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SUMMARY: Potentially suboptimal antibiotic treatment was common in a national cohort of residents with urinary tract infections. Predictors of suboptimal antibiotic treatment included prior fluoroquinolone exposure, chronic renal disease, and older age. These should be targeted in future antibiotic stewardship interventions.

ABSTRACT

BACKGROUND: Unnecessary antibiotic treatment of suspected urinary tract infection (UTI) is common in long-term care facilities (LTCFs). However, less is known about the extent of suboptimal treatment, in terms of antibiotic choice, dose, and duration, after the decision to use antibiotics has been made.

METHODS: We described the frequency of potentially suboptimal treatment among residents with an incident UTI (first during the study with none in the year prior) in Veterans Affairs' (VA) Community Living Centers (CLCs, 2013-2018). Time trends were analyzed using Joinpoint regression. Residents with UTIs receiving potentially suboptimal treatment were compared to those receiving optimal treatment to identify resident characteristics predictive of suboptimal antibiotic treatment, using multivariable unconditional logistic regression models.

RESULTS: We identified 21,938 residents with an incident UTI treated in 120 VA CLCs, of which 96.0% were male. Potentially suboptimal antibiotic treatment was identified in 65.0% of residents and decreased 1.8% annually ($p<0.05$). Potentially suboptimal initial drug choice was identified in 45.6% of residents, suboptimal dose frequency in 28.6%, and longer than recommended duration in 12.7%. Predictors of suboptimal antibiotic treatment included: prior fluoroquinolone exposure (adjusted odds ratio [aOR] 1.38), chronic renal disease (aOR 1.19), age $\geq$85 years (aOR 1.17), prior skin infection (aOR 1.14), recent high white blood cell count (aOR 1.08), and genitourinary disorder (aOR 1.08).

CONCLUSION: Similar to findings in non-VA facilities, potentially suboptimal treatment was common but improving in CLC residents with an incident UTI. Predictors of suboptimal antibiotic treatment should be targeted with antibiotic stewardship interventions to improve UTI treatment.

KEYWORDS: urinary tract infection; suboptimal antibiotic treatment; Veterans Affairs; Community Living Center

BACKGROUND

Inappropriate antibiotic use has become a major public health threat due to the widespread emergence of antibiotic resistant bacteria. In long-term care facilities (LTCFs), antibiotics are among the most commonly used medications with between 47-79% of residents receiving one or more antibiotics each year.[1] It has been estimated that up to 75% of antibiotic use in LTCFs is inappropriate.[2]

Suspected urinary tract infection (UTI) is the most common indication for antibiotics and drives inappropriate antibiotic treatment in LTCFs. Approximately, 32% of the antibiotics given to residents are for UTIs and between 25-85% of antibiotic prescriptions for UTIs among residents are inappropriate.[3-6] Inappropriate antibiotic treatment for UTI may include unnecessary use when an antibiotic is not indicated or suboptimal use based on antibiotic drug choice, dose, and/or duration of treatment. Unnecessary treatment of asymptomatic bacteriuria is among the greatest contributors to inappropriate antibiotic use in LTCFs.[1] Suboptimal antibiotic treatment is also common, however previous work in this area has largely focused on unnecessary UTI treatment without evaluating suboptimal antibiotic treatment.[3,5,6] Prior assessments of suboptimal antibiotic drug choice, dose, and duration among residents in LTCFs are limited.[4,6,7]

Large-scale evaluations of suboptimal antibiotic treatment and type of suboptimal treatment in LTCFs are necessary to identify target areas for improvement. The aims of this work were to define potentially suboptimal antibiotic treatment, as assessed from drug choice, dose frequency, and duration, among residents with an incident UTI treated in Veterans Affairs' (VA) LTCFs (known as Community Living Centers [CLCs]) nationally and to identify predictors of potentially suboptimal antibiotic treatment. Though unnecessary antibiotic treatment is also a major problem in LTCFs, our study focused on suboptimal antibiotic treatment which could be improved with regards to the choice of drug, dose frequency, and duration used after the decision to use antibiotics had been made.[8]

METHODS

Study design, setting, and population.

We conducted a retrospective cohort study among adult (age ≥18 years) residents in VA long-term care units, called CLCs with a suspected UTI between January 2013 and December 2018. UTIs required collection of a urine culture and an antibiotic given on the culture collection date or within 3 days after culture collection.[9] We based our definition of UTI on Infectious Diseases Society of America (IDSA) guidelines which require detection of bacteriuria (in addition to symptoms) for UTI diagnosis.[10,11] When a UTI is suspected, providers frequently obtain a urine culture before treatment is started, but often do not adjust treatment based on urine culture results.[12] As such, a suspected UTI required collection of a urine culture, regardless of whether the microbiology results were ultimately positive or negative for bacterial growth. For each UTI, the antibiotic treatment period was defined as the interval of antibiotic therapy from the start to the end of treatment, identified by gaps of 2 or more consecutive days in antibiotic treatment.[13] All urine cultures collected during the UTI treatment period were considered to be for the same UTI. We included only residents with an incident CLC UTI, defined as the first during the study period with no UTIs treated in a CLC in the year prior.

Residents with suspected UTIs could have had culture-negative or culture-positive urine culture results (*defined in Table 1*). Culture-positive UTIs were further categorized by the number of organisms identified and the organisms identified.[14] Residents with UTIs could have had a UTI diagnosis during the UTI treatment period, identified using International Classification of Diseases (ICD), 9th or 10th Revision diagnosis codes, but this was not a requirement for inclusion.[15]

IDSA guidelines recommend treatment of asymptomatic bacteriuria, a condition distinct from UTI, only in the presence of pregnancy or planned urologic procedure.[11] We thus excluded female residents of child bearing age and residents with a urologic procedure within 2 weeks of the index date.[9] We excluded residents with a UTI associated with chronic antibiotic treatment (>30 days).[16] To avoid capturing treatment of another potential infection, we excluded residents with a positive culture from another source during the UTI treatment period, unless it was a blood culture growing the same organism/s as in the urine.[9] We excluded residents in which any non-UTI or uncommon antibiotics were used (*defined in Figure 1)*.

