Antimicrobial Prescription Practices for Outpatients with Cystitis: A Multicenter, Medical Record-Based Study

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Abstract

To promote antimicrobial stewardship (AMS) and appropriate antibiotic use, we studied antimicrobial prescription rates for uncomplicated cystitis, a common outpatient disease requiring antibiotic treatment in Japan. This multicenter retrospective study was performed from January 1, 2018, to December 31, 2020, targeting outpatients aged ≥20 years whose medical records revealed International Classification of Diseases (ICD-10) codes suggesting uncomplicated cystitis (N300). We divided eligible cases into two age groups (20–49 years and ≥50 years) and defined broad-spectrum antimicrobials as fluoroquinolones, third-generation cephalosporins, and faropenem. Primary and secondary outcomes were defined as the prescription rates of broad-spectrum antimicrobials for the disease and the association of antimicrobial types with recurrence. The data of 1,445 patients were collected and that of 902 patients were analyzed. The overall proportion of broad-spectrum antimicrobial prescriptions was 69.1%. The broad-spectrum agents were prescribed frequently in the older group, male patients, and internal medicine. Recurrence was observed in 37 (4.1%) cases, and age, sex, or antimicrobial types were not associated with the recurrence. Hence, approximately two-thirds of antimicrobials prescribed for uncomplicated cystitis were broad-spectrum agents. Administration of broad-spectrum antimicrobials was not associated with the prevention of the recurrence of cystitis.

Introduction

With an unprecedented spread of pathogens demonstrating antimicrobial resistance (AMR) worldwide, the global AMR Action Plan was issued in 2015, emphasizing the importance of the appropriate use of antimicrobial agents in medical practices [1]. For international comparison, the average daily use of antimicrobial agents per thousand population is considered as an indicator of appropriate use of antimicrobial agents. In 2013, the antimicrobial use in Japan was approximately 15.8 per thousand population per day [2], which was the second-lowest rate after that of Germany when compared to the developed countries of the European Union [3, 4]. However, the use of oral broad-spectrum antimicrobials, including fluoroquinolones, cephalosporins, and macrolides, was still higher than those in other countries [2]. To combat the domestic spread of AMR in Japan, the Japanese national AMR Action Plan was launched in 2016 to further reduce the overall use of antimicrobial agents by 33% by 2020 compared to that noted in 2013 [2]. However, it is still unclear whether the usage of antimicrobial agents has been favorably optimized in Japan.

Urinary tract infections (UTIs), especially cystitis, are representative of common infectious diseases that clinicians frequently encounter in daily practice. More than 30% of females contract cystitis at least once in their lifetime [3, 4], and globally, over 250 million people reportedly suffer from the disease every year [5]. Recurrence is also common and 30-44% of females experiencing cystitis report a second episode within three months [6]. Thus, antimicrobials are frequently prescribed for the treatment of cystitis in outpatient settings. Additionally, clinical isolations of AMR pathogens, such as extended-spectrum beta-lactamase (ESBL) producing, fluoroquinolone-resistant, or carbapenem-resistant gram-negative bacilli, have been increasingly reported in patients with UTIs [7, 8]. All these findings imply the need of antimicrobial stewardship (AMS) to be further evaluated and promoted in this field.

European and American guidelines recommend several drugs such as sulfamethoxazole-trimethoprim combination, fosfomycin, nitrofurantoin, and pivmecillinam for uncomplicated cystitis [7–9]. Nitrofurantoin and pivmecillinam are currently unavailable in Japan, and the JAID/JSC Infectious Disease Treatment Guide recommends fluoroquinolones as first-line drugs for uncomplicated cystitis [10]. To avoid over-prescription, the use

of fluoroquinolones should be limited to selected cases of complicated or severe UTIs. However, owing to its superiority with respect to both pharmacokinetics and pharmacodynamics, fluoroquinolones have been heavily used for the treatment of UTIs [11]. Consequently, isolation rates of fluoroquinolone-resistant *Escherichia coli* increased from 24% in 2007 to 41.5% in 2020 in Japan according to the national surveillance data [12, 13]. Similarly, administration of third-generation cephalosporins in 3–7 day regimens is recommended in the Japanese guideline [10], which also potentially induces the development of AMR pathogens.

A recent, national surveillance study based on domestic administrative data demonstrated that fluoroquinolones and third-generation cephalosporins accounted for more than 90% of the antimicrobials prescribed for female patients aged ≥15 years with uncomplicated cystitis [11]. This was highly indicative of the need for proceeding with AMS in outpatient UTI treatment; however, due to the nature of the database, the study lacked clinical data endorsing a definitive diagnosis of UTI. This study aimed to investigate antimicrobial prescriptions for uncomplicated cystitis and underlying factors for such prescriptions based on the analysis of medical records.

