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National trends in the treatment of urinary tract infections among Veterans' Affairs Community Living Center residents

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TITLE PAGE

TITLE: National Trends in Treatment of Urinary Tract Infections among Veterans Affairs Community Living Center Residents

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ABSTRACT

OBJECTIVE: To describe urinary tract infection (UTI) treatment among Veterans Affairs (VA) Community Living Centers (CLCs) nationally and assess trends in antibiotic use.

DESIGN: Descriptive study.

SETTING AND PARTICIPANTS: All UTI episodes treated from 2013-2017 among residents in 110 VA CLCs. UTI episodes required collection of a urine culture, antibiotic treatment, and a UTI diagnosis code. UTI episodes were stratified into culture-positive and negative.

METHODS: Frequency and rate of antibiotic use were assessed for all UTI episodes overall and stratified by culture-positive and negative episodes. Joinpoint Software was used for regression analyses of trends over time.

RESULTS: We identified 28,247 UTI episodes in 14,983 Veterans. The average age of Veterans was 75.7 and 95.9% were male. About half (45.7%) of UTI episodes were culture-positive and 25.7% were culture-negative. *Escherichia coli* was recovered in 34.1% of culture-positive UTI episodes, followed by *Proteus mirabilis* and *Klebsiella* recovered in 24.5% and 17.4% of culture-positive UTI episodes, respectively. The rate of total antibiotic use in DOT/1,000 bed days decreased by 10.1% per year (95% CI -13.6 - -6.5%) and fluoroquinolone use (ciprofloxacin or levofloxacin) decreased by 14.5% per year (95% CI -20.6 - -7.8%) among UTI episodes overall. Similar reductions in rates of total antibiotic use and fluoroquinolone use were observed among culture-positive and among culture-negative UTI episodes.

CONCLUSION:

Over a 5-year period, antibiotic use for UTIs significantly decreased among VA CLCs, as did use of fluoroquinolones. Antibiotic stewardship efforts across VA CLCs should be applauded and continue to be an ongoing effort.

TEXT

BACKGROUND

Antibiotics are among the most frequently used medications in long-term care facilities (LTCFs), however up to 75% of antibiotic use in LTCFs may be inappropriate.[1,2] The greatest contributor to inappropriate antibiotic use in LTCFs is the misuse of antibiotics for urinary tract infections (UTIs).[2-7] The most common problem in the treatment of UTIs among residents is misdiagnosis and treatment of asymptomatic bacteriuria with antibiotics.[8] Another common problem is the use of agents that are overly broad-spectrum or carry an increased risk of adverse drug events, such as fluoroquinolones.[9] Data from 2010 and more recent data from 2014-2016 demonstrate that fluoroquinolones are the most commonly used agents used for treatment of UTI among LTCF residents.[9-11] This has been in spite of recommendations specific to LTCF residents which call for restricted use of fluoroquinolones due to their risk for *Clostridium difficile* infection, adverse drug events, and selection of resistance since 2000.[12,13] Per 2004 and 2011 treatment guidelines of the Infectious Diseases Society of America (IDSA), labeled warnings from the Food and Drug Administration, and expert opinion, fluoroquinolones should only be used for the treatment of acute cystitis when other UTI antibiotics cannot be used due to their propensity for collateral damage.[14-16]

While previous research suggests that antibiotic selection for UTIs may often be suboptimal, large-scale studies of how LTCF residents are treated for UTIs nationally are limited. Quantifying how UTIs are treated is a first step in improving the use of antibiotics.[17] Knowledge of the most commonly used antibiotic agents and the trends in use can inform future efforts to optimize antibiotic use among LTCF residents nationally. Such data can also identify problem areas, allowing the development of targeted interventions to improve antibiotic use, ultimately improving the care of residents with UTIs. As such, the aim of this work was to describe antibiotic use for UTI among all VA LTCFs (known as Community Living Centers or CLCs) nationally from 2013 to 2017 and assess trends in antibiotic use.

METHODS

We conducted a retrospective study using national VA microbiology and pharmacy data accessed through the VA Informatics and Computing Infrastructure (VINCI). We included all adult (age $\geq$18 years) residents with a UTI episode during an inpatient stay in a VA CLC unit between January 2013 to December 2017. Three inclusion criteria were applied to identify episodes of UTI: (1) collection of urine culture, (2) initiation of a UTI-related antibiotic on the date the urine culture was taken or within the 3 days after culture collection, and (3) a diagnosis code for UTI (International Classification of Diseases, 9th or 10th edition).[18]

We excluded episodes that likely represented treatment of asymptomatic bacteriuria for urologic procedure or pregnancy.[19] Urologic procedures (e.g. transurethral resection of the prostate, prostate biopsy, cycstoscopy, urodynamic surgery) were identified using previously reported diagnosis and procedure codes and using text searches of procedure names.[20,21] All residents with a urologic produce that occurred within 2 weeks of the date of the index urine culture were excluded. We also excluded women of childbearing age (females < 45 years at the time of urine culture). To avoid capturing treatment of another potential infection, we excluded episodes in which another positive culture (i.e. blood, respiratory, tissue, bone) was identified within 3 days of the index culture, unless it was a positive blood culture for the same organism growing in the urine.[22] In the case of multiple UTI episodes during the study period, we excluded subsequent UTI episodes within 30 days of the first episode.

UTI episodes were stratified by urine culture results into culture-negative, culture-positive, and other episodes. Culture-negative UTI episodes were those in which no growth was identified from the urine culture. Culture-positive UTI episodes were defined as those in which no more than two typical uropathogens (*Escherichia coli, Proteus mirabilis, Klebsiella species [spp], Pseudomonas aeruginosa, Providencia* spp, *Enterobacter spp, Citrobacter spp., Morganella morganii, Serratia marcescens, Enterococcus spp, Staphylococcus aureus*) were isolated with quantitative counts $\geq 10^5$ CFU/mL from the urine culture.[14,19,23,24] Uropathogens of interest were chosen based on earlier work indicating these were the most frequently isolated organisms from urine samples obtained from LTCF residents.[25] All other UTI episodes were defined as those in which typical uropathogens were isolated with low quantitative counts ($\leq 10^5$ CFU/mL), more than two uropathogens were identified, or any other organisms were isolated from the urine culture.

We quantified the frequency and rate of antibiotic use for all UTI episodes overall and stratified by culture-positive and culture-negative UTI episodes. Frequency of use was the proportion of the number UTI episodes treated with a specific antibiotic agent/class divided by the total number of UTI episodes that met study criteria as defined above. The rate of antibiotic use was defined as antibiotic days of therapy (DOT).[22] One DOT represents administration of a single agent on a given day regardless of frequency, dose, or route of administration. For each UTI episode, we calculated the DOT for each antibiotic used from the start to the end of the treatment up to 30-days post-treatment start. End of treatment was identified from gaps in antibiotic therapy of more than 2 consecutive calendar days.

We summed all UTI specific antibiotic use for our study cohort and standardized it to 1,000 bed days of care (DOT/1,000 bed days). Antibiotics were grouped into the following classes: typical genitourinary tract agents (nitrofurantoin, sulfamethoxazole/ trimethoprim, fosfomycin, trimethoprim), fluoroquinolones (ciprofloxacin, levofloxacin), 1st-2nd generation cephalosporins (cefaclor, cefazolin, cefotetan, cefoxitin, cefuroxime, cephalexin), 3rd-4th generation cephalosporins (cefdinir, cefepime, cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftriaxone), aminopenicillins (amoxicillin, ampicillin, amoxicillin/clavulanate, amipicillin/sulbactam), carbapenems and piperacillin/ tazobactam (imipenem, meropenem, ertapenem, doripenem, piperacillin/ tazobactam), other multidrug resistant [MDR] gram-negative agents (amikacin, gentamicin, tobramycin, avibactam/ceftazidime, aztreonam, ceftazidime\avibactam, tigecycline), anti-methicillin resistant *Staphylococcus aureus* [MRSA] directed agents (ceftaroline, daptomycin, linezolid, vancomycin), and other agents.

We identified time trends over the study period using joinpoint regression models. The Joinpoint Regression Program version 4.6.0.0 (National Cancer Institute, Bethesda, MD, USA) was used to calculate average annual percent change (AAPC) and 95% confidence intervals (CI).[26] Significance was set at $p<0.05$. The AAPC is a weighted average of the average percent change (APC) segments from a joinpoint model with the weights equal to the duration of each APC segment.

RESULTS

We identified a total of 28,247 UTI episodes diagnosed and treated with antibiotics within 3 days of urine culture among 14,983 Veterans admitted to 110 VA CLCs nationally. The median number of UTI episodes per Veteran was 1.0 (interquartile range [IQR] 1-2) and the median length of stay among unique Veteran admissions (n=15,829) was 127 days (IQR 43-717). At the time of the first UTI episode, the average age of Veterans was 75.7 years (+/- 11.5 standard deviation) and 95.9% (n=14,363) were male. Additional baseline characteristics are presented in Table 1.

Urine culture results are presented in Table 2. Approximately half of UTI episodes were culture-positive (n=12,905, 45.7%) and 25.7% (n=7,265) were culture-negative. *Escherichia coli* was recovered in 34.1% (n=4,400) of culture-positive UTI episodes, followed by *Proteus mirabilis* and *Klebsiella* spp. recovered in 24.5% (n=3,160) and 17.4% (n=2,244) of culture-positive UTI episodes, respectively.

Among all UTI episodes, the most frequently used antibiotic agents were ciprofloxacin (31.2%, n=8,818), sulfamethoxazole/trimethoprim (20.9%, n=5,908), and ceftriaxone (16.3%, n=4,591, Table 3). Ciprofloxacin, sulfamethoxazole/trimethoprim, and ceftriaxone also had the greatest usage in DOT, accounting for 19.4% (DOT=57,579), 14.6% (DOT=43,244), and 8.2% (n=24,231) of the total DOT used, respectively. Use of broad-spectrum intravenous antibiotic agents accounted for approximately 20% of the total DOT used. The rate of total antibiotic use decreased significantly by 10.1% per year (95% CI -13.6 – -6.5%) from 20.7 DOT/1,000 bed days in 2013 to 13.2 DOT/1,000 bed days in 2017. The rate of fluoroquinolone (ciprofloxacin and levofloxacin) use in DOT/1,000 bed days decreased significantly by 14.5% per year (95% CI -20.6 – -7.8%). The proportion of UTI episodes treated with fluoroquinolones decreased significantly by 6.0% per year (95% CI -10.4 – -1.3%) over the study period. Fluoroquinolones were used in 44.2% (n=2,958/6,693) of suspected UTI episodes in 2013 and in 35.2% of episodes in 2017 (n=1,645/4,675).

Among culture-positive UTI episodes, ciprofloxacin (33.5%, n=4,323), sulfamethoxazole/ trimethoprim (23.4%, n=3,015), and ceftriaxone (16.7%, n=2,149) remained the most frequently used antibiotic agents. Several significant changes in the rate of antibiotic use for culture-positive UTI episodes were observed (Figure 1). The rate of total antibiotic use for culture-positive episodes decreased significantly by 9.6% per year (95% CI -13.1 – -6.0%). The rate of fluoroquinolone use decreased significantly by 14.9% per year (95% CI -22.0 – -7.3%).

Among culture-negative UTI episodes, ciprofloxacin (26.1%, n=1,899), sulfamethoxazole/ trimethoprim (16.6%, n=1,203), and ceftriaxone (16.1%, n=1,167) also remained the most frequently used antibiotic agents. Among culture-negative UTI episodes, 19,376 fluoroquinolone DOT were used, accounting for 25.4% of all fluoroquinolone use (DOT=76,162). Trends in antibiotic use for culture-negative UTI episodes are presented in Figure 2. Significant reductions in the rates of total antibiotic use (by 11.2% per year, 95% CI -14.8 – -7.4%) and fluoroquinolone use (by 14.8% per year, 95% CI -19.6 – -9.7%) were observed.

DISCUSSION

In our study of about 15,000 Veterans diagnosed and treated for UTIs in CLCs nationally, fluoroquinolone use decreased, as did overall antibiotic days of therapy. Results stratified by culture-positive and culture-negative UTI episodes were similar.

Ciprofloxacin, sulfamethoxazole/trimethoprim, and ceftriaxone were the most commonly used antibiotic agents. Previous work among Veteran cohorts from outpatient and acute care inpatient settings have also found that these agents are among the most commonly used antibiotics for UTI.[27,28] Data from non-VA LTCFs has similarly identified fluoroquinolones as the most commonly used antibiotic class for UTIs.[9-11]

As expected, the typical uropathogens, including *E. coli*, *Proteus,* and *Klebsiella* spp., were the most commonly identified uropathogens among culture-positive UTI episodes.[31] Similar to our findings, *E. coli* was the most common (53.6%) organism identified among 240 episodes of UTI among residents in 5 Connecticut LTCF, followed by *Proteus* spp (14.6%) and *Klebsiella* spp (13.9%).[25] About 25% of the UTI episodes in our study were culture-negative, and suggest potential overtreatment. Previous work has confirmed the overtreatment of UTI, in both the presence and absence of positive urine cultures, among older adults without symptoms of a UTI. In a study of 153 older women diagnosed with a UTI, only 87 (57%) had microbiological evidence of a UTI, yet 95% of the 66 patients with negative cultures received antibiotics.[32]

While our work does suggest potential overtreatment, our work also demonstrated several impressive reductions in the use of antibiotics for UTI in VA CLCs nationally. We found that total antibiotic use decreased by approximately 10% per year from 2013 to 2017 for all UTI episodes, and by 10% among culture-positive episodes and 11% among culture-negative episodes. Improving the diagnosis and treatment of UTIs is a well-recognized antibiotic stewardship target among LTCFs.[33] Among VA medical centers, previous work has confirmed an increase antibiotic stewardship over the study period.[34] However, there may be facility level or regional variation in application of antibiotic stewardship principles, which warrant future investigation. Previous work has demonstrated variation in antibiotic use at the facility and regional levels in non-VA LTCFs and in VA facilities.[35-37]

Another encouraging trend we observed was the decrease in fluoroquinolone use among all UTI episodes overall and stratified by culture-positive and culture-negative episodes. Overall the proportion of UTI episodes treated with fluoroquinolones decreased by 6.0% each year, as did the rate of fluoroquinolones use (by 14.5%). Reductions in use may be related to growing evidence on fluoroquinolone-related adverse effects, especially in older patients.[16,38] In 2008, a boxed warning for an increased risk of tendinitis and tendon rupture with fluoroquinolones was mandated by the Food and Drug Administration (FDA). Since that time, the FDA has issued warnings for other serious adverse effects, including exacerbation of myasthenia gravis, *C. difficile* infection, QT-interval prolongation, severe hypoglycemia, and mental health effects.[38] In 2013 the FDA updated label warnings for fluoroquinolones and in 2016 the FDA specifically recommended use of fluoroquinolones be avoided for uncomplicated UTIs, unless no alternative treatment options were available.[16] Nitrofurantoin and sulfamethoxazole/trimethoprim are suggested empiric UTI treatment options for older patients without complicated coexisting conditions and mild UTI symptoms.[13,41,42] However, nitrofurantoin should be avoided in patients with pyelonephritis or a history of UTI due to *P. mirabilis*. Given the high prevalence of *P. mirabilis* we observed across VA nursing homes nationally, our results suggest avoidance of nitrofurantoin as empiric therapy, however local resistance patterns should guide empiric therapy. Nitrofurantoin may be an option once urine culture results are available.