Data sources.

This study included data from the national VA Corporate Data Warehouse and the Minimum Data Set (MDS). VA data used included: microbiology, inpatient and outpatient care, diagnoses, procedures, surgeries, demographics, vital status, inpatient and outpatient medications, laboratory, and vital measurements including temperature. We obtained urine culture data from microbiology data and medications from barcode medication administration and pharmacy dispensing data.

Variables.

Exposures:

In *Table 2*, we present detailed definitions for potentially suboptimal antibiotic treatment. We defined potentially suboptimal antibiotic treatment based on exposure to any subtype of suboptimal initial drug choice, dose frequency, and/or duration. We considered an initial drug choice to be potentially suboptimal based on evidence of resistance to that agent considering the resident's previous urine culture and susceptibility (C&S) results in the previous 180-days.[17] If no previous urine 180-day C&S were available, we assessed for insufficient coverage (*described in Table 2*) with the agents used considering the local CLC-urinary antibiogram for the year prior.[17] As previously described in prior work, we created annual urine antibiograms for every CLC according to Clinical and Laboratory Standards Institute (CLSI) recommendations of using the first clinical isolate cultured per patient per bacterial species.[18,19] We considered dose frequency to be potentially suboptimal if it was not in accordance with recommendations for dosing based on renal function.[4] We considered duration to be potentially suboptimal if treatment duration was longer than expert recommendations, defined as greater than 14 days.[16,20] We also identified de-escalation of antibiotic therapy among the study population. We assessed rates of de-escalation of antibiotic therapy from initial broad-spectrum coverage to targeted, narrow-spectrum coverage by day 4 (*defined in Table 2*).[21,22] The antibiotic spectrum index (ASI) was used to determine antibiotic spectrum, where the antibiotics used were assigned a score from 1 (most narrow spectrum) to 13 (most broad spectrum agents).[22]

Potential predictors.

We evaluated baseline resident characteristics as potential independent predictors of potentially suboptimal antibiotic treatment. Potential predictors were based on clinical relevance and/or previous work and selected *a priori*.[23-26] Resident characteristics assessed included socio-demographics, comorbidities, comorbidity burden, prior healthcare exposures, prior infections, prior antibiotic exposures, prior positive cultures, prior urine culture collection, and prior laboratory results.

Analytic approach.

We quantified the frequency of potentially suboptimal antibiotic treatment, subtypes of potentially suboptimal treatment, and de-escalation among our study population of CLC residents with an incident UTI. Stratified results were assessed by urine culture results (positive or negative) and presence or absence of a current UTI diagnosis during antibiotic treatment. Time trends were analyzed using Joinpoint regression. Joinpoint regression software was used to calculate average annual percent changes (AAPC) and 95% confidence intervals (CI) for the frequency of potentially suboptimal antibiotic treatment over the study period.

We compared resident characteristics between residents receiving potentially suboptimal and optimal antibiotic treatment. Differences in resident characteristics between groups were analyzed using chi-square for categorical data and Student's *t* test or the Wilcoxon rank sum test for continuous data, as appropriate.

We used backwards, manual, stepwise unconditional logistic regression to identify resident characteristics that were predictors of potentially suboptimal antibiotic treatment.[27] We included variables with a p-value of <0.10 from univariate analysis in subsequent multivariable analysis. We removed variables one-by-one from the multivariable model until remaining variables in the final model demonstrated statistical significance (p-value <0.05).[27] We checked variables in the final model for tolerance and variance inflation. Variables in the final model demonstrated tolerance above 0.1 and variance inflation below 2, indicating absence of collinearity between predictors.[27] We used the final multivariable logistic regression model to calculate adjusted odds ratios (aOR) and 95% CI. Sensitivity analyses were conducted to determine whether predictors varied by subtype of potentially suboptimal antibiotic treatment (drug choice, dose frequency, and longer than recommended duration).

RESULTS

We identified 21,938 CLC residents from 120 VA CLCs with an incident UTI after applying all inclusion and exclusion criteria (*Figure 1*). The median resident age was 74 years (interquartile range [IQR] 67-85) and 96.0% were male. Positive cultures with one organism (51.0%) or two or more organisms (15.2%) were common, and 33.8% were culture negative (*Table 1*). Initial antibiotic treatment with fluoroquinolones (36.2%), cephalosporins (27.6%), and typical genitourinary tract agents (20.8%) were common (*supplemental Table 1*).

Potentially suboptimal antibiotic treatment was identified in 65.0% (n=14,267) of residents (*Table 3*). Potentially suboptimal antibiotic treatment decreased by 1.8% (95% CI -2.8% – -0.7%) per year (*see Supplementary Figure 1*). A potentially suboptimal initial drug choice was identified in 45.6% (n=10,012) of residents, suboptimal dose frequency in 28.6% (n=6,272), and longer than recommended duration in 12.7% (n=2,787). Antibiotics were not de-escalated by day 4 in 74.0% (n=16,239) of residents. Results were similar by urine culture result and presence or absence of a current UTI diagnosis (*Table 3*) and by initial antibiotic treatment class (*supplemental Table 2*).

A larger proportion of the group that received potentially suboptimal antibiotic treatment were in the oldest age group (age ≥ 85 years: 26.9% vs 24.0%, p<0.001); had chronic renal disease (30.2% vs 28.1%, p=0.002); and had prior fluoroquinolone exposure (15.4% vs 11.6%, p<0.001,*Table 4*).

We identified the following 6 resident characteristics that were predictive of potentially suboptimal antibiotic treatment in CLC residents with UTI (*Table 5*): fluoroquinolone exposure in previous 30 days (aOR 1.38), comorbid chronic renal disease (aOR 1.19), age ≥85 years (aOR 1.17), skin or soft tissue infection in the previous year (aOR 1.14), recent high white blood cell count (WBC; aOR 1.08), and comorbid genitourinary disorder (aOR 1.08).

Results of sensitivity analyses can be found in the supplemental material (*Supplementary Table 3*). For suboptimal drug choice, prior fluoroquinolone exposure and age ≥85 years remained significant predictors. For suboptimal dose frequency, prior fluoroquinolone exposure, comorbid chronic renal disease, age ≥ 85 years, and recent high WBC remained significant predictors. For longer than recommended duration, prior skin or soft tissue infection and recent high WBC remained significant predictors.

DISCUSSION

In this retrospective cohort study of 21,938 CLC residents with an incident UTI treated in 120 VA CLCs nationally, 65.0% of residents received potentially suboptimal antibiotic treatment but was decreasing over the study period. Improvements in suboptimal antibiotic treatment over the study period are likely related to increased antibiotic stewardship efforts among VA facilities nationally, such as a mandate for VA facilities to implement and maintain antibiotic stewardship programs since January 2014.[28]

The lack of a standard definition for suboptimal antibiotic treatment and subtypes of potentially suboptimal treatment hinders comparisons between studies.[3] One previous study evaluated the frequency of subtypes of potentially suboptimal antibiotic treatment among residents with UTI treated in two non-VA community-based nursing homes in Rhode Island.[4] We found a lower frequency of potentially suboptimal drug choice (46% vs 72%), drug dosing frequency based on creatine clearance (29% vs 46%), and an overly long duration (13% vs 67%) as compared to the previous work, likely due to differing suboptimal treatment definitions and study populations.[4] As clinical treatment guidelines for complicated UTIs in older adults, in particular males, have not been developed, definitions of appropriate antibiotic treatment are adapted from expert opinion and IDSA treatment guidelines for uncomplicated UTI in women.[16,17,29]

Further, 78% of the other study population was female, as compared with our largely male (96%) study population.[4] UTIs in males are generally considered complicated and fluoroquinolones are often considered first-line in men with severe UTI symptoms or concern for prostate involvement.[20] In women with uncomplicated cystitis, empiric use of fluoroquinolones is generally not recommended first-line due to an increased risk for *Clostridioides difficile* infection, adverse drug events, and resistance as compared with other agents.[17,30] Initial fluoroquinolone use was not considered suboptimal in our study, but in previous work among the largely female non-VA nursing home population, empiric fluoroquinolone use was the most common reason for suboptimal drug choice.[4] Fluoroquinolones were the most common initial antibiotic treatment in our study (36.2%). The frequency of potentially suboptimal drug choice would have been higher had we defined fluoroquinolone use as suboptimal.

There are differences in recommended treatment durations between male and female study populations. Durations as short as 3 days are recommended in females with uncomplicated UTIs.[17] The optimal duration of treatment for men is less well studied, however longer durations between 7-14 days are generally recommended.[16,20] The prior study among a largely female (78%) non-VA nursing home population found that 64% of antibiotics were continued too long, which was defined as over 3 days in female residents, except for those treated with nitrofurantoin in which over 7 days was deemed too long, and over 14 days in male residents.[4] As our study was among mostly males, we defined suboptimal duration as over 14 days. Interestingly, the average duration of treatment was similar in both our study and the prior study at about 8 days and had we used a more stringent definition of 7 days to be suboptimal, the frequency of suboptimal duration in our study would have increased to 68.4%.

The strongest predictor of potentially suboptimal antibiotic treatment was prior fluoroquinolone exposure. Our finding may be related to "prescribing tendencies" for use of suboptimal antibiotics. Previous work among 1,695 long-term care physicians demonstrated that a prescriber's tendency to select fluoroquinolone antibiotics and to select prolonged antibiotic treatment durations correlated strongly with these tendencies in the previous year.[31] It is plausible that residents were treated by CLC prescribers that used fluoroquinolones as a suboptimal UTI drug choice repeatedly.

We found that a recent high WBC and age ≥85 years were also predictive of potentially suboptimal UTI treatment. These findings may be related to differences in the way UTIs are treated when there is concern for more severe infection with systemic involvement, particularly among older patients. Prescribers, for example, may not dose adjust for renal impairment in the presence of severe UTIs. In older patients, prescribers may prefer certain antibiotics or alternative durations compared with younger patients. A prospective audit and feedback approach where a clinical pharmacist or infectious diseases expert reviews antibiotic treatments and tailors the drug choice, dose frequency, and duration of each UTI episode may be most helpful among older residents and those with severe disease, to improve antibiotic treatment. Older residents may also be more likely to receive suboptimal antibiotics due to inappropriate dose adjustments for renal dysfunction. As expected, we found that chronic renal disease remained a significant predictor of suboptimal dose frequency, as drugs are commonly dosed incorrectly in residents with renal dysfunction. As such, renal dose adjustment protocols and guidance for older residents may improve treatment. The VA is a national leader in antibiotic stewardship, and antibiotic stewardship activities such as these have already been implemented in many VAs and may explain the trend in improving antibiotic treatment we observed over the study period.[28,32]

Interestingly, we found several characteristics that were protective against potentially suboptimal antibiotic treatment. These factors included a UTI diagnosis in the year prior, urine cultures in the year prior, and hospitalization in the 30 days prior. This suggests that residents were more likely to receive optimal antibiotic treatment if they had a prior UTI in another setting, such as the VAMC or outpatient setting, or a prior urine culture collection in any setting. The empiric treatment of residents with UTIs without any prior microbiology results or without any previous UTI treatment to guide current treatment is challenging, and continued work should investigate novel strategies to improve treatment in these residents.

