

Low Concordance With Guidelines for Treatment of Acute Cystitis in Primary Care

Larissa Grigoryan,¹ Roger Zoorob,¹ Haijun Wang,¹ and Barbara W. Trautner^{2,3}

¹Department of Family and Community Medicine, ²Section of Infectious Diseases, Departments of Medicine and Surgery, Baylor College of Medicine, and ³Houston VA Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas

Background. The updated 2010 Infectious Diseases Society of America guidelines recommended 3 first-line therapies for uncomplicated cystitis: nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX), and fosfomycin, while fluoroquinolones (FQs) remained as second-line agents. We assessed guideline concordance for antibiotic choice and treatment duration after introduction of the updated guidelines and studied patient characteristics associated with prescribing of specific antibiotics and with treatment duration.

Methods. We used the Epic Clarity database (electronic medical record system) to identify all female patients aged ≥ 18 years with uncomplicated cystitis in 2 private family medicine clinics in the period of 2011–2014. For each eligible visit, we extracted type of antibiotic prescribed, duration of treatment, and patient and visit characteristics.

Results. We included 1546 visits. Fluoroquinolones were the most common antibiotic class prescribed (51.6%), followed by nitrofurantoin (33.5%), TMP-SMX (12.0%), and other antibiotics (3.2%). A significant trend occurred toward increasing TMP-SMX and toward decreasing nitrofurantoin use. The duration of most prescriptions for TMP-SMX, nitrofurantoin, and FQs was longer than guidelines recommendations (longer durations were prescribed for these agents in 82%, 73%, and 71% of the prescriptions, respectively). No patient or visit characteristic was associated with use of specific antibiotics. Older age and presence of diabetes were independently associated with longer treatment duration.

Conclusions. We found low concordance with the updated guidelines for both the choice of drug and duration of therapy for uncomplicated cystitis in primary care. Identifying barriers to guideline adherence and designing interventions to decrease overuse of FQs may help preserve the antimicrobial efficacy of these important antimicrobials.

Keywords. antibacterial agents; guideline adherence; urinary tract infections.

Acute uncomplicated cystitis is a common condition encountered in primary care with more than 8 million office visits annually [1]. Management of cystitis is evolving because increasing antimicrobial resistance limits options for oral therapy [2]. Guidelines for the treatment of cystitis were first published by the Infectious Diseases Society of America (IDSA) in 1999 [3]

and recommended the use of trimethoprim-sulfamethoxazole (TMP-SMX) for 3 days as standard therapy for the treatment of uncomplicated cystitis. Fluoroquinolones (FQs) were not recommended as first-line, empirical therapy due to concerns over the emergence of bacterial drug resistance [3]. The updated 2010 IDSA guidelines [4] essentially retain these principles, with some additional details. The 2010 guidelines recommended 3 first-line therapies: TMP-SMX, nitrofurantoin, and fosfomycin. Specifically, TMP-SMX can be a first-line therapy for uncomplicated cystitis if the resistance prevalence is $<20\%$. Nitrofurantoin for 5 days or a single dose of fosfomycin should also be considered as first-line therapies for uncomplicated cystitis [2, 4]. Fluoroquinolones were considered alternative antimicrobials due to their propensity to cause adverse ecological effects and due to rising rates of resistance to these agents [2, 4]. All of these recommendations were

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Correspondence: Larissa Grigoryan, MD, PhD, Department of Family and Community Medicine, 3701 Kirby Drive, Houston, TX 77098. (grigorya@bcm.edu).

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confirmed by a more recent, comprehensive, systematic review [2].

Few studies have described prescribing patterns since the release of the updated 2010 IDSA urinary tract infection (UTI) guidelines. In a small study including 61 patients at a university-based internal medicine clinic, the overall concordance for the entire regimen with the guidelines was 34% during the year following publication of the guideline [5]. In a before and after study in an emergency department between 2010 and 2012, adherence to guidelines increased from 44% to 68%, and prescription of FQs for uncomplicated cystitis decreased from 44% to 14% after implementation of the electronic UTI order set [6]. Because family practitioners commonly treat women with uncomplicated cystitis, it is important to assess concordance with the guidelines in a family medicine setting. Accordingly, we assessed concordance with the IDSA cystitis management guidelines for antibiotic choice and treatment duration after introduction of the 2010 update in family medicine clinics in the period of 2011 to 2014. We also studied patient characteristics associated with prescribing of specific antibiotics (FQs, TMP-SMX, and nitrofurantoin) and with duration of antibiotic treatment.

METHODS

Setting and Study Population

The study included 2 private family medicine faculty clinics in a large urban area. The clinics were staffed by 33 primary care providers (28 family physicians and 5 physician assistants). Approximately 18 768 patients attend 10 306 appointments each month. Patients in both clinics are predominantly female (58%) and white (54%).

Deidentified records were extracted from the Epic Clarity database (electronic health record system). We selected all female patients 18 years and older who had any of 3 *International Classification of Diseases, Ninth Revision* (ICD-9) codes for UTI listed as a diagnosis: 595.0 (acute cystitis) and 595.9 (unspecified cystitis) and 599.0 (UTI) in 2 private family medicine faculty clinics during the period of 2011–2014. Figure 1 shows our selection process for identifying uncomplicated cystitis visits. Patients were excluded if they had an additional code for pregnancy, genitourinary malignancies or abnormalities, sexually transmitted diseases, active malignancies, recurrent UTI (≥ 3 UTI in the past 12 months preceding the current visit), or

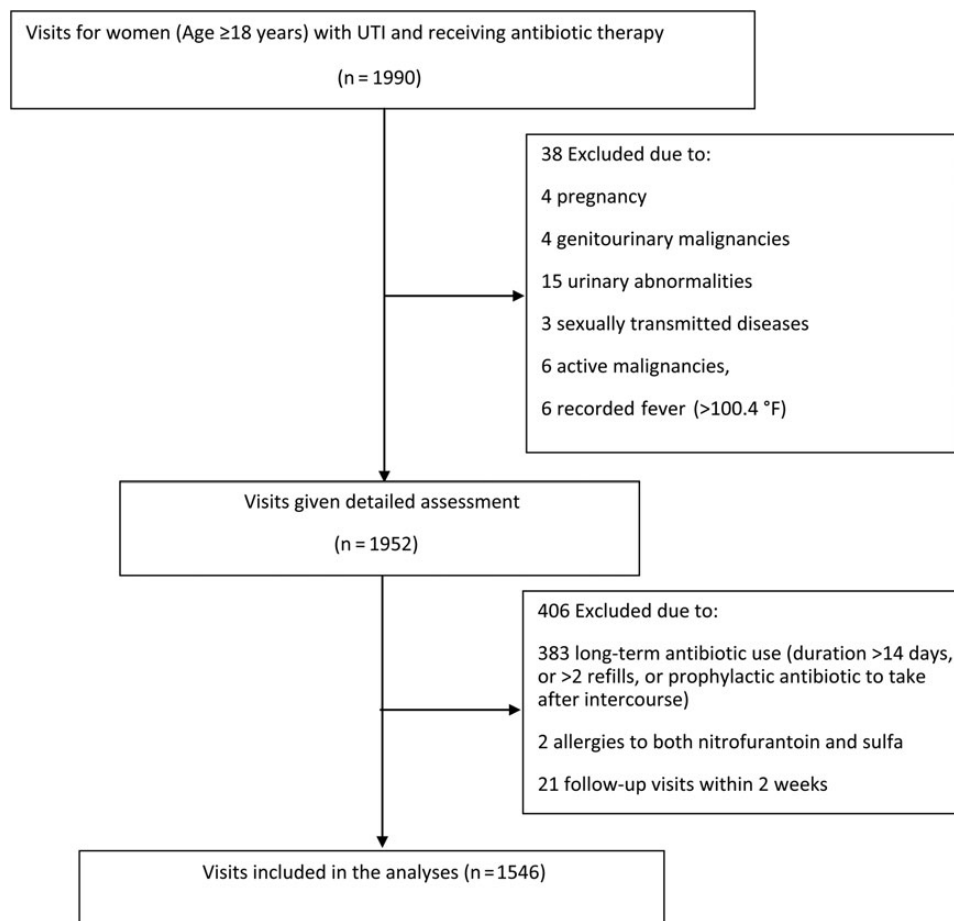


Figure 1. Selection process used to determine uncomplicated cystitis visits. Abbreviation: UTI, urinary tract infection.

recorded fever (>100.4°F). For each eligible visit, we extracted the following variables: patient age, race, insurance status, presence of diabetes, date of office visit, antibiotic allergies, health-care provider, type of antibiotic prescribed, and duration of treatment. We excluded patients who had allergies to both nitrofurantoin and sulfa. We also excluded visits with long-term antibiotics prescribed for >14 days or visits with >2 refills, indicating prophylaxis for recurrent UTI. We also excluded visits with prophylactic antibiotics prescribed to be taken after intercourse. If a patient returned to the clinic within 2 weeks of initial treatment due to UTI, their case was considered as a failure of previous treatment. In these cases, only the original visits were included in the study.

We included women with diabetes because recent evidence suggests that diabetic women presenting with acute cystitis in primary care should be managed similarly to women without diabetes [2]. We also included women aged ≥65 years because treatment recommendations for otherwise healthy older women are similar to those for younger women [7]. This study was considered nonhuman subject research by The Baylor College of Medicine Institutional Review Board (IRB), and IRB approval was not required.

Statistical Analysis

Descriptive statistics were performed on the general characteristics of UTI visits, the type of antibiotic used, and treatment duration in each visit. Trends in the prescribing of TMP/SMX, nitrofurantoin, FQs, and other antibiotics were assessed using the Mantel-Haenszel χ^2 test for trend.

Table 1. Characteristics of Visits for Uncomplicated Cystitis in Women, 2011–2014^a

Visit Characteristics (n = 1546)	
Age, years	43.5 ± 16.2
Presence of diabetes	153 (10)
Race ^b	
White	976 of 1407 (69.4)
Black	196 of 1407 (13.9)
Other ^c	235 of 1407 (16.7)
Insurance status	
Private	1353 (87.5)
Medicare	152 (9.8)
Medicaid	11 (0.7)
Self-pay	30 (1.9)
Year of visit	
2011	391 (25.3)
2012	418 (27.0)
2013	345 (22.3)
2014	392 (25.4)

^a Data are presented as no. (%) or mean ± standard deviation.

^b Data missing for 139 patients.

^c Includes Asian, native Hawaiian, American Indian, or Alaska Native.

Separate multivariable logistic regression analysis was used to determine predictors of TMP/SMX, nitrofurantoin, and FQs. Independent variables included age, presence of diabetes, race, and insurance status. We performed multiple linear regression analysis to study predictors of duration of treatment. Independent variables included age, presence of diabetes, race, insurance status, and type of antibiotic. Analyses were carried out using SPSS (version 22; SPSS, Chicago, IL).

RESULTS

Our study included 1546 visits representing 1273 unique patients over the period of 2011–2014. Most patients were young (mean age, 43 years), white, and had private insurance (Table 1). Throughout the study period, FQs were the most common antibiotic class prescribed (51.6% of visits), followed by nitrofurantoin (33.5%), TMP-SMX (12.0%), and other antibiotics (3.2%). Ciprofloxacin was the most frequently prescribed FQ (97%), followed by levofloxacin (3%). Other antibiotics included amoxicillin-clavulanate in 20 of 49 visits (41%), other β -lactams in 24 (49%), and methenamine, clindamycin, and azithromycin, each in 1 visit (2%). Figure 2 shows prescribing trends in the period of 2011–2014. A significant trend occurred toward increasing TMP-SMX with each successive year ($P = .02$) and toward decreasing nitrofurantoin use ($P = .03$). The majority of primary care providers in both clinics, 30 (91%) of 33 providers, prescribed an FQ for at least 1 visit with uncomplicated cