, medication use in

the last seven days of care, and location of hospice care. Each patient received only one current primary diagnosis code which referred to the patient's primary diagnosis at discharge.

NHHCS medication data were collected using hospice care discharge medical records. The names of up to 25 medications that the patient received in the 7 days prior to and on the day of death were recorded. The medications were not recorded in any specified order and some patients may have received more than 25 drugs. Medications were categorized by therapeutic class using the Multum Lexicon.(10) We identified antibiotics using the Multum level 2 and level 3 categories which grouped these into 13 classes based on chemical structure. A 14th class, called "miscellaneous antibiotics" included aztreonam, bacitracin, atovaquone, linezolid, rifaximin, daptomycin, and vancomycin.

For descriptive purposes, we categorized the most prevalent primary diagnoses using International Classification of Diseases, Ninth Revision (ICD-9) codes. These categories included cancer (140.xx-239.xx), heart failure (428.xx), cardiovascular disease (CVD) (410.92, 413.9, 414.00, 414.9, 424.0, 424.1, 427.31, 427.9, 441.4, 441.9, 443.9, and 447.), chronic obstructive pulmonary disease (COPD;490.xx – 496.xx), dementia (290.0, 290.42, 294.8, 294.9, 331.0, 331.11, 331.4, 331.82, and 331.9), debility (799.3 and 783.7), cerebrovascular disease (430.x, 431.x, 432.1, 432.9, 434.11, 434.90, 437.3, 437.9, 438.20, 438.31, 438.89, and 438.9), renal disease (585.6, 585.9, and 586.x), and liver disease (570.x, 571.2, 571.3, 571.5, 571.9, 572.2, 572.3, 572.4, 572,8, and 573.9). The remaining primary diagnoses were grouped as 'other' in our analyses.

Potential infectious indications were identified using ICD-9 codes assigned for the current primary diagnosis and up to 15 current secondary diagnoses. The NHHCS does not

include infection-specific variables beyond urinary tract infections, respiratory tract infections, and wound infections as 'reasons for obtaining emergent care.' The diagnosis codes used to identify potential infectious indications are displayed in Table 1.

The location of hospice care corresponded to the site where the patient received hospice care on the day of discharge or death. Hospice care locations were categorized as one of the following: agency-run inpatient or residential facility, a private home, a residential care facility (assisted living), a nursing home or skilled nursing facility or a hospital. Profit status of the hospice agency was derived from agency-level data and coded as either for-profit or other, which included non-profit and government run hospices.

Data analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) and all percentage and confidence interval estimates were weighted to account for the survey's complex sampling design. The frequencies reported are unweighted to provide a clear description of the underlying data distribution. Descriptive statistics were calculated for patients' demographics, patients' clinical characteristics relating to hospice care, and hospice characteristics. The overall frequency of antibiotic use was calculated. The patient's primary diagnosis, presence of any infectious diagnosis, demographic, and facility characteristics were evaluated as potential factors associated with antibiotic use. The frequency of antibiotic use was compared between patient groups using chi-square tests for categorical variables and t-tests for continuous variables. All comparisons accounted for the sample weighting using subgroup analysis. This was accomplished in SAS using indicator variables in the SURVEYFREQ procedure for chi-square tests and indicator variables in the SURVEYREG procedure for t-tests. All tests were assessed for statistical significance at the $p<0.05$ level.

The institutional review boards (IRBs) at the University of Maryland, Baltimore and Oregon State University determined that this study was exempt from IRB oversight due to the use of publically-available, fully de-identified data.

Results

The 2007 NHHCS contains data on 4,733 hospice discharges, 3,884 (84%) of whom were deceased at the time of discharge. Characteristics of the sample are given in Table 2. The mean age of patients at discharge was 78 (standard deviation (SD): 0.4) years and 55% were female. The mean number of days of hospice care was 52 (SD: 3) days. The majority of the patients were non-Hispanic white (88%) and either married (42%) or widowed (38%).

Cancer, heart failure, CVD, chronic obstructive pulmonary disease (COPD), dementia, debility, cerebrovascular disease, renal and liver disease accounted for 87% of all current primary diagnoses with cancer representing the majority (45%). At discharge, the majority of patients were receiving care in a private homes (49%), followed by a nursing home/skilled nursing facility (23%). Not-for-profit hospices, including both government-run and traditional non-profits, provided services for 71% of hospice patients.

Hospice patients received a mean of 10 (95% confidence interval (CI): 9, 10) different medications in the last 7 days of life. There were 63 (1.5%) patients with the maximum number of medications documented (i.e., 25 medications). Approximately 27% of patients received antibiotics in the last 7 days of life. The mean number of antibiotics received by these patients was 1.3 (95% CI: 1.3, 1.4) and the maximum number of antibiotics received was 6. Furthermore, 1.3% of patients received 3 or more antibiotics. Among patients who received antibiotics, macrolide derivatives (49%), fluoroquinolones (26%) and miscellaneous antibiotics (19%) were

most frequently received (Table 3). The class-specific frequencies of antibiotics received by patients differed by their primary current diagnosis (data not shown).

Patients who received antibiotics differed from patients who did not receive antibiotics (Table 2). They were younger, with a mean age of 76 (SD, 0.7) years vs. 78 (SD, 0.5) years (p=0.001). Patients who received antibiotics had a longer duration of care; the mean length of hospice stay was 60 (SD 7) days compared to 48 (SD 4) days for those who did not receive antibiotics (p=0.001). Approximately 91% of patients who received antibiotics had advanced directives compared to 92% of those who did not receive antibiotics (p=0.4). Few patients (2%) had documented preferences to limit medications such as antibiotics. These did not differ significantly between patients who received antibiotics and did not receive antibiotics (1.6% vs. 2.4%, p=0.4).

Antibiotic use also varied significantly by current primary diagnosis. When the proportion of patients receiving antibiotics was examined within each diagnoses group, we observed that hospice discharges with a current primary diagnosis of COPD were more likely to receive antibiotics (34%) compared to discharges with cancer (23%), heart failure and CVD (16%), dementia (18%), debility (16%), cerebrovascular disease (6%), renal and liver disease (11%) or other diseases (24%)(p=0.008).

Among patients receiving antibiotics, 129 (15%) had documentation (primary or secondary ICD-9 diagnosis codes) for potential infectious indications (Figure 1). Pneumonia (7%), urinary tract infections (UTI) (4%), and skin and soft tissue infections including pressure ulcers (3%) accounted for the majority of these indications. Other documented infectious disease ICD-9 codes were for endocarditis, septicemia, tuberculosis, HIV, candidiasis, and intestinal infections. Patients with a documented UTI were not more likely to receive fluoroquinolones

(p=0.7), the antibiotic class most frequently used to treat UTIs, although patients receiving any antibiotic were significantly more likely to have a documented urinary catheter than patients who did not receive antibiotics (43% vs. 35%; p<0 .001). Among patients receiving antibiotics, those with documentation of a potential infectious indication differed significantly by facility type and primary diagnosis. Patients in nursing homes were most likely to have a documented potential infectious indication (26%) while those receiving hospice at a residential care place (were least likely (8%) (p=0.01). Finally, among those receiving antibiotics, patients with cerebrovascular disease were most likely to have a potential infectious indication documented (32%) while patients with cancer were least likely (8%) (p=0.004).

Discussion

There is ongoing debate regarding the appropriateness of antibiotic use in hospice patients. Concerns regarding antibiotic use in this patient population include potential lack of efficacy in reducing symptoms, increased patient burden, excess costs and risk of adverse effects, and increased antibiotic selective pressure and subsequent resistance. We examined the magnitude of antibiotic use in a nationally-representative sample of hospice patients and observed that 27% of hospice patients received antibiotics in the last 7 days of life. While lower than previous estimates of antibiotic utilization in hospice patients, which ranged from 36-84%, those studies focused on specific patient sub-groups, e.g. cancer patients, and examined antibiotic utilization for the entire duration of hospice care.(3, 11-13)

In addition to the providing estimates of antibiotic use, we sought to better understand facility and patient characteristics associated with receiving antibiotics. We observed that only

15% of patients who received antibiotics had an infectious disease diagnosis code. Medicare and most commercial hospice benefits provide reimbursement at a predetermined per diem rate for all hospice care, and as such, hospice providers do not have an incentive to document an infectious indication for antibiotic reimbursement. However, previous research has also suggested that outside of UTIs, treatment of known or suspected infections often does not improve symptoms among hospice patients.(3, 7, 8, 14) Additional research with better documentation of therapeutic rationale and symptom outcomes would improve current understanding of why antibiotics are prescribed in the last week of hospice care and whether or not they are effective.

Patients with a longer length of hospice care were more likely to receive antibiotics. However, underlying rationale for this association could not be explored in this cross-sectional study. Patients may have developed infections as a result of a longer length of hospice care or receiving antibiotics may have prolonged their lives. Previous research is divided on an explanation for this association. Some studies have observed a longer survival time in patients receiving antibiotics, while others have noted no significant difference in survival time.(3, 7, 8) Taken together with the observation that patients who received antibiotics were younger on average, it is also possible that those not receiving antibiotics were more severely ill and therefore survived a shorter period of time.

We observed that most patients had advanced directives, but few patients had specific directives regarding life-sustaining medications. A previous study of 255 advanced cancer patients upon admission to a community-based outpatient hospice facility observed that 79% of patients stated a preference for either no antimicrobial use or use directed only at alleviating symptoms.(7) However, a study of 870 patients in nursing facilities with POLST (Physician

Orders for Life Sustaining Treatment) antibiotic orders observed that the small proportion of patients with orders to limit antibiotics received them approximately as often as patients without orders to limit antibiotics.(15) Currently, the role of advance care planning in directing antibiotic therapy is unclear and warrants further study.

This study had several limitations. The NHHCS was designed to provide descriptive data on home health and hospice agencies, providers and patients. As such, data on route of administration or whether medication use resulted in symptom improvement were not available. In addition, and as was described earlier, the NHHCS data created antibiotic categories based upon therapeutic class, but also combined several antibiotics including bacitracin and vancomycin into a miscellaneous category. As such the frequency of these individual and potentially frequently used medications could not be estimated. Furthermore, documented infectious indications necessitating antibiotic use were identified using diagnosis codes; microbiology culture data were not available. Therefore, potentially appropriate empiric or prophylactic use of antibiotics may have seemed otherwise due to the lack of an infectious indication.

Despite these limitations, our study has several strengths. This is the first study to examine nationally-representative data on antibiotic utilization in the last 7 days of life for hospice patients. Previous studies examining antibiotic usage in hospice or palliative care have been limited to small studies of a single hospice facility or have focused primarily on cancer or dementia patients.(3, 12, 16, 17) As such, the generalizability of these studies may have been limited by geographic, cultural, and socioeconomic differences which could influence hospice care decisions including use of antibiotics.

The decision to use antibiotics in hospice care is difficult and complicated by provider, patient, and family beliefs. The probability of symptom improvement must be weighed against the burdens imposed on the patient as well as against hospital and societal concerns regarding increasing antibiotic resistance. The increasing utilization of hospice care and lack of clear guidelines regarding antibiotic use may lead to a growing number of patients receiving potentially unnecessary treatment for infection or not receiving potentially palliative treatments, thus further research is needed to guide antibiotic use in hospice care.

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Table 1. Potential infectious indications among patients receiving antibiotics from primary and secondary current diagnoses codes, n=1,028

Infection	ICD-9 Codes	n (%) [1]
Urinary Tract Infection	*590.x infections of kidney, *595.x cystitis, *599.0 urinary tract infection, *996.62 due to vascular device, implant and graft, 996.64 infection and inflammatory reaction due to indwelling urinary catheter	32 (4)
Respiratory Tract Infections	382.x suppurative and unspecified otitis media, 460 acute nasopharyngitis, 461.x acute sinusitis, 465.x acute upper respiratory infections of multiple or unspecified sites, 466.x acute bronchitis and bronchiolitis, *472.0 chronic rhinitis, *473.9, unspecified chronic sinusitis, *490.x bronchitis, not specified as acute or chronic	0
Rheumatic Fever, Bloodstream Infection, Endocarditis	390.x – 392.x acute rheumatic fever, 421.x acute and sub-acute endocarditis, *424.9 endocarditis valve unspecified, 790.7 bacteremia of blood	4 (1)
Mouth/pharynx infections	034 streptococcal sore throat and scarlet fever, 462 acute pharyngitis, 463 acute tonsillitis	0
Skin and Soft Tissue Infections	035 erysipelas, 680.x carbuncle and furuncle, *681.x cellulitis and abscess of finger and toe, *682.x other cellulitis and abscess, 684 impetigo, *686.x other local infections of skin and subcutaneous tissue *	9 (<1)
Pressure Ulcers	707.0x pressure ulcer, *707.1x ulcer of lower limbs, except pressure ulcer, *707.9 chronic ulcer unspecified	20 (2)

Pneumonia	*480.x -483.x pneumonia, 484.x pneumonia in infectious diseases classified elsewhere, *486.x organism unspecified, 487.x influenza	54 (7)
HIV	*042 human immunodeficiency virus [HIV] disease	9 (1)
Thrush	*112.x candidiasis	1 (<1)
Gastrointestinal Tract Infections	001.x cholera, 002.x typhoid and paratyphoid fevers, 003.x other salmonella infections, 004.x shigellosis, 005.x other food poisoning (bacterial), 006.x amebiasis, 007.x other protozoal intestinal diseases, *008.x intestinal infections due to other organisms (includes *Clostridium difficile*), 009.x ill-defined intestinal infections, *567.x peritonitis and retroperitoneal infections	5 (<1)
Tuberculosis/Other Mycobacteria	*010.x – 018.x tuberculosis, 031.x diseases due to other mycobacteria	2 (<1)
Septicemia	*038.x septicemia	7 (<1)
Other Bacterial Diseases	030.x leprosy, 032.x diphtheria, 033.x whooping cough, 036.x meningococcal infection, 037 tetanus, 039.x actinomycotic infections, 040 other bacterial diseases	0
Infections in Other Conditions	*041.xx bacterial infection in conditions classified elsewhere and of unspecified site	8 (<1)
Any Infectious Indication		129 (15)[2]

*ICD-9 codes marked with an * represent infections present at least once in this dataset

[1]Weighted percentages, [2] Column doesn't add to 129 due to multiple diagnoses per patient

Table 2. Characteristics of Hospice Discharges by Antibiotic Utilization in Last 7 Days of Life, N=3,884[*]

Characteristic	All Hospice Discharges N=3,884	Antibiotics N=1,028	No Antibiotics N=2,856	P-Value[†]
Age				
mean (standard deviation)	77.9 (0.4)	76.3 (0.7)	78.4 (0.5)	0.001
< 65 years, n(%)	668 (17)	210 (20)	458 (16)	0.09
≥ 65 years, n(%)	3,216 (83)	818 (80)	2,398 (84)	
Sex, n(%)				0.2
Female	2,103 (55)	522 (52)	1,581 (56)	
Male	1,781 (45)	506 (48)	1,275 (44)	
Days Received Hospice Care, mean,(standard deviation)	51.6 (3.1)	60.2 (6.9)	48.4 (3.6)	0.001
Race and Ethnicity				0.2
Hispanic	119 (4)	37 (5)	82 (3)	
White	3,435 (88)	906 (86)	2,529 (89)	
Black	195 (6)	53 (7)	142 (6)	
Other	58 (2)	13 (1)	45 (2)	
Marital Status				0.2
Married	1,728 (42)	478 (31)	1,250 (70)	
Widowed	1,475 (38)	384 (27)	1,091 (73)	
Divorced	270 (6)	73 (27)	197 (73)	
Other	411 (13)	93 (25)	318 (75)	

Primary Current Diagnosis				0.008
Cancer	1,847 (45)	509 (45)	1,338 (45)	
Heart Failure and CVD[¥]	377 (9)	80 (8)	297 (9)	
COPD[‖]	214 (5)	96 (8)	118 (4)	
Dementia	336 (11)	83 (10)	253 (11)	
Debility	369 (10)	84 (9)	285 (10)	
Cerebrovascular Disease	176 (5)	30 (2)	146 (5)	
Renal and Liver Disease	109 (2)	27 (2)	82 (2)	
Other	456 (13)	119 (15)	337 (13)	
Location of Hospice Care				0.1
Agency Inpatient/Residential	377 (14)	74 (13)	303 (15)	
Private Home	2,011 (49)	578 (53)	1,433(47)	
Residential Care Place	187 (5)	50 (4)	137 (5)	
Nursing Home/Skilled Nursing	913 (23)	241 (24)	672 (22)	
Hospital	335 (8)	73 (6)	262 (9)	
Other	45 (1)	12 (1)	33 (1)	
Profit Status				0.6
For-Profit	778 (29)	219 (30)	559 (28)	
Other	3,106 (71)	809 (70)	2,297 (72)	
Infectious Disease Diagnosis	380 (11)	129 (15)	251 (9)	0.01

*Weighted frequencies

†P-values from Chi-square test for categorical variables and t-test for continuous variables.

¥ Cardiovascular disease

|| Chronic obstructive pulmonary disease

Table 3.Distribution of Antibiotic Classes among Deceased Patients who Received Antibiotics in the Last 7 Days of Life, N=3,884[*]

Antibiotic Class	All N(%)
Aminoglycosides	11 (0.6)
Carbapenems	2 (0.4)
Cephalosporins	104 (9)
Miscellaneous[†]	171 (19)
Nitrofurans	44 (3)
Penicillins	73 (9)
Fluoroquinolones	234 (26)
Sulfanomides	101 (9)
Tetracyclines	26 (2)
Macrolides	520 (49)
Lincomycin Deriv.	12 (0.5)
Antimalarials	36 (3)
Antituberculosis	3 (0.4)
Any Antibiotic	1,028 (27)

*Weighted percents

†Category included aztreonam, bacitracin, atovaquone, linezolid, rifaximin, daptomycin, and vancomycin.