We acknowledge the limitations of this retrospective study. We included only residents with a first UTI in which a urine culture was obtained and that was treated with antibiotics in a VA CLC. Suboptimal treatment may be higher or lower in subsequent UTIs. Accurately defining UTIs in long-term care residents can be challenging, and despite requiring the presence of a urine culture and antibiotic treatment, we may have included residents with colonization that were not true symptomatic UTIs (33.8% culture negative, 75.4% without diagnosis) but were still treated with antibiotics. Additionally, the antibiotic treatment we captured may have been for another infection type. Older adults can often have muddled clinical findings upon presentation prompting a "treat with the kitchen sink" approach in order to cover respiratory and urinary pathogens. However, our results were similar when stratified by UTI diagnosis and urine culture results, which suggests the antibiotic treatment captured was likely for a suspected UTI. Additionally, sometimes providers only obtain a urinary dipstick and/or urinalysis without a urine culture when they suspect a UTI. We did not capture dipstick or urinalysis results, and as such our study population did not include residents treated for UTI without urine cultures. There are limitations with our definition of potentially suboptimal antibiotic treatment. No established definitions for potentially suboptimal antibiotic treatment or each subtype of suboptimal treatment have been developed and thus we made assumptions for what constitutes suboptimal antibiotic treatment based on available guidelines and expert opinion.[17] We described the frequency of de-escalation in all residents, and did not assess the necessity of de-escalation. Our predictive analysis is limited by the variables included in the model. We were unable to capture urinary catheter use in our population which may predict suboptimal treatment. The generalizability of findings to non-VA nursing home populations may be limited.

In this large national study of 21,938 CLC residents with an incident UTI treated in 120 VA CLCs, potentially suboptimal antibiotic treatment was common but improving. We defined and described several subtypes of potentially suboptimal treatment, including drug choice, dose frequency, and longer than recommended duration. Several resident predictors of potentially suboptimal treatment were identified. These may be important targets for antibiotic stewardship intervention to further improve the treatment of UTI in VA CLCs nationally and warrant future research. Targeted areas for antibiotic stewardship activities in VA CLCs should be in residents with UTIs who have had prior fluroquinolone exposure, those who are older, and those who have chronic renal disease.

NOTES:

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Table 1. Characteristics of urine cultures collected among residents with an incident urinary tract infection treated in VA Community Living Centers.

Microbiology characteristic	**Number (%)**
Urine culture results	
Culture-negative	7,413 (33.8)
Culture-positive (single organism)	11,190 (51.0)
Culture-positive (≥ two organisms)*	3,335 (15.2)
Organism exposure	
*Gram-negatives***	
Escherichia coli	3,928 (17.9)
Proteus mirabilis	2,466 (11.2)
Klebsiella spp.	2,209 (10.1)
Pseudomonas aeruginosa	1,206 (5.5)
Enterobacter spp.	501 (2.3)
Citrobacter spp.	330 (1.5)
Providencia spp.	283 (1.3)
Morganella morganii	197 (<1)
Gram-positives	
Enterococcus spp.	1906 (8.7)
Staphylococcus aureus	567 (2.6)
Other organisms	3,088 (14.1)

CLC= Community Living Center, spp.=species, UTI=Urinary tract infection, VA=Veterans Affairs

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

Characteristics of urine microbiology cultures are presented for 21,938 CLC residents with an incident UTI between 2013 to 2018.

Culture results were considered culture-negative if no growth was identified from any of the urine cultures collected during the UTI treatment period.

Culture results were considered culture-positive if growth was identified from any of the urine cultures collected during the UTI treatment period with no minimum organism quantitative count. No minimum urine quantitative counts were required for culture-positive UTIs, as previous work has shown that minimum quantitative thresholds may not be appropriate to detect all UTIs and infection is likely to occur at lower quantitative levels in certain patients including those with catheters or chronic kidney disease.[33,34]

Potentially suboptimal antibiotic treatment was measured in the same manner for both positive and negative cultures (see Table 2).

*Most positive cultures with growth of two or more organisms only grew two organisms (n=2,878, 86.3%).

**Not mutually exclusive (does not add to 100%).

Table 2. Study definitions used to measure potentially suboptimal antibiotic treatment, subtypes of potentially suboptimal antibiotic treatment and antibiotic de-escalation among residents with an incident urinary tract infection treated in VA Community Living Centers.

Exposure	Definition	Methods	Justification
Potentially suboptimal antibiotic treatment	Use of a potentially suboptimal: 1) antibiotic drug choice; 2) antibiotic dose frequency; and/or 3) antibiotic treatment duration.	Each subtype measured as below.	
Potentially suboptimal antibiotic drug choice	Use of a suboptimal initial antibiotic drug choice on day 1 based on: 1) evidence of resistance to that agent considering the resident's urine culture and susceptibly (C&S) results from the previous 180 days, or otherwise 2) the local CLC antibiogram (if no previous urine culture and susceptibly results).	First, if previous urine C&S results were available in the previous 180-days, defined as administration of antibiotic despite previous resistance to that agent. Otherwise, if no previous urine C&S results were available in the previous 180-days, defined as administration of only antibiotics with insufficient coverage considering the local CLC-	Defined suboptimal drug choice based on resident's previous urine C&S, as previous microbiology data are highly predictive of current antibiotic susceptibly and it is recommended that previous urine C&S guide initial empiric treatment when available.[35,36] When previous cultures not available, local antibiograms or facility-level antibiotic susceptibility reports should guide therapy.[35] In general, it is recommended that antibiotics

		urinary antibiogram for the year prior.[17]** Insufficient coverage was defined as percent susceptibility less than 80%.[17]	be avoided as initial empiric therapy for UTI when facility resistance rates for the most common organisms causing UTI exceed 10 to 20% (thus percent susceptibility <90-80%).[16,17]
Potentially suboptimal antibiotic dose frequency	Use of a suboptimal antibiotic dose frequency based on renal function.	Renal function was estimated using the Cockcroft–Gault equation using the most recent serum creatine within the 365 days prior. Assessed if the average number of doses per day were concordant with recommended dosage based on renal function.[4] If the number of doses administered per day were not available, dose frequency was estimated by diving	We based definitions on antibiotic dosing guidelines for adult patients based on renal function (estimated using Cockcroft–Gault). Dose frequency could have been suboptimal if an agent was given more or less frequenty than recommened.

		the quantity dispensed by the days' supply. If renal function could not be estimated due to missing serum creatine, dose frequency was defined as suboptimal, as without an estimate of renal function, clinicians could not renally dose adjust medications.	
Potentially suboptimal treatment duration	Use of a longer than recommended antibiotic treatment duration.	A excessive duration was defined as a duration greater than 14 days.	We used a generous definition as a duration up to 14 days is recommended for patients with complicated UTI.[16,20] While shorter treatment durations of 7 days or less are recommended for women with uncomplicated cystitis and may even be appropriate for men with non-severe disease and no complicating conditions, UTIs in males are generally considered complicated and may warrant up

			to 14 days of therapy.[17]
De-escalation	Use of antibiotics with a lower antibiotic spectrum on day 4 of the treatment period as compared to day 1.[22]	The antibiotic spectrum index (ASI) used to determine the antibiotic spectrum on days 1 and 4.[22] ASI scores used to rank each antibiotic used from 1 for the most narrow spectrum agents to 13 for the most broad spectrum agents.[22] De-escalation events identified by subtracting the day 4 ASI from the day 1.[21] De-escalation was defined as a positive change in score.[21]	ASI is a score that was developed to classify commonly used antibiotics based on their spectrum of activity.[22]

UTI=Urinary tract infection

**We created annual antibiograms for every CLC facility according to Clinical and Laboratory Standards Institute (CLSI) recommendations of using the first clinical isolate cultured per patient per bacterial species.[18,19] Individual antibiotics were grouped into antibiotic classes and an overall percent susceptibility was determined considering the most common urinary gram-negative organisms (*Escherichia coli, Proteus mirabilis, and Klebsiella species [spp.])* for agents with primarily gram-negative coverage or considering *Enterococcus spp. and Staphylococcus aureus* for agents with primarily gram-positive coverage.

Table 3. Frequency of potentially suboptimal antibiotic treatment, subtype of potentially suboptimal antibiotic treatment and antibiotic de-escalation among residents with an incident urinary tract infection treated in VA Community Living Centers.

	Total	Urine Culture Result[a]			UTI Diagnosis[b]	
	21,938	**Culture-negative (n=7,413, 33.8%)**	**Culture-positive (one organism, n= 11,190, 51.0%)**	**Culture-positive (≥2 organisms, 3,335, 15.2%)**	**Current UTI diagnosis (n=5,408, 24.7%)**	**No current UTI diagnosis (n=16,530, 75.4%)**
Potentially suboptimal antibiotic treatment*	14,267 (65.0)	5,288 (71.3)	6,857 (61.3)	2,122 (63.6)	3,662 (67.7)	10,605 (64.2)
- Only one suboptimal subtype	9,908/ 14,267 (69.4)	3,783/ 5,288 (71.5)	4,741/ 6,857 (69.1)	1,384/ 2,122 (65.2)	2,346/ 3,662 (64.1)	7,562/ 10,605 (71.3)
- Two suboptimal	3,914/ 14,267	1,399/ 5,288 (26.5)	1,876/ 6,857 (27.4)	639/ 2,122 (30.1)	1,124/ 3,662	2,790/ 10,605

subtypes	(27.4)				(30.7)	(26.3)
- Three suboptimal subtypes	445/ 14,267 (3.1)	106/ 5,288 (2.0)	240/ 6,857 (3.5)	99/ 2,122 (4.7)	192/ 3,662 (5.2)	253/ 10,605 (2.4)
Subtype of potentially suboptimal antibiotic treatment						
*Drug choice***	10,012 (45.6)	4,029 (54.4)	4,624 (41.3)	1,359 (40.7)	2,393 (44.2)	7,619 (46.1)
*Dose frequency****	6,272 (28.6)	2,092 (28.2)	3,174 (28.4)	1,006 (30.2)	1,842 (34.1)	4,430 (26.8)
*Duration*****	2,787 (12.7)	778 (10.5)	1,415 (12.6)	594 (17.8)	935 (17.3)	1,852 (11.2)
- Duration in days (median, interquartile	8 (5-11)	7 (3-10)	8 (7-11)	9 (7-12)	9 (7-12)	8 (5-11)

range)						
- Duration > 7 days	14,998 (68.4)	3,935 (53.1)	8,468 (75.7)	2,595 (77.8)	4,182 (77.3)	10,816 (65.4)
- Duration > 10 days	7,939 (36.2)	1,956 (26.4)	4,436 (39.6)	1,547 (46.4)	2,505 (46.3)	5,434 (32.9)
No antibiotic de-escalation by day 4******	16,239 (74.0)	5,004 (67.5)	8,603 (76.9)	2,632 (78.9)	4,091 (75.6)	12,148 (73.5)

CLC= Community Living Center, UTI=urinary tract infection, VA=Veterans Affairs

Data are n (%) unless otherwise specified.

Frequency of potentially suboptimal antibiotic treatment, subtypes of potentially suboptimal antibiotic treatment and antibiotic de-escalation are presented for 21,938 CLC residents with an incident UTI between 2013 to 2018 overall, by urine culture result; and by presence or absence of a current UTI diagnosis.

[a]Culture results were considered culture-negative if no growth was identified from any of the urine cultures collected during the UTI treatment period. Culture results were considered culture-positive if growth was identified from any of the urine cultures collected during the UTI treatment period with no minimum organism quantitative count.

[b]A current UTI diagnosis required a UTI diagnosis during the UTI treatment period.

*Potentially suboptimal antibiotic treatment was defined as exposure to any of subtype of potentially suboptimal antibiotic treatment (drug, dose frequency dose frequency, and/or duration).

**Potentially suboptimal initial drug choice was defined based on previous urine cultures and susceptibilities or local CLC urine antibiogram. Initial treatment was defined as antibiotics given on the first day of the UTI treatment period.

***Potentially suboptimal dose frequency was defined based on renal function.

****Potentially suboptimal antibiotic duration was defined as a treatment duration greater than 14 days.

******De-escalation was defined as use of antibiotics with a lower antibiotic spectrum on day 4 as compared to day 1. We presented the percent of residents with a UTI episodes not de-escalated by day 4. All residents were assessed for de-escalation, regardless of the necessity of de-escalation. If antibiotics were stopped prior to day 4, this was considered a de-escalation event.

Table 4. Comparison of baseline characteristics for residents with incident UTIs receiving potentially suboptimal antibiotic treatment versus optimal antibiotic treatment.

Characteristic	**Potentially suboptimal antibiotic treatment (n=14,267)**	**Potentially optimal antibiotic treatment (n=7,671)**	**P value**
Age			<0.001
< 65 years	2,405 (16.9)	1,334 (17.4)	
65-74 years	4,606 (32.3)	2,669 (34.8)	
75-84 years	3,414 (23.9)	1,825 (23.8)	
≥ 85 years	3,842 (26.9)	1,843 (24.0)	
Male gender	13,701 (96.0)	7,356 (95.9)	0.617
White race	10,670 (74.8)	5,799 (75.6)	0.187
Married	5,896 (41.3)	3,188 (41.6)	0.738
Hispanic ethnicity	633 (4.4)	309 (4.0)	0.155
Comorbidities*			
Hypertension	10,833 (75.9)	5,912 (77.1)	0.058
Cardiopulmonary disease	10,298 (72.2)	5,675 (74.0)	0.004
Genitourinary disorder	7,568 (53)	4,215 (54.9)	0.007
Diabetes	6,883 (48.2)	3,688 (48.1)	0.813
Gastrointestinal/ nutritional disorder	6,260 (43.9)	3,428 (44.7)	0.249
Atherosclerosis	5,597 (39.2)	3,016 (39.3)	0.900
Benign prostatic hyperplasia	5,012 (35.1)	2,788 (36.3)	0.073
Rheumatic disease	5,012 (35.1)	2,726 (35.5)	0.548
Chronic renal disease	4,305 (30.2)	2,159 (28.1)	0.002
Cancer	4,074 (28.6)	2,259 (29.4)	0.164
Chronic ulcer	4,003 (28.1)	2,201 (28.7)	0.320

Dementia	3,185 (22.3)	1,725 (22.5)	0.782
Obesity	2,526 (17.7)	1,438 (18.7)	0.056
Parkinson's disease	972 (6.8)	520 (6.8)	0.924
Liver disease	925 (6.5)	520 (6.8)	0.401
Previous infections and other diagnoses*			
Urinary tract infection	4,903 (34.4)	3,119 (40.7)	<0.001
Acute respiratory failure	4,221 (29.6)	2,326 (30.3)	0.256
Pneumonia	3,148 (22.1)	1,674 (21.8)	0.679
Skin or soft tissue infection	2,936 (20.6)	1,456 (19.0)	0.005
Complication of surgery or medical care	2,170 (15.2)	1,269 (16.5)	0.010
Complication of device, implant or graft	1,734 (12.2)	984 (12.8)	0.149
Fever	1,380 (9.7)	784 (10.2)	0.195
Adverse effect of medical care	1,192 (8.4)	659 (8.6)	0.549
Adverse effect of drug	1,139 (8.0)	692 (9.0)	0.008
Fracture of the hip	809 (5.7)	475 (6.2)	0.117
Shock	696 (4.9)	408 (5.3)	0.155
Bronchitis	520 (3.6)	297 (3.9)	0.397
Elixhauser score at or above the median	7,845 (55.0)	4,321 (56.3)	0.057
Cognitive function**			0.002
Severely impaired	992 (7.0)	523 (6.8)	
Moderately impaired	2,300 (16.1)	1,185 (15.4)	
Mildly impaired	3,161 (22.2)	1,803 (23.5)	
Cognitively intact	5,591 (39.2)	3,094 (40.3)	
Unknown	2,223 (15.6)	1,066 (13.9)	
Severe functional limitation (ADL $\geq$ 23)***	1,909 (13.4)	1,005 (13.1)	0.561
Previous healthcare exposures			

Time since admission to UTI in days (median, interquartile range)	28 (8.0 - 118.0)	29 (9.0 - 102.0)	0.923
Hospitalization, 30 days prior treatment	4,279 (30.0)	2,400 (31.3)	0.047
Intensive care unit, 30 days prior treatment	1,052 (7.4)	599 (7.8)	0.244
Surgery, 30 days prior treatment	960 (6.7)	506 (6.6)	0.708
Previous antibiotic exposures			
Any antibiotic, 30 days prior to treatment	6,570 (46.1)	3,358 (43.8)	0.001
Fluoroquinolone, 30 days prior to treatment	2,192 (15.4)	893 (11.6)	<0.001
Previous resistant urine cultures, 30 days prior to treatment****			
Fluoroquinolone resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	777 (5.4)	543 (7.1)	<0.001
Extended spectrum cephalosporin resistant *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	467 (3.3)	345 (4.5)	<0.001
Aminoglycoside resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	348 (2.4)	258 (3.4)	<0.001
Piperacillin-tazobactam resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	306 (2.1)	228 (3)	<0.001
Multidrug resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	290 (2.0)	174 (2.3)	0.247
Carbapenem resistant *Pseudomonas*	156 (1.1)	100 (1.3)	0.167

aeruginosa, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*			
Methicillin-resistant *Staphylococcus aureus*	122 (0.9)	109 (1.4)	<0.001
Vancomycin-resistant *Enterococcus spp.*	108 (0.8)	64 (0.8)	0.536
Previous resistant non-urine cultures, 30 days prior to treatment** **			
Fluoroquinolone resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	131 (0.9)	83 (1.1)	0.239
Extended spectrum cephalosporin resistant *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	97 (0.7)	65 (0.8)	0.167
Aminoglycoside resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	75 (0.5)	40 (0.5)	0.967
Piperacillin-tazobactam resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	77 (0.5)	44 (0.6)	0.747
Multidrug resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	59 (0.4)	39 (0.5)	0.315
Carbapenem resistant *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Escherichia coli,* or *Enterobacter spp.*	187 (1.3)	122 (1.6)	0.094
Methicillin-resistant *Staphylococcus aureus*	219 (1.5)	103 (1.3)	0.259
Vancomycin-resistant *Enterococcus spp.*	34 (0.2)	11 (0.1)	0.138