While fluoroquinolone use decreased over the study period, our results demonstrated that fluoroquinolones are still a preferred treatment choice. Fluoroquinolones remained the most frequently used antibiotic class for UTIs over the entire study period, even in 2017 (35.5% of episodes). These findings may be related to our complicated study population of mostly older male Veterans. All urinary tract infections in males are generally considered complicated.[19,23] Moreover, approximately 45% of Veterans in our study had comorbid benign prostatic hyperplasia, which may lead to complicated UTIs and prostatitis due to obstructed and turbulent urine flow.[39] Fluoroquinolones achieve reliable tissue concentrations in the prostate and are considered first-line in men with severe UTI symptoms or concern for prostate involvement.[39] While our findings do demonstrate impressive reductions in fluoroquinolone use for UTIs among VA CLCs nationally, there may be room for further improvement in reducing fluoroquinolone use. Focused antibiotic stewardship efforts to further fluoroquinolone use which have been successful in single center studies include the removal of fluoroquinolones from local formularies and order sets.[40,41] Overall, about 76,000 fluoroquinolone DOT were used over our study period, and 25% of that use was for culture-negative UTI episodes. Thus, negative cultures may be an easy target for antibiotic stewardship in CLCs to further reduce fluoroquinolone use in residents who do not have symptoms of urinary infection.

There are limitations to this retrospective study. We defined UTIs as a urine culture plus antibiotic treatment in the presence of a UTI diagnosis code. We were unable to capture treatment practices for UTIs in which no cultures were obtained, that were culture-positive and treated without a UTI diagnosis code, or that were treated outside the VA CLC setting. We assumed that antibiotic administrations were intended for the treatment of a UTI, since antibiotic indication is often missing. To minimize the possibility of treatment for anther infection type, we excluded UTI episodes in which there were concomitant positive cultures from other sources and required a diagnosis code for UTI. Another limitation is we were interested in the real-world treatment of UTIs, we did not attempt to distinguish treatment of asymptomatic bacteriuria versus truly symptomatic UTI. We did attempt to exclude asymptomatic bacteriuria in the presence of urologic procedure or pregnancy. Additionally, we were unable to capture urinary catheter use and thus unable to quantify the prevalence of caterer use in our population. It is possible that catheter use declined over the study period and may account in part for the observed decreases in antibiotic use. Finally, the generalizability of our findings to other populations may be limited, as our population is predominantly male.

In conclusion, our study of over 28,000 UTI episodes in VA CLCs nationally demonstrated a decrease in overall antibiotic use for UTIs, including the use of fluoroquinolone antibiotics. Antibiotic stewardship efforts across VA CLCs should be applauded and should continue to be an ongoing effort, especially in reducing the overtreatment of UTI, in both the presence and absence of positive urine cultures, in patients without urinary symptoms.

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Table 1. Baseline characteristics of Veterans admitted to VA nursing homes nationally with treated urinary tract infection

Characteristic	Number	Percent
Demographics		
Age in years (mean, standard deviation)[a]	75.7	11.5
Male gender	14,363	95.9
Comorbidities		
Hypertension	11,399	76.1
Dementia	9,076	60.6
Diabetes	7,143	47.7
Benign prostatic hyperplasia	6,791	45.3
Atherosclerosis	6,467	43.2
Nutritional deficiencies	6,370	42.5
Chronic respiratory disease	6,124	40.9
Congestive heart failure	4,980	33.2
Chronic renal disease	5,069	33.8
Complication of device, implant or graft[b]	2,587	17.3
Adverse effects of medical care[c]	1,681	11.2

Data are presented as the number and percent, unless otherwise indicated.

Characteristics presented for 14,983 unique Veterans at the time of the first UTI episode included over the study period.

[a] Age measured at time of urine culture collection

[b] Includes breakdown, leakage, or complication of urinary catheter

[c] Includes all misadventures to patients during surgical or medical care, medical devices associated with adverse incidents in diagnostic and therapeutic use, and surgical or medical care causing abnormal reaction or complication to the patient, such as urinary catherization as a cause of complication.

Table 2. Urine culture results obtained from 28,247 episodes of urinary tract infections in VA Community Living Centers nationally, 2013 to 2017

Organism	**Frequency (n)**	**Percent (%)**
Culture-positive	12,905	45.7
Escherichia coli	4,400	34.1
Proteus mirabilis	3,160	24.5
Klebsiella spp.	2,244	17.4
Pseudomonas aeruginosa	1,136	8.8
Providencia spp.	526	4.1
Enterobacter spp.	404	3.1
Citrobacter spp.	305	2.4
Morganella morganii	300	2.3
Serratia marcescens	126	1.0
Enterococcus spp.	1,403	10.9
Staphylococcus aureus	594	4.6
Culture-negative	7,265	25.7
Other	8,077	28.6

Spp= species

Culture-positive UTI episodes were defined as those in which no more than two typical uropathogens were isolated with quantitative counts $\geq 10^5$ CFU/mL from the urine culture.

Culture-negative UTI episodes were those in which no growth was identified from the urine culture.

All other UTI episodes were defined as those in which typical uropathogens were isolated with low quantitative counts ($\leq 10^5$ CFU/mL), more than two uropathogens were identified, or any other organisms were isolated from the urine culture.

Table 3. Antibiotic use by agent for urinary tract infections in VA Community Living Centers nationally, 2013 to 2017

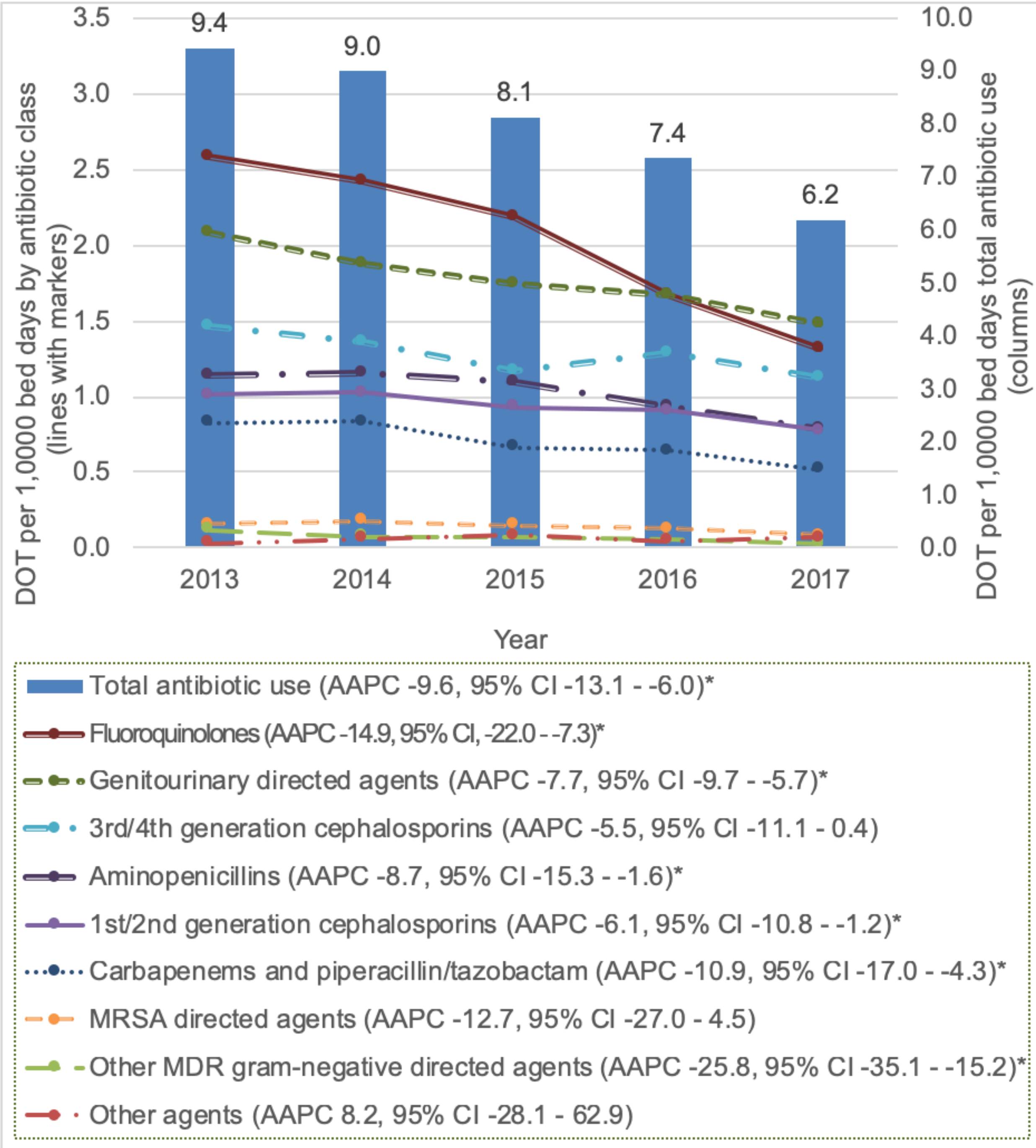
Antibiotic agent	Antibiotic use in days of therapy (DOT)	Percent of total antibiotic use (%)	Frequency of use (n)	Percent of total UTI episodes (%)
Ciprofloxacin	57,579	19.4	8,818	31.2
Sulfamethoxazole/ Trimethoprim	43,244	14.6	5,908	20.9
Ceftriaxone	24,231	8.2	4,591	16.3
Amoxicillin/ clavulanate	22,873	7.7	3,161	11.2
Cephalexin	18,855	6.4	2,566	9.1
Levofloxacin	18,583	6.3	3,179	11.3
Piperacillin/ tazobactam	17,659	6.0	2,983	10.6
Nitrofurantoin	15,222	5.1	1,953	6.9
Cefpodoxime	9,431	3.2	1,242	4.4
Vancomycin	8,312	2.8	1,120	4.0
Amoxicillin	7,849	2.7	1,036	3.7
Cefepime	7,711	2.6	1,200	4.2
Ertapenem	7,487	2.5	934	3.3
Cefuroxime	7,326	2.5	934	3.3

Other agents	-	<2% of total DOT	-	Exposure in <2% of UTI episodes
Total		296,176 DOT		28,247 UTI episodes

DOT= Days of therapy; UTI= Urinary tract infection

Frequency of antibiotic use is not mutually exclusive, as UTI episodes could be treated with more than one antibiotic.

Figure 1. Trends in rate of antibiotic use among culture-positive urinary tract infections in VA Community Living Centers nationally, 2013 to 2017



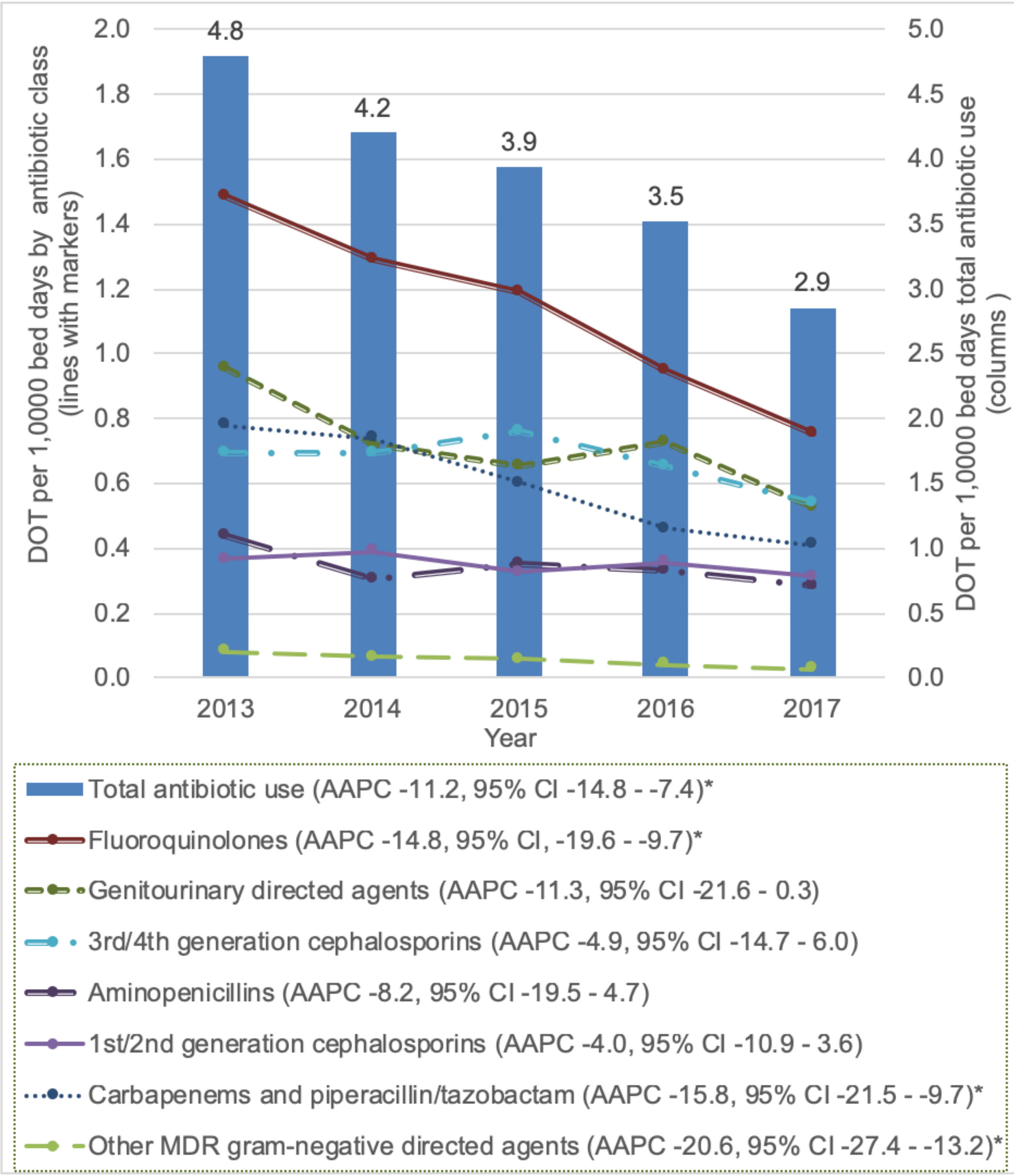
AAPC= average annual percent change; CI=confidence interval; UTI= urinary tract infection; MDR= Multidrug resistant; MRSA= methicillin resistant *Staphylococcus aureus*

AAPCs represent the average percent change per year in rate of antibiotic use in DOT per 1,000 bed days; *=Significant trend at $p<0.05$

Solid blue columns represent the rate of antibiotic use per year in DOT per 1,000 bed days (range 9.4 to 6.2 DOT/1,000 bed days)

Lines with markers represent the rate of antibiotic use by class per year in DOT per 1,000 bed days

Figure 2. Trends in rate of antibiotic use among culture-negative urinary tract infections in VA Community Living Centers nationally, 2013 to 2017



AAPC= average annual percent change; CI=confidence interval; DOT= Days of therapy; UTI= urinary tract infection; MDR= Multidrug resistant

AAPCs represent the average percent change per year in rate of antibiotic use in DOT per 1,000 bed days; *=Significant trend at p<0.05

Solid blue columns represent the rate of all antibiotic use per year in DOT per 1,000 bed days (range 4.8 to 2.9 DOT/1,000 bed days)

Lines with markers represent the rate of antibiotic use by class per year in DOT per 1,000 bed days