Results

We collected the data of 1,455 patients from six medical institutions. Of these, 902 cases, for which the clinical symptoms and results of urinalysis were well documented in the medical records, were included for the analysis. The numbers of patients whose data was collected from each institute are listed as follows: Okayama University Hospital (n=233), Tsuyama Chuo Hospital (n=83), Brain Attack Center Ota Memorial Hospital (n=269), Kasaoka City Hospital (n=196), Marugame Medical Center (n=18), and Tamano City Hospital (n=103) (Fig. 1). The overall median patient age [IQR] was 71 [57, 79] years and a proportion of those aged less than 50 years was 18.8% (Table 1) with a female dominance (745 females [82.6%] and 157 males [17.4%]). The numbers (percentages) of patients with respect to consulting departments are listed as follows: 85 cases (9.4%) in internal medicine, 670 cases (74.3%) in urology, and 44 cases (4.9%) in other departments (Gynecology, 30; Surgery, 13; Dental, 1). The departments for 103 cases (11.4%) were unaccounted for in the medical records. Of the 902 eligible cases, urine culture was submitted for 616 (68.3%) of the cases before the antimicrobial prescriptionbing, of which 573 patients (93.0%) were tested positive. *E. coli* (58.4%) was the most common organism detected (Table 2).

Table 1
The numbers and percentages of background data of the eligible cases in each medical institute

		Medical institutes					
	Overall	OUH	TsCH	OMH	KCH	MMC	TaCH
The number of cases	902	233	83	269	196	18	103
Median age [IQR], years	71 [57, 79]	71 [60, 76]	68 [46, 81]	67 [48, 79]	76 [67, 82]	47 [29, 74]	71 [66, 82]
Age group (%)							
<50 years	170 (18.8)	34 (14.6)	25 (30.1)	73 (27.1)	20 (10.2)	10 (55.6)	6 (7.1)
≥50 years	732 (81.2)	199 (85.4)	58 (69.9)	196 (72.9)	176 (89.8)	8 (44.4)	79 (92.9)
Sex (F/M) (%)	745/157	142/91	70/13	246/23	171/25	17/1	99/4
	(82.6/17.4)	(60.9/39.1)	(84.3/15.7)	(91.4/8.6)	(87.2/12.8)	(94.4/5.6)	(96.1/3.9)
Consulting department (%)							
Internal Medicine	85 (9.4)	31 (13.3)	6 (7.2)	2 (0.7)	38 (19.4)	8 (44.4)	0
Urology	670 (74.3)	175 (75.1)	72 (86.8)	266 (98.9)	150 (76.5)	7 (38.9)	0
Others	44 (4.9)	27 (11.6)	5 (6.0)	1 (0.4)	8 (4.1)	3 (16.7)	0
Unrecorded	103 (11.4)	0	0	0	0	0	103 (100)
Bacterial culture (%)							
Tested	616 (68.3)	121 (51.9)	69 (83.1)	239 (88.9)	107 (54.6)	2 (11.1)	78 (75.7)
Not tested	286 (31.7)	112 (48.1)	14 (16.9)	30 (11.2)	89 (45.4)	16 (88.9)	25 (24.3)

The International Classification of Diseases (ICD-10) codes were endorsed in May 1990 by the Forty-third World Health Assembly to develop the diagnostic classification standard for all clinical and research purposes. IQR, interquartile range. ND, no data.

Table 2
Breakdown list of the isolated pathogens.

Pathogens		Age group		Sex	
	Overall (%)	≤50 years (%)	>50 years (%)	Female (%)	Male (%)
Gram-negative rods					
E.coli (ESBL 39, non-ESBL 306)	345 (58.4)	64 (55.7)	281 (58.9)	317 (62.6)	28 (32.9)
Klebsiella pneumoniae (ESBL 1, non-ESBL 19)	20 (3.4)	1 (0.9)	19 (4.0)	16 (3.2)	4 (4.7)
Proteus species	16 (2.7)	1 (0.9)	15 (3.1)	13 (2.6)	3 (3.5)
Citrobacter species	10 (1.7)	1 (0.9)	9 (1.9)	8 (1.6)	2 (2.4)
Pseudomonas aeruginosa	10 (1.7)	0 (0.0)	10 (2.1)	4 (0.8)	6 (7.1)
Klebsiella oxytoca	7 (1.2)	0 (0/0)	7 (1.5)	5 (1.0)	2 (2.4)
Enterobacter species	5 (0.8)	1 (0.9)	4 (0.8)	2 (0.4)	3 (3.5)
Gram-positive cocci					
Coagulase-negative Staphylococci	30 (5.1)	9 (7.8)	21 (4.4)	25 (4.9)	5 (5.9)
Enterococcus species	21 (3.6)	2 (1.7)	19 (4.0)	9 (1.8)	12 (14.1)
Streptococcus species	38 (6.4)	11 (9.6)	27 (5.7)	32 (6.3)	6 (7.1)
Staphylococcus aureus (MSSA 8, MRSA 3)	11 (1.9)	2 (2.6)	9 (1.9)	10 (2.0)	1 (1.2)
Others	78 (13.2)	22 (19.1)	56 (11.7)	65 (12.8)	13 (15.3)

ESBL, extended-spectrum beta-lactamases; MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

The frequency and details of antimicrobial prescriptions with respect to sex, age group, and consulting department are summarized in Table 3 and Fig. 2. Overall, antimicrobials were prescribed for 884 patients (98.0%). No differences were observed in the proportions of antimicrobial prescriptions with respect to age, sex, and the consulting department. Fluoroquinolones were the most commonly prescribed agents (325 cases, 36.0%), followed by third-generation cephalosporins (270 cases, 29.9%) and faropenem (28 cases, 3.1%); a total of 623 patients (69.1%) were treated with these broad-spectrum drugs. Amoxicillin (AMPC) with or without clavulanate (CVA) (184 cases, 20.4%), first- or second-generation cephalosporins (32cases, 3.5%), and sulfamethoxazole-trimethoprim (20 cases, 2.2%) were less frequently administered; a total of 26.2% of the patients were treated with narrow-spectrum antimicrobials. When stratified by age, the numbers of patients in the younger and older age groups were 170 (18.8%) and 732 (81.2%), respectively. Fluoroquinolones were most frequently prescribed in both the younger group (36.5%) and the older group (35.9%). The second most commonly prescribed agents in the younger group were AMPC with or without CVA (34.7%), followed by third-generation cephalosporins (18.2%). While in the older age group, third-generation cephalosporins (32.7%) were prescribed more often than AMPC with or without CVA

(17.1%). When stratified by sex, more than half (62.8%) of the male cases were prescribed fluoroquinolones, followed by third-generation cephalosporins (23.1%). Hence, 86.6% of the male patients were subjected to broad-spectrum antimicrobial treatment. However, fluoroquinolones (30.4%), third-generation cephalosporins (31.4%), and AMPC with or without CVA (23.7%) were almost equally prescribed to female patients. When stratified by the consulting department, fluoroquinolones (40.0%) and third-generation cephalosporins (34.1%), but not AMPC with or without CVA, were the major drugs prescribed to patients in the internal medicine department. The first and second-generation cephalosporins (11.8%) and sulfamethoxazole-trimethoprim combination (7.1%) were rather frequently used. In urology, patients were most frequently prescribed fluoroquinolones (33.7%), followed by third-generation cephalosporins (27.6%) and AMPC with or without CVA (26.7%). Faropenem was prescribed to 24 patients (3.6%), which was not prescribed in the internal medicine department.

Table 3
Numbers and proportions of antimicrobial prescriptions for cystitis by age group, sex, and consulting department

	Visits	**Antimicrobial prescription**			
	Numbers	Numbers	% (95% CI)	Odds ratio (95% CI)	*p* values
Overall	902	884	98.0% (96.9 – 98.8)	-	-
Age group (%)					
<50 years	170 (18.8)	166	97.6% (94.1 – 99.4)	*reference*	-
≥50 years	732 (81.2)	718	98.1% (96.8 – 99.0)	1.24 (0.29 – 4.00)	0.76
Sex (%)					
Female	745 (82.6)	728	97.7% (96.4 – 98.7)	*reference*	-
Male	157 (17.4)	156	99.4% (96.5 – 100)	3.64 (0.56 – 153.1)	0.34
Consulting department					
Internal Medicine	85 (9.4)	84	98.8% (93.6 – 100)	*reference*	-
Urology	670 (74.3)	656	97.9% (96.5 – 98.9)	0.56 (0.01 – 3.76)	1.00
Others	44 (4.9)	44	100.0% (92.0 – 100)	*Not compared*	-
Unrecorded	103 (11.4)	-	-	-	-

CI, confidence interval.

The results of univariate and multivariate analysis for broad-spectrum antimicrobial prescriptions for cystitis are summarized in Table 4. Compared to the younger group, the older group received broad-spectrum drugs (57.1% vs 71.9%; OR [95% CI], 1.83 [1.23 – 2.71]). Compared to female patients, male patients were treated with broad-spectrum antimicrobial drugs (65.4% vs 86.6%; OR [95% CI], 4.68 [2.66 – 8.25]). With respect to the consulting department, compared to the internal medicine department, broad-spectrum antimicrobials were less frequently prescribed in the urology department (74.1% vs 64.9%; OR [95% CI], 0.53 [0.31 – 0.92]).

Table 4
Univariate and multivariate analysis for broad-spectrum antimicrobial prescriptions for cystitis

	Visits	**Broad-spectrum**		**Narrow-spectrum**	**Univariate analysis**		**Multivariate analysis**	
	Number (%)	Number	% (95% CI)	Number (%)	OR (95% CI)	*p* values	OR (95% CI)	*p* values
Overall	902	623	69.1% (65.9 – 72.1)	236 (26.2%)	-	-	-	-
Age group								
<50 years	170 (18.8)	97	57.1% (49.3 – 64.6)	65 (38.2%)	*reference*	-	*reference*	-
≥50 years	732 (81.2)	526	71.9% (68.4 – 75.1)	171 (23.4%)	1.92 (1.34 – 2.75)	<0.001	1.83 (1.23 – 2.71)	0.003
Sex								
Female	745 (82.6)	487	65.4% (61.8 – 68.8)	220 (29.5%)	*reference*	-	*reference*	-
Male	157 (17.4)	136	86.6% (80.3 – 91.5)	16 (10.2%)	3.43 (2.09 – 5.86)	<0.001	4.68 (2.66 – 8.25)	<0.001
Department								
Internal Medicine	85 (9.4)	63	74.1% (63.5 – 83.0)	19 (22.4%)	*reference*	-	*reference*	-
Urology	670 (74.3)	435	64.9% (61.2 – 68.5)	206 (30.7%)	0.65 (0.37 – 1.10)	0.11	0.53 (0.31 – 0.92)	0.025
Others	44 (4.9)	33	75.0% (59.7 – 86.8)	10 (22.7%)	*Not compared*	-	*Not compared*	-

CI, confidence interval; OR, odds ratio. Total number of 902 cases were subjected to the univariate analysis (Chi-square test) and multivariate analysis (logistic regression model).

We finally investigated potential factors responsible for the recurrence of cystitis (Table 5). The total number of patients demonstrating recurrence was 37 (4.1%). The recurrence rates in the younger and the older group were 2.4% and 4.5%, respectively, and those in the female and male patients were 4.4% and 2.5%, respectively. Narrow-spectrum antimicrobials were prescribed in 3.0% of recurrence cases, while broad-spectrum antimicrobials were prescribed in 4.2% of the cases. Univariate analysis did not suggest any statistical differences among each category. Then, we incorporated age, sex, and antimicrobial types into the logistic regression model. These factors were not related to the recurrence. Particularly, compared to the narrow-spectrum antimicrobials, the broad-spectrum agents were not associated with recurrence (3.0% vs 4.2%; OR [95% CI], 1.42 [0.60 – 3.35]).

Table 5
Univariate and multivariate analysis for recurrence of cystitis

	Visits	Recurrence		No recurrence	Univariate analysis		Multivariate analysis	
	Number	Number	% (95% CI)	Number (%)	OR (95% CI)	*p* values	OR (95% CI)	*p* values
Overall	900	37	4.1% (2.9 – 5.6)	863 (95.9%)	-	-	-	-
Age group								
<50 years (%)	169 (18.8)	4	2.4% (0.6 – 5.9)	165 (97.6%)	*reference*	-	*reference*	-
≥50 years (%)	731 (81.2)	33	4.5% (3.1 – 6.3)	698 (95.5%)	1.95 (0.68 –7.68)	0.28	2.42 (0.72 – 8.09)	0.15
Sex								
Female (%)	743 (82.6)	33	4.4% (3.1 – 6.2)	710 (95.6%)	*reference*	-	*reference*	-
Male (%)	157 (17.4)	4	2.5% (0.7 – 6.4)	153 (97.4%)	0.56 (0.14 – 1.62)	0.38	0.54 (0.19 – 1.59)	0.27
Antimicrobials								
Narrow-spectrum	236 (26.2)	7	3.0% (1.2 – 6.0)	229 (97.0%)	*reference*	-	*reference*	-
Broad-spectrum	623 (69.2)	26	4.2% (2.7 – 6.1)	597 (95.8%)	1.42 (0.59 – 3.94)	0.55	1.42 (0.60 – 3.35)	0.42

OR, odds ratio.

Of the total 902 cases, 2 cases were excluded from the analysis since they were lack of information on the recurrence. Consequently, 900 cases were subjected to the univariate analysis (Chi-square test) and multivariate analysis (logistic regression model).

Discussion

In this multi-centered study involving six Japanese medical institutes, we examined the antimicrobial prescriptions for patients diagnosed with uncomplicated cystitis. In comparison with the administrative claims database that reported that more than 90% of the antimicrobials prescribed for uncomplicated cystitis were either fluoroquinolones or third-generation cephalosporins [11], the proportion of broad-spectrum antimicrobials in our cohort was lower at approximately two-thirds of the eligible cases. The broad-spectrum agents were prescribed frequently in the older group (≥50 years) and to male patients. Neither age, sex, or antimicrobial types were associated with the recurrence of simple cystitis.

The primary aim of this study was to elucidate the rates of antimicrobial prescriptions for cystitis by directly drawing clinical data from medical records. Based on the health insurance claims data [11], fluoroquinolones (52.7%) and third-generation cephalosporins (36.9%) accounted for most of the prescriptions for female patients aged ≥15 years with uncomplicated cystitis. This result indicates that the prescription rates of broad-spectrum antimicrobial agents for cystitis in female patients reach nearly 90% in Japan. Our clinical database, however, demonstrated that the overall prescription rates of fluoroquinolones and third-generation cephalosporin were comparatively lower at 36.0% and 29.9%. Focusing on female patients, these broad-spectrum agents, namely, fluoroquinolones and third-generation cephalosporin were prescribed to 30.4% and 31.4% of the patients, respectively. Including faropenem, the prescription rate of broad-spectrum antimicrobials for simple cystitis in women was 65.4%, which was much lower than the data described in the administrative database study [11]. A potential explanation for the differences in the prescription rates of broad-spectrum antimicrobials includes a discrepancy in patient demographics. In order to collect data for patients with uncomplicated cystitis, we used ICD-10 code N300 similar to that employed in the previous study [11]. Thus, we believe that patients with similar clinical backgrounds could be recruited. Upon examination of the patient age, more than 80% of the patients in our cohort were aged ≥50 years, while more than half of the patients in the administrative data were aged <50 years. The high proportion of aged patients in our study may yield higher prescriptions of broad-spectrum antimicrobials, which, however, was not observed. While the previous study included teenagers (patients aged ≥15 years,) our study involved only those aged 20 years and more. This difference, however, would not influence the manner of prescriptions remarkably, considering the fact that fluoroquinolones are typically not recommended for pediatric patients by package inserts in Japan. Another factor for fewer prescriptions of the broad-antimicrobials may involve further promotion of AMS in the regions of medical institutes included in this study. However, this should be compared with similar studies conducted in different regions.

Among our patients, the broad-spectrum antimicrobials were prescribed frequently to patients in the high-age group, male patients, and those treated at the internal medicine department. In the previous study [11], the broad-spectrum antimicrobial prescription rates for simple cystitis were 91.1% in the young group (<50 years) and 90.1% in the older group (≥50 years), showing little difference. In contrast, in our results, the proportions of broad-spectrum antimicrobial prescriptions among the older and younger groups were 71.9% and 57.1% (OR, 95%CI; 1.83 [1.23 – 2.71]), indicating that aged patients were more likely to be prescribed broad-spectrum drugs. This could be rationalized by the fact that aged people tend to present more frequently with underlying diseases, conceivably leading to complicated or severe UTIs. This tendency of frequent prescription of more broad-spectrum drugs among the elderly has also been observed in other studies [11, 14, 15].

The differences in the prescription of broad-spectrum drugs between females (65.4%) and males (86.6%) should be discussed as well. Males do not typically contract cystitis owing to the anatomical advantage [16, 17]. The prevalence of UTIs in females is approximately 50 times higher than that in males [4]. Thus, male patients with UTIs do present with certain underlying disorders, such as urinary tract stones/malignancy, neurogenic bladder, spinal cord injury, and post-kidney transplantation [18, 19]. Our observations of the significantly higher proportion of prescriptions of broad-spectrum drugs among male patients may be attributed to this dissimilarity between the sexes in terms of vulnerability to UTIs. Considering the limitations of the feasibility of the study, we did not collect detailed data of patient characteristics, and hence, could not adjust their backgrounds.

Of note, a single-facility study suggested that organisms isolated from patients visiting urologists with uncomplicated cystitis tend to show resistance to various antibiotics compared to hospital-wide antibiograms [20]. Hence, a higher number of prescriptions of broad-spectrum drugs should have been observed at the Urology

Department in our cohort. However, our investigation found significantly fewer prescriptions of broad-spectrum agents by urologists, which can be attributed to inter-facility or inter-physician differences. Future studies should incorporate these factors that potentially affect antimicrobial prescriptions.

Importantly, our multivariate analysis suggested that prescriptions of the broad-spectrum antimicrobials were not associated with the prevention of the recurrence of cystitis. In view of AMS, broad-spectrum drugs should not be prescribed for common diseases like simple cystitis. Particularly focusing on fluoroquinolones, they are widely active against the urinary pathogens, and a recent meta-analysis based on the systematic review of 47 randomized controlled trials demonstrated the superiority of the drugs compared to that of other antimicrobial agents in terms of clinical remission rates, bacteriological eradication, the emergence of resistance, and relapsing rates [21]. A retrospective population-based cohort study based on administrative health data extracted from six Canadian provinces also verified the advantages of fluoroquinolone prescriptions, such as fewer revisits of outpatients and emergency patients, hospital admission, and re-prescription of antimicrobials within 30 days [22]. However, fluoroquinolones have a variety of adverse drug effects, including QT elongation, glucose intolerance, retinal detachment, tendinitis, aortic aneurysm, and neurologic disorders [23]. Also, the increasing trend of clinical isolations of fluoroquinolone-resistant organisms in UTIs has been corroborated by recent surveillance studies in Japan [12, 13, 20, 24, 25]. Although these facts may make us reluctant to treat patients with simple cystitis with fluoroquinolones, our data demonstrated that many such cases are still treated with the drugs. Our analysis, however, indicated that the administration of narrow-spectrum antimicrobials is not associated with the recurrence, supporting the safety of the treatment of patients with uncomplicated cystitis with amoxicillin, first- or second-generation cephalosporins, and sulfamethoxazole-trimethoprim.

The strength of the present study lies in the direct collection of clinical data from medical records. Previous larger studies were based on health insurance claims data [11], and therefore, the validity of the clinical diagnosis was unreliable. However, there are several limitations to this study. First, despite the multi-centered database, the data of our cohorts were derived merely from six medical institutes. Thus, the generalizability of the study should be evaluated by larger investigations. Second, the ages of the patients were higher with respect to cystitis, since cystitis is typically observed in a younger population. This could be attributed to the fact that we primarily collected data from regional hospitals in rural areas where the population is aging rapidly. Third, information essential to the selection of antimicrobials, such as the history of medication allergies, was not collected. Fourth, the ICD-10 codes given in the medical records may be labeled just for convenience so as to not interrupt their antimicrobial orders. Despite these downsides, our data was of help in comprehending the current practice of antimicrobial prescriptions for uncomplicated cystitis, which can be one of the cornerstones of AMS promotion.

In summary, amid the promotion of AMS to combat AMR, two-thirds of antimicrobials prescribed for cystitis were broad-spectrum agents, primarily fluoroquinolones or third-generation cephalosporin. Male gender, higher age, and visits to the internal medicine department were statistically associated with such prescriptions. Notably, prescriptions of broad-spectrum antimicrobials were not related to the prevention of recurrence. Our present finding would be an indicator for monitoring the antimicrobial prescriptions for patients with cystitis, which, we expect, can be useful data for health policymakers.

Methods

Study subjects and duration

This was a multicentered, retrospective study of patients who visited the outpatient clinics of six medical institutions in Okayama or Kagawa prefectures in Japan (Okayama University Hospital, Kasaoka City Hospital, Tamano City Hospital, Marugame Medical Center, Tsuyama Chuo Hospital, and Brain Attack Center Ota Medical Hospital) between January 1, 2018, and December 31, 2020.

Definition of UTIs and data collection

We included outpatients aged ≥20 years whose medical records were registered with International Classification of Diseases (ICD-10) codes of N300 that define uncomplicated cystitis, similar to previous studies [11]. By reviewing the medical records of the patients, we collected data on age, sex, the outpatient department consulted, presence of urinary tract symptoms (frequent urination, dysuria and pain during urination), urinalysis (leukocyturia, proteinuria, and bacteriuria), bacterial culture, antimicrobial prescriptions, and revisit within one month due to recurrence. We listed the total numbers of isolated pathogens but excluded any of them if three or more organisms were detected in urine. We considered fluoroquinolones, third-generation cephalosporins, and faropenem as broad-spectrum antimicrobials, while we regarded penicillins, first- or second-generation cephalosporins, and sulfamethoxazole-trimethoprim combination as narrow-spectrum antimicrobials. In Japan, only medical doctors are authorized to prescribe antimicrobials but not nurse practitioners or other healthcare professionals. The antimicrobial prescriptions included in this study were not limited to either general practitioners or organ specialists. Patients were categorized into two age groups for the analysis: ≤50 years (younger group) or >50 years (older group). Exclusion criteria were as follows, (i) no clinical symptoms suggestive of cystitis (frequent urination, discomfort during urination, and lower abdominal pain), (ii) no urinalysis tested or no abnormalities detected in urinalysis, and (iii) no data on consulting department.

Outcomes and Statistical analysis

The primary outcome was defined as the prescription rates of broad-spectrum antimicrobials for uncomplicated cystitis in association with factors such as sex, age, and consulting department. The secondary outcome was the association of antimicrobial types (broad-spectrum or narrow-spectrum) with recurrence. The eligible cases were stratified by the age of the patient (<50 years or ≥50 years), sex (female or male), and consulting department (either internal medicine, urology, or others). Categorical variables were shown in numbers, percentages, and odds ratios (OR) with their 95% confidential intervals (CIs), which were assessed with the Chi-square test or Fisher's exact test as appropriate. Continuous variables were summarized with median and interquartile range (IQR). For multivariate analysis, we applied a logistic regression model. The data were analyzed using EZR software, a graphic user interface for the R 4.0.3 software (The R Foundation for Statistical Computing, Vienna, Austria). All estimates were expressed as point estimates with 95% CI, and all reported *p*-values less than 0.05 were considered statistically significant.

Abbreviations

AMR; antimicrobial resistance, AMS; antimicrobial stewardship.

Declarations

Ethics approval

The study was approved by the Okayama University's Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital's Ethics Committee (No. 1907-036). Informed consent was not necessary because the data were fully anonymized and the study protocol was approved by the Ethical Committees of Okayama University Hospital (No. 1907-036). Please refer to the following URL for the Ethical Committees of Okayama University Hospital, although it is written in Japanese.

http://www.hsc.okayama-u.ac.jp/ethics/files/rk/decision_tree.pdf

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Data Availability

The data set for this study is available upon request.

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Author contributions

Study concept: H. Hagiya. Data extraction: M. Takahashi, T. Higashionna, Y. Nakano, K. Sato,Y. Haruki, M. Haruki, H. Honda, and K. Ueda. Data management: M. Takahashi. Statistical analysis: M. Takahashi and H. Hagiya. Drafting of the manuscript: M. Takahashi and H. Hagiya. Critical revision: H. Ogawa and F. Otsuka.

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Conflicts of Interest

The authors have declared that no competing interests exist.

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Figures

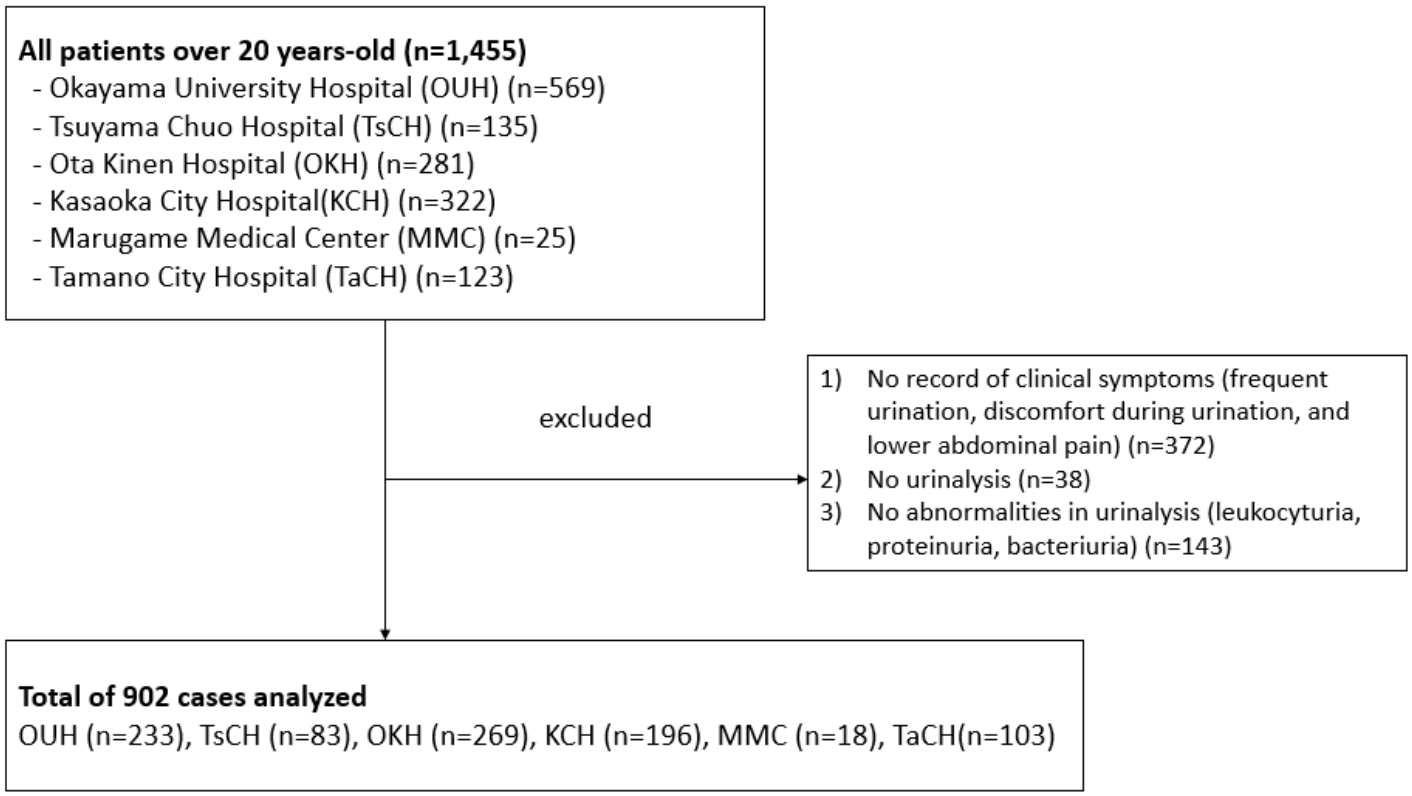

Figure 1

Overall study flow.

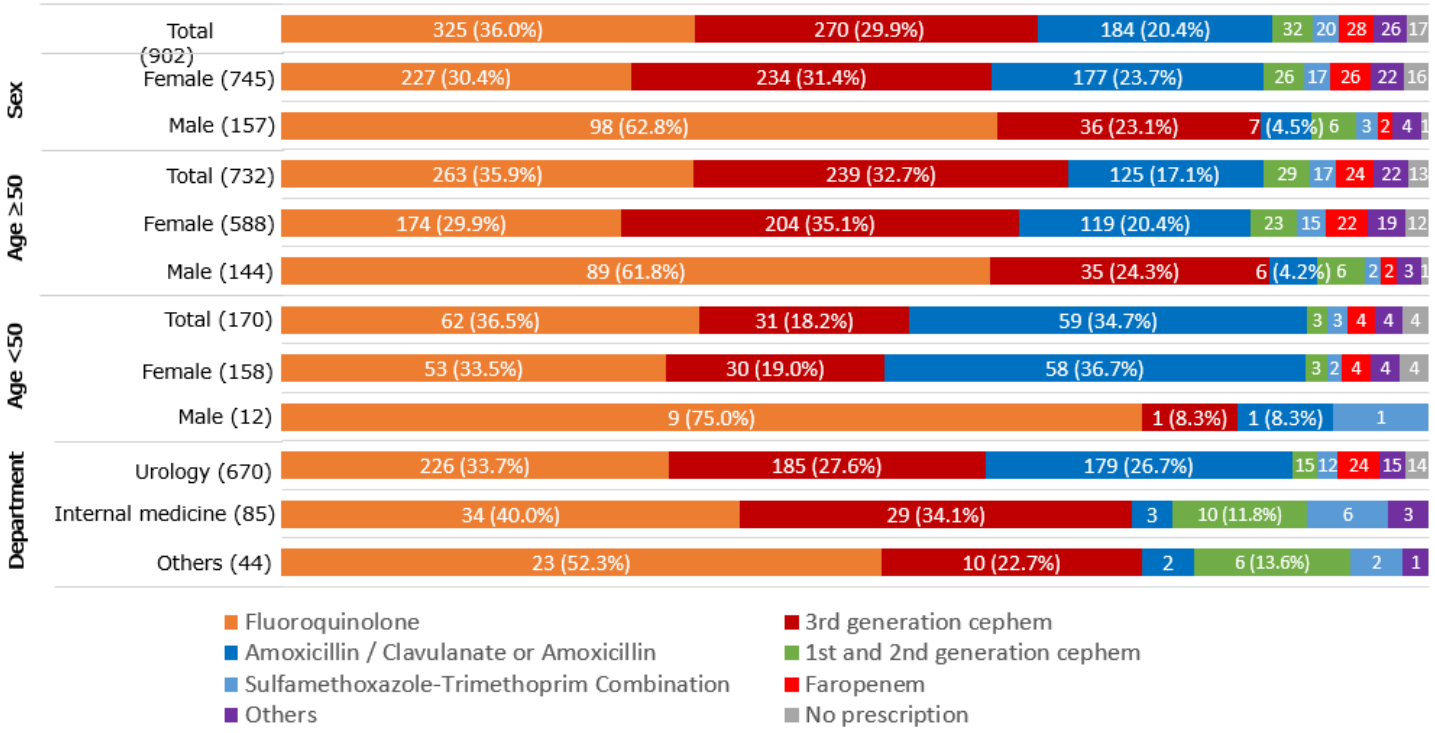

Figure 2

Details of antimicrobial prescriptions for cystitis by sex, age group, and consulting department.