Previous urine culture collection, year prior to treatment*****			
Outpatient urine culture	9,443 (66.2)	6,222 (81.1)	<0.001
CLC urine culture	6,419 (45)	5,004 (65.2)	<0.001
VAMC urine culture	5,367 (37.6)	3,413 (44.5)	<0.001
Previous laboratory results			
Recent high WBC (> 10 x 10^3/μL, within 7 days prior to treatment)******	4,386 (30.7)	2,173 (28.3)	<0.001
Recent high temperature (> 100.0 degrees F, within 7 days prior to treatment) *******	297 (2.1)	123 (1.6)	0.014

CLC= Community Living Center; UTI= Urinary tract infection; VA= Veterans Affairs; VAMC= Veterans Affairs Medical Center; WBC= White blood cell count

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

Characteristics of residents are presented for 21,938 CLC residents with an incident UTI treated between 2013 to 2018.

We compared CLC residents with an incident UTI receiving potentially suboptimal antibiotic treatment and those receiving potentially optimal antibiotic treatment. Potentially suboptimal antibiotic treatment was defined as exposure to any subtype of potentially suboptimal antibiotic treatment: drug choice (based on previous urine cultures and susceptibilities or local CLC urine antibiogram), dose frequency (based on renal function), and/or longer than recommended duration (greater than 14 days).

*Comorbidities and prior infections were identified using ICD-9 or 10 diagnosis and procedure codes within one year prior to the UTI. The Clinical Classifications Software of the Agency for Healthcare Research and Quality categorizations were used to group specific diagnoses and procedures into comorbid conditions and infection type and used to calculate the Elixhauser score.[15]

**Prior antibiotic exposures (fluoroquinolones and/or any other antibiotic) and positive cultures (*E. coli*, *Klebsiella spp.*, *Enterobacter*, and *P. aeruginosa* antibiotic resistant phenotypes, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin resistant *Enterococcus* spp. (VRE) as defined by the Centers for Disease Control and Prevention [CDC]) were assessed in the 30 days prior to the first day of treatment.[37]

***Cognitive function was defined using the MDS 3.0 Cognitive Function Scale (CFS).[38]

****Physical functional status was dichotomized into severe functional limitation based on an activities of daily living score (ADL) $\geq$ 23 and non-severe functional limitation (ADL < 23).[39]

*****Prior positive urine cultures were assessed separately from all other positive culture types.

***** Prior urine culture collection (positive or negative) in the CLC, VAMC, or outpatient settings were assessed in the 365 days prior to the first day of treatment.

******Recent high WBC was defined as a WBC > 10 x $10^3/\mu L$ within 7 days prior to treatment as compared to a measurement below or missing.

*******Recent high temperature > 100.0 degrees within 7 days prior to treatment as compared to a measurement below or missing.

Table 5. Resident characteristics identified as independent predictors of potentially suboptimal antibiotic treatment in multivariable analysis among CLC residents with an incident UTI.

Predictor	**Adjusted odds ratio**	**Lower 95% confidence limit**	**Upper 95% confidence limit**
Fluoroquinolone exposure, 30 days prior to treatment	1.38	1.27	1.51
Chronic renal disease	1.19	1.12	1.27
Age*			
≥ 85 years	1.17	1.07	1.29
75-84 years	1.07	0.98	1.17
65-74 years	0.99	0.91	1.08
Prior skin or soft tissue infection	1.14	1.06	1.23
Recent high WBC**	1.08	1.02	1.15
Genitourinary disorder	1.08	1.02	1.15

CLC= Community Living Center, UTI= Urinary tract infection; WBC= White Blood Cell Count

We compared CLC residents with an incident UTI receiving potentially suboptimal antibiotic treatment and those receiving potentially optimal antibiotic treatment. Potentially suboptimal antibiotic treatment was defined as exposure to any subtype of potentially suboptimal antibiotic treatment: drug choice (based on previous urine cultures and susceptibilities or local CLC urine antibiogram), dose frequency (based on renal function), and/or longer than recommended duration (greater than 14 days).

The adjusted odds ratios are estimated from multivariable analysis of the data. The final multivariable unconditional logistic regression model included all predictive variables listed in the table above (odds ratio >1) and also the following variables with odds ratios <1: UTI diagnosis in the year prior, VAMC urine culture in the year prior, CLC urine culture in the year prior, outpatient urine culture in the year prior, cardiopulmonary disease comorbidity, hospitalization in the 30 days prior, and year.

*Age compared to age < 65 years.

**Recent high WBC was defined as a WBC > 10 x 10^3/μL within 7 days prior to treatment as compared to a measurement below or missing.

Figure 1. Flow chart for study population.

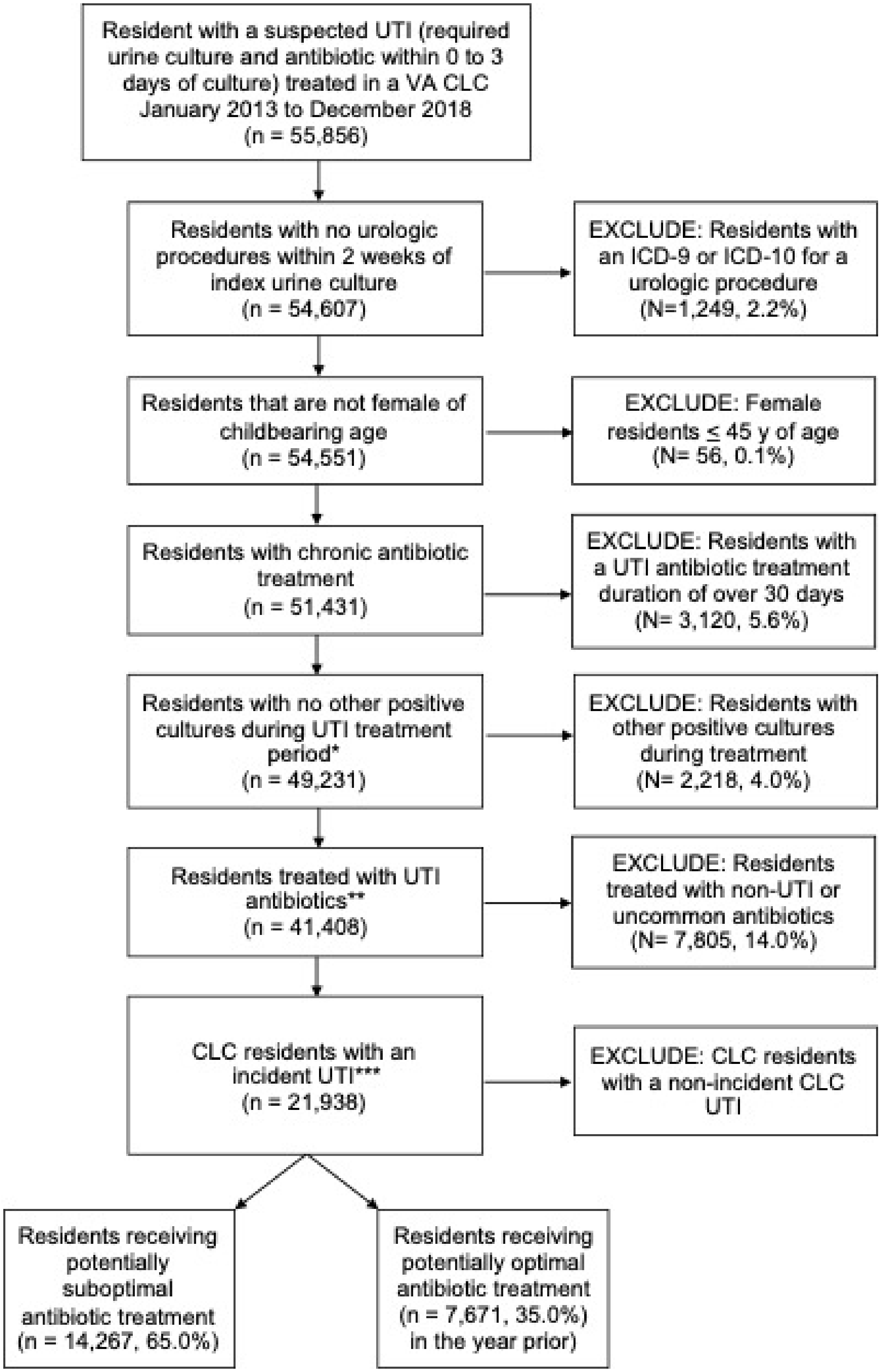
CLC= Community Living Center, ICD-9/ICD-10= International Classification of Diseases, 9th or 10th Revision diagnosis codes, UTI= Urinary tract infection; VA=Veterans Affairs, y=Years

*Other positive culture from another non-urine source (i.e. blood, respiratory, tissue, bone) during the UTI treatment period were excluded, unless it was a blood culture growing the same organism/s as in the urine.

**Non-UTI antibiotics were defined as those not recommended by national treatment guidance and/or without reliable urine concentrations. Uncommon antibiotics were defined as those used in less than 10 residents. Non-UTI and uncommon antibiotics included the following: azithromycin, cefadroxil, cefotaxime, ceprozil, clarithromycin, colistemethate, dalbavancin, demeclocycline, erythromycin, fidaxomicin, methenamine, minocycline (used in less than 10 residents with *Stenotrophomonas maltophilia* and *Acinetobacter spp.*), moxifloxacin, oritavancin, penicillin, piperacillin, rifampin,streptomycin, telavancin, tetracycline, ticaracillin/clavulanate, and tigecycline (used in less than 10 residents with *S. aureus, Klebsiella spp., E. coli, and Acinetobacter spp.*). For all residents except those with UTIs due to *S. aureus* and *Enterococcus* spp., non-UTI and rare included the following: daptomycin, linezolid, ceftaroline (*S. aureus* only), clindamycin (*S. aureus* only), oxacillin (*S. aureus* only), and nafcillin (*S. aureus* only).

***We included only residents with an incident CLC UTI, defined as the first UTI identified during the study period with no previous UTIs treated in a CLC in the year prior. Any other subsequent UTI identified in the CLC during the study period would be a non-incident CLC UTI, and was not included.

Figure 1


Resident with a suspected UTI (required urine culture and antibiotic within 0 to 3 days of culture) treated in a VA CLC January 2013 to December 2018 (n = 55,856)
Residents with no urologic procedures within 2 weeks of index urine culture (n = 54,607)
EXCLUDE: Residents with an ICD-9 or ICD-10 for a urologic procedure (N=1,249, 2.2%)
Residents that are not female of childbearing age (n = 54,551)
EXCLUDE: Female residents ≤ 45 y of age (N= 56, 0.1%)
Residents with chronic antibiotic treatment (n = 51,431)
EXCLUDE: Residents with a UTI antibiotic treatment duration of over 30 days (N= 3,120, 5.6%)
Residents with no other positive cultures during UTI treatment period* (n = 49,231)
EXCLUDE: Residents with other positive cultures during treatment (N= 2,218, 4.0%)
Residents treated with UTI antibiotics** (n = 41,408)
EXCLUDE: Residents treated with non-UTI or uncommon antibiotics (N= 7,805, 14.0%)
CLC residents with an incident UTI*** (n = 21,938)
EXCLUDE: CLC residents with a non-incident CLC UTI
Residents receiving potentially suboptimal antibiotic treatment (n = 14,267, 65.0%)
Residents receiving potentially optimal antibiotic treatment (n = 7,671, 35.0%) in the year prior)