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Patterns of Antimicrobial Use Among Nursing Home Residents With Advanced Dementia

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Abstract

Background—Nursing home residents with advanced dementia are at high risk of infections and antimicrobial exposure near the end of life. Detailed studies quantifying antimicrobial prescribing practices among these residents have not been performed.

Methods—A cohort of 214 residents with advanced dementia from 21 Boston-area nursing homes were followed up prospectively for 18 months or until death. We analyzed antimicrobial use, including type, indication, and quantity, by days of therapy per 1000 resident-days.

Results—During an average of 322 days of follow-up, 142 residents (66.4%) with advanced dementia received at least 1 course of antimicrobial therapy (mean [SD] number of courses per resident, 4.0 [3.7]). The mean (SD) number of days of therapy per 1000 resident-days for the entire cohort was 53.0 (4.3). Quinolones and third-generation cephalosporins were the most commonly prescribed antimicrobials, accounting for 38.3% and 15.2%, respectively, of 540 prescribed antimicrobial therapy courses. A respiratory tract infection was the most common indication (46.7% of all antimicrobial therapy courses). Among 99 decedents, 42 (42.4%) received antimicrobials during the 2 weeks before death, of which 30 of 72 courses (41.7%) were administered via the parenteral route. The number of decedents receiving antimicrobials ($P < .001$), the number of antimicrobials prescribed ($P = .01$), and the days of therapy per 1000 resident-days ($P < .001$) increased significantly as subjects approached death.

Conclusions—Persons with advanced dementia are frequently exposed to antimicrobials, especially during the 2 weeks before death. The implications of this practice from the perspective of the individual treatment burden near the end of life and its contribution to the emergence of antimicrobial resistance in the nursing home setting need further evaluation.

Approximately 70% of the more than 5 million Americans with dementia will reside in nursing homes during the final stage of their disease.¹ Recurrent infections and febrile episodes typically occur during this stage.^{2,3} Therefore, nursing home residents with advanced dementia

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are at high risk for exposure to antimicrobial agents. However, it remains unclear whether treatment of infections confers any life-prolonging or symptomatic benefit in this population.^{4,5} At the same time, administration of antimicrobials to frail older patients who are near the end of life is also a potentially burdensome intervention.⁶

From a broader public health perspective, antimicrobial use is the primary factor leading to the emergence of antimicrobial-resistant bacteria. Antibiotic resistance among bacteria implicated in the most common infections is rising exponentially throughout the world. Infections caused by antimicrobial-resistant bacteria are associated with up to 5 times higher mortality rates and lead to more frequent and prolonged hospitalizations compared with infections caused by antimicrobial-susceptible bacteria.⁷⁻⁹ These issues are particularly relevant for older patients, who harbor relatively high rates of antimicrobial-resistant bacteria, and in nursing homes, where antimicrobials are the most frequently prescribed pharmaceutical agents.¹⁰⁻¹²

Taken together, the potential for widespread use of antimicrobial agents in advanced dementia raises concerns not only from the perspective of individual benefits and burdens but also from a public health standpoint with respect to the emergence and spread of antimicrobial resistance.

A few earlier reports have described patterns of antimicrobial use in patients with terminal cancer.¹³⁻¹⁵ However, to the best of our knowledge, these data have not been reported in end-stage dementia. Therefore, the main objective of this study was to better examine how infections in advanced dementia are currently being managed. To achieve this objective, the report describes the quantity, type, and pattern of antimicrobials prescribed and the indication for therapy in a cohort of nursing home residents with advanced dementia living in 21 Boston-area facilities who underwent repeated assessment and prospective follow-up for 18 months or until death. These data are needed as a first step toward providing benchmarks for antimicrobial use in advanced dementia and understanding how this use may contribute to the development and spread of antimicrobial resistance.

METHODS

STUDY POPULATION AND FACILITIES

Nursing home residents with advanced dementia living in 21 Boston-area facilities were recruited from February 1, 2003, until September 30, 2006, as part of the ongoing prospective cohort Choices, Attitudes and Strategies for Care of Advanced Dementia at the End-of-Life (CASCADE) study.¹⁶ The overriding goal of the CASCADE study was to describe multiple facets of the end-of-life experience of nursing home residents with advanced dementia and their families. Data available for this report were derived from the first 241 subjects recruited into the study.

Details of the complete CASCADE study protocol are provided elsewhere.¹⁶ Briefly, to identify a cohort with advanced dementia, the residents' most recent Minimum Data Set assessments were used to identify those with a Cognitive Performance Scale score of 5 or 6, indicating severe to very severe cognitive impairment.¹⁷ Once identified, the charts of residents with a Cognitive Performance Scale score of 5 or 6 underwent screening for full eligibility, which included (1) age of 60 years or older, (2) length of stay of 30 days or longer, (3) cognitive impairment due to dementia, (4) Global Deterioration Scale score of 7,¹⁸ and (5) an appointed health care proxy who could communicate in English. The diagnosis of dementia was confirmed with the resident's physician if it was ambiguous in the record. At a Global Deterioration Scale score of 7, patients with dementia are characterized by very severe cognitive decline, minimal to no verbal communication, dependence for eating and toileting, incontinence of urine and stool, and loss of the ability to walk.¹⁸ Residents were excluded if they were in a subacute or short-term rehabilitative unit; had cognitive impairment due to

stroke, traumatic brain injury, tumor, or a chronic psychiatric condition; or were in a coma. Finally, participant facilities were required to have at least 60 beds and be located within a 60-mile radius of Boston.

DATA COLLECTION AND RESIDENT ASSESSMENTS

Data presented in this report were abstracted from the subjects' medical records and a brief mental status examination. Assessments were conducted at baseline and quarterly thereafter for a maximum of 18 months. If the resident died during the follow-up period, an assessment was obtained within 14 days of death.

The subjects' age, sex, and race (white vs other) were obtained at the baseline assessment. Additional descriptive variables collected at baseline included whether the subjects lived in a special-care dementia unit, their length of nursing home stay (in days), and the cause of their dementia (Alzheimer disease, vascular, or other). Cognitive disability was determined by direct clinical examination of the resident using the Test for Severe Impairment (range of 0–24, with lower scores indicating greater cognitive impairment).¹⁹

ANTIMICROBIAL USE

At each quarterly and death assessment, the number of courses of antibiotic therapy prescribed for the resident since the prior assessment was obtained from the medicine administration records. The following details were determined for each course: the name of the antibiotic, start and stop dates of therapy, route of administration, and indication. Indication was categorized according to the suspected diagnosis documented by a physician as 1 of the following infections: respiratory tract; skin; urogenital; ear, nose, or throat; gastrointestinal tract; and others (ie, prophylaxis for pacemaker placement and dental procedures). The days of therapy (DOT) value was defined as the total number of days that a single antimicrobial (parenteral or oral) was administered, regardless of dosage.²⁰ The DOT was further specified per 1000 resident-days of observation.

To describe the pattern of antimicrobial use specifically among the subjects who died, the period before death was categorized by 14-day intervals, a common duration for a course of antimicrobial therapy.

STATISTICAL ANALYSIS

We used descriptive statistics to present the subject characteristics and patterns of antimicrobial use, with means (SDs) for continuous variables and proportions for categorical variables. Among the decedents, the Spearman correlation coefficient was used to analyze the association between the total number of antimicrobial therapy courses prescribed per resident and the number of days before death. Similarly, we used the Spearman rank correlation coefficient to examine the association between the proportion of subjects who received antimicrobials and the number of days before death. The association between the antimicrobial indication and the timing of administration (ie, 2-week intervals) before death was analyzed using the χ^2 test for linear trend. We used Stata statistical software (release 7.0; Stata Corp, College Station, Texas) for all statistical analyses.

RESULTS

STUDY POPULATION

A total of 240 subjects with advanced dementia were recruited into the study at the time of this report. The study is ongoing, and 26 subjects were excluded from these analyses because only a single baseline evaluation was completed and no follow-up data regarding antibiotic use were

available. Among the remaining 214 subjects included in the analyses, 99 (46.3%) died during the observation period.

The mean age of the subjects was 85.2 (7.9) years; 184 (86.0%) were female; and 189 (88.3%) were white (Table 1). The causes of the subjects' dementia were as follows: Alzheimer disease (149 subjects [69.6%]), vascular (39 [18.2%]), and other (30 [14.0%]) (4 subjects had more than 1 cause). Among the cohort, 100 subjects (46.7%) resided in special-care dementia units, and the median length of stay was 41.2 months (Table 1). Subjects were severely cognitively impaired, with 162 (75.7%) scoring 0 on the Test for Severe Impairment. The entire cohort of 214 subjects contributed a total of 68 861 follow-up days (mean, 322 [191]; range, 11–603 days) to the analyses.

ANTIMICROBIAL USE AMONG ALL SUBJECTS

Table 2 presents the use of antimicrobials in the entire cohort (N=214). During the follow-up period, 142 of the 214 subjects (66.4%) received at least 1 dose of antimicrobials. A total of 540 courses were prescribed (mean number of courses per subject who received antimicrobials, 4.0 [3.7]; range, 1–20). The mean DOT per 1000 resident-days for all antimicrobials was 53.0 (4.3). The areas of infection for which the 540 courses of antimicrobial therapy were prescribed were as follows: respiratory tract (252 infections [46.7%]); urinary tract (192 [35.6%]); skin (71 [13.1%]); ear, nose, or throat (12 [2.2%]); gastrointestinal tract (8 [1.5%]); and other (5 [0.9%]).

Quinolones were the most commonly prescribed agent, accounting for 207 of all antimicrobial therapy courses (38.3%), with 96 subjects (44.9%) receiving at least 1 course of quinolone therapy. The DOT per 1000 resident-days for quinolones was 16.9. Among all quinolones, levofloxacin (171 courses [82.6%]) was the most commonly prescribed antimicrobial, followed by ciprofloxacin (33 [16.0%]) and gatifloxacin (3 [1.4%]). Third-generation cephalosporins were the second most common antimicrobials prescribed, accounting for 82 antimicrobial therapy courses (15.2%), with 47 residents (22.0%) receiving at least 1 dose. The DOT per 1000 resident-days for third-generation cephalosporins was 4.6. Ceftriaxone was the most commonly prescribed third-generation cephalosporin, accounting for 80 of 82 therapy courses (97.6%). The third most common antimicrobials were first-generation cephalosporins, accounting for 61 antimicrobial therapy courses (11.3%), with 39 residents (18.2%) receiving at least 1 course. The DOT per 1000 resident-days for first-generation cephalosporins was 6.3. Cephalexin, cefazolin, and cefadroxil accounted for 53 (86.9%), 6 (9.8%), and 2 (3.3%) of all 61 first-generation cephalosporin therapy courses, respectively.

ANTIMICROBIAL USE AMONG DECEDENTS BEFORE DEATH

Among the 99 subjects who died, those available for analysis during the 14-day intervals before death included 99 at 0 to 14 days, 94 at 15 to 28 days, 88 at 29 to 42 days, and 83 at 43 to 56 days.

A total of 52 decedents (51.5%) received at least 1 dose of antimicrobials within the 8 weeks before death. As subjects approached death, the proportion of subjects receiving at least 1 antimicrobial ($P<.001$), the number of antimicrobial therapy courses per resident prescribed ($P=.01$), and the DOT per 1000 resident-days ($P<.001$) all increased significantly (Figure 1 and Figure 2). The proportions of antimicrobial therapy courses administered parenterally (total number of residents receiving antimicrobials parenterally/total number of residents receiving antimicrobials, interval before death) were as follows: 20.0% (2/10, 43–56 days), 26.3% (5/19, 29–42 days), 28.0% (7/25, 15–28 days), and 41.7% (30/72, 0–14 days) ($P=.07$). The 3 most commonly prescribed antimicrobials during the 8 weeks before death were quinolones, third-generation cephalosporins, and first-generation cephalosporins (Table 3). The number of

antimicrobial therapy courses, the number of residents receiving at least 1 antimicrobial agent, and the DOT per 1000 resident-days increased for all other individual antimicrobial groups as the subjects approached death (data not shown).

Among the 126 courses of antimicrobial therapy prescribed for all 99 decedents during the 8 weeks before death, the sites of infection prompting treatment were as follows: respiratory tract (80 courses [63.5%]), urogenital (22 [17.5%]), skin (21 [16.7%]), and gastrointestinal tract (3 [2.4%]). There was a statistically significant increase in the diagnosis of respiratory tract illness as the indication for antimicrobial treatment as the decedents approached death ($P=.01$) (Table 4).

COMMENT

This prospective cohort study demonstrates that antimicrobial exposure among nursing home residents with advanced dementia is extensive and steadily increases toward the end of life. During the follow-up period (mean follow-up, 322 days), two-thirds of the subjects were prescribed at least 1 course of antimicrobial therapy and, on average, a total of 4 courses. Among the residents who died, 42.4% received antimicrobials during the last 2 weeks of life, often via a parenteral route. The proportion of residents taking antimicrobials was 7 times greater in the last 2 weeks of life compared with 6 to 8 weeks before death. This extensive use of antimicrobials and pattern of antimicrobial management in advanced dementia raises concerns not only with respect to individual treatment burden near the end of life but also with respect to the development and spread of antimicrobial resistance in the nursing home setting.

To our knowledge, this is the first comprehensive, prospective study to describe the quantity, type, and pattern of antimicrobials prescribed and the indication for therapy among patients with advanced dementia in the long-term care setting. Earlier studies that focused on the treatment of specific infections (ie, pneumonia) in advanced dementia were retrospective or cross-sectional in design, examined hospitalized patients, or studied only a single institution.^{2–5,21,22} Despite these differences, our study corroborates that antimicrobial agents are commonly prescribed in advanced dementia and extends these findings by demonstrating a marked increase in antimicrobial use as death becomes imminent. Terminally ill patients with cancer in palliative care settings also frequently receive antimicrobial therapy.^{13,14} White et al¹³ reported that approximately 30% of hospice recipients with advanced cancer are prescribed antibiotics. Although a urinary tract infection was the most frequent indication for treatment among patients with cancer who were dying, a respiratory tract infection was the most common diagnosis in our cohort with end-stage dementia.

Treatment decisions for infections in advanced dementia can be difficult for family members and care-givers. The 2 purported reasons to administer antimicrobials are life prolongation and symptom control. Limited observational studies^{4,5,22} have failed to demonstrate that antimicrobial treatment achieves either outcome in this frail population; however, randomized trials have not been conducted. Our findings further support that antimicrobials may not meaningfully extend the life of patients with advanced dementia for whom infections are frequently a terminal event. Palliation is often the main goal of care in this condition.²³ It is difficult to assess the extent to which infections cause suffering in patients with advanced dementia. Previous work demonstrates that pneumonia is an uncomfortable experience for these patients and suggests that antimicrobial therapy may improve symptoms.⁵ However, it remains unclear whether antimicrobial therapy promotes symptomatic relief beyond what can be achieved by high-quality palliative treatment with more conservative modalities (eg, oxygen and acetaminophen). Finally, it is also important to minimize inappropriate antimicrobial exposure. For example, up to one-third of antimicrobials prescribed in nursing homes are for asymptomatic bacteriuria, for which treatment is not indicated.²⁴

Antimicrobial administration has associated risks in the frail elderly population that merit consideration. Older persons are particularly susceptible to the adverse effects of antimicrobials owing to altered pharmacokinetics, polypharmacy, dosing errors, and an increased risk of *Clostridium difficile* infections.^{25–27} Moreover, parenteral administration, which was common in our cohort, can be an uncomfortable procedure in advanced dementia.⁶ Thus, from the individual patient's perspective, the balance of advantages and disadvantages of antimicrobial treatment of infections in advanced dementia remains unclear, regardless of the primary goal of care.

On a broader level, the emergence and spread of antimicrobial-resistant bacteria is a major public health concern. Older persons account for one of the largest patient reservoirs of these organisms.^{10,28} In particular, up to 40% of residents living in nursing homes harbor at least 1 species of antimicrobial-resistant bacteria.^{29–31} Once admitted to the hospital, these nursing home residents contribute substantially to the influx and spread of antibiotic-resistant bacteria.^{28,29} Exposure to antibiotics is strongly associated with the development of antibiotic resistance. Quinolones and third-generation cephalosporins were the most frequently prescribed antimicrobials in our cohort. Several studies have reported that more than 50% of isolates recovered from nursing home residents are resistant to these 2 classes of drugs.^{31–33} These observations and the extensive use of antibiotics found in this study raise the serious concern that nursing home residents with advanced dementia may be contributing to the emergence and spread of antimicrobial-resistant bacteria, posing health risks that extend beyond the individual being treated.

Future initiatives aimed at optimizing antimicrobial use will require standardized units of measurement. In this study, a DOT value was used to quantify antimicrobial utilization. The DOT quantifies the mean duration of therapy adjusted for the total time that the population was observed and does not take into consideration the actual dose administered. The DOT value was developed as an alternative to the defined daily dose measure.^{20,34} The daily defined dose assumes that all patients receive standard antimicrobial doses, and therefore does not take into consideration unique patient characteristics that require dosage adjustments. This limitation is especially relevant to elderly patients, who often require alternative dosing to adjust for low body mass and renal insufficiency.²⁵ Measures of antimicrobial DOT have not been previously reported for patients with advanced dementia. Thus, the DOT values found in this study provide a benchmark for future research in this area and for comparing prescribing practices between institutions.

This study has limitations that warrant comment. First, this prospective cohort study did not include a comparison group. Therefore, we do not know whether the pattern of antimicrobial use observed in our subjects with advanced dementia differs from that of other long-term care residents. Second, data were not collected to determine the presence of antimicrobial-resistant bacteria. Thus, although our study raises concerns that nursing home residents with advanced dementia are reservoirs of antimicrobial-resistant organisms, this supposition remains to be proved. Finally, this observational study was not designed to study the outcomes of antimicrobial therapy in advanced dementia, despite the fact that many subjects died shortly after receiving treatment.

Infections and febrile episodes are a hallmark of end-stage dementia. The extensive antimicrobial use demonstrated in this study is concerning given the lack of demonstrable benefits and the potential burdens of treatment in this terminally ill population for whom the goal of care is often palliation.²³ Moreover, we believe that the widespread use of antibiotics in advanced dementia may pose a potential public health risk through the emergence of antibiotic resistance. This hypothesis requires further research. Meanwhile, from individual

and societal perspectives, our study supports the development of programs and guidelines designed to reduce the use of antimicrobial agents in advanced dementia.

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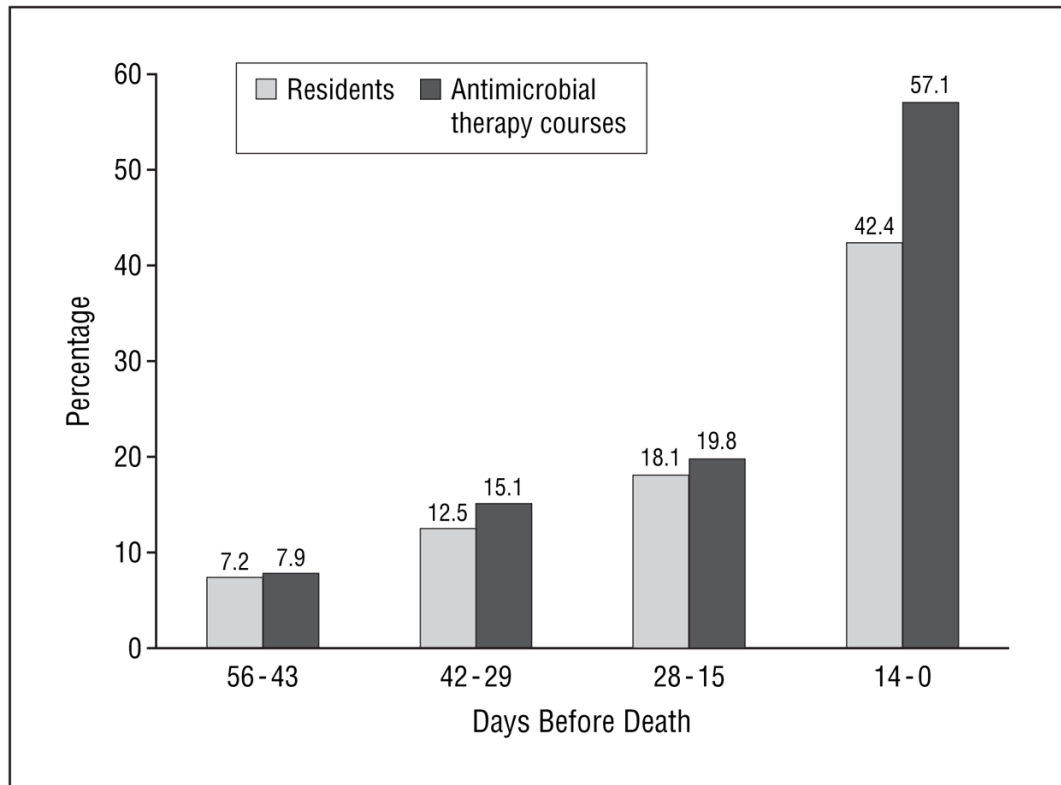


Figure 1.

Percentages of nursing home residents with advanced dementia receiving antimicrobials and of antimicrobial therapy courses, among a total of 126 courses prescribed, during the last 8 weeks of life. The total number of residents and antimicrobial courses during each 14-day interval before death were as follows: 99 and 10 at 0 to 14 days; 94 and 19 at 15 to 28 days; 88 and 25 at 29 to 42 days; and 83 and 72 at 43 to 56 days, respectively.

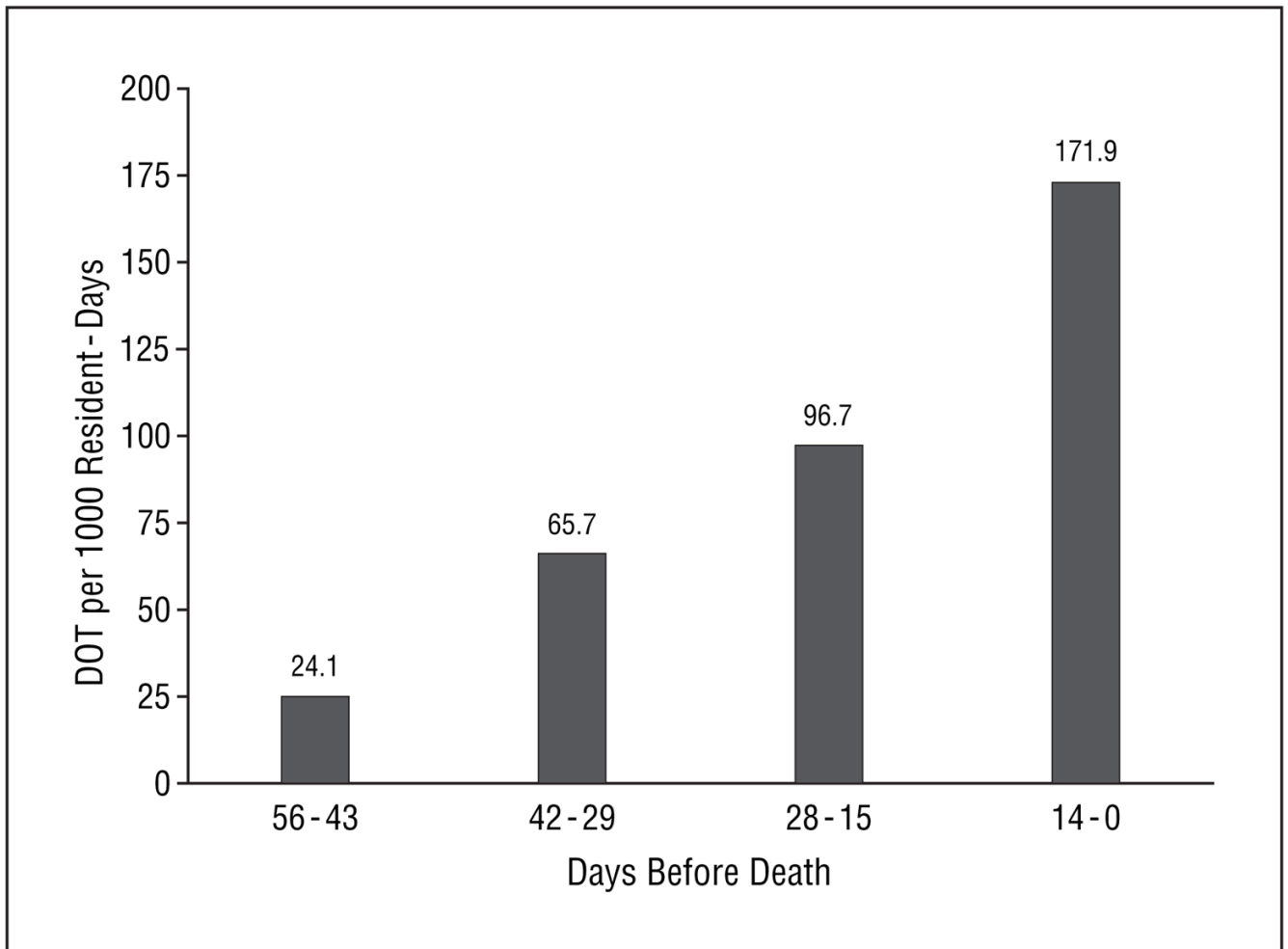


Figure 2.

Days of therapy (DOT) per 1000 resident-days for any antimicrobial received by nursing home residents with advanced dementia during the last 8 weeks of life. The total number of subjects at each 14-day interval before death was as follows: 99 at 0 to 14 days; 94 at 15 to 28 days; 88 at 29 to 42 days; and 83 at 43 to 56 days.

Table 1
Baseline Characteristics of 214 Nursing Home Residents With Advanced Dementia

Characteristic	No. (%)
Age, mean (SD), y	85.2 (7.9)
Female	184 (86.0)
White	189 (88.3)
Cause of dementia	
Alzheimer	149 (69.6)
Vascular	39 (18.2)
Other	30 (14.0)
Special-care dementia units	
Reside in unit	100 (46.7)
Median length of stay, mo	88 (41.2)
Test for Severe Impairment score of 0	162 (75.7)

Table 2
Antimicrobial Use Among 214 Nursing Home Residents With Advanced Dementia (N=214)

Antimicrobial Group	No. (%) of Subjects Receiving at Least 1 Antimicrobial Therapy Course	No. (%) of Antimicrobial Therapy Courses	No. of Courses per Subject, Mean (SD)	DOT per 1000 Resident-Days, Mean ^a
Any antimicrobial	142 (66.4)	540 (100.0)	4.0 (3.7)	53.0 (4.3)
Quinolones	96 (44.9)	207 (38.3)	2.2 (1.8)	16.9
Third-generation cephalosporins	47 (22.0)	82 (15.2)	1.7 (1.4)	4.6
First-generation cephalosporins	39 (18.2)	61 (11.3)	1.6 (0.7)	6.3
Penicillins	27 (12.6)	44 (8.1)	1.6 (1.0)	4.6
Macrolides	25 (11.7)	30 (5.6)	1.2 (0.5)	2.7
Nitrofurantoin	16 (7.5)	25 (4.6)	1.6 (1.2)	5.6
Trimethoprim-sulfamethoxazole	15 (7.0)	25 (4.6)	1.7 (1.3)	6.0
Metronidazole	15 (7.0)	24 (4.4)	1.6 (1.1)	2.5
Tetracyclines	10 (4.7)	14 (2.6)	1.4 (0.5)	1.2
Vancomycin hydrochloride	6 (2.8)	8 (1.5)	1.3 (0.8)	0.9
Second-generation cephalosporins	6 (2.8)	8 (1.5)	1.3 (0.5)	0.9
Clindamycin	4 (1.9)	4 (0.7)	1.3 (0.5)	0.3
Gentamicin sulfate	2 (0.9)	2 (0.4)	1.0 (0.0)	0.2

Abbreviation: DOT, days of therapy.

^aThe standard deviation could be generated for "any antimicrobial" only, not for individual antimicrobials.

Table 3
Antimicrobial Exposure, Therapy Courses, and DOT per 1000 Resident-Days for the 3 Most Commonly Prescribed Antimicrobials Among Nursing Home Residents With Advanced Dementia During the 8 Weeks Before Death

Antimicrobials	Days Before Death			
	0–14 (n=99)	15–28 (n=94)	29–43 (n=88)	43–56 (n=83)
Quinolones				
No. (%) of residents	23 (23.2)	10 (10.6)	3 (3.4)	3 (3.6)
Total No. of courses	27	11	3	3
DOT per 1000 resident-days	62.4	37.8	16.2	6.0
Third-generation cephalosporins				
No. (%) of residents	18 (18.2)	5 (5.3)	3 (3.4)	1 (1.2)
Total No. of courses	24	5	6	1
DOT per 1000 resident-days	36.3	14.4	21.1	0.9
First-generation cephalosporins				
No. (%) of residents	7 (7.1)	4 (4.3)	3 (3.4)	2 (2.4)
Total No. of courses	7	4	3	2
DOT per 1000 resident-days	21.0	18.1	9.7	5.2

Abbreviation: DOT, days of therapy.

Table 4

Indications for Administration of 126 Courses of Antimicrobial Therapy Among Nursing Home Residents With Advanced Dementia During the 8 Weeks Before Death

Site of Infection	No. (%) of Decedents by Days Before Death			
	0–14 (n=99)	15–28 (n=94)	29–42 (n=88)	43–56 (n=83)
Respiratory tract	56 (77.8)	13 (52.0)	8 (42.1)	3 (30.0)
Urogenital	8 (11.1)	5 (20.0)	6 (31.6)	3 (30.0)
Skin	6 (8.3)	6 (24.0)	5 (26.3)	4 (40.0)
Gastrointestinal tract	2 (2.8)	1 (4.0)	0	0
All Sites	72	25	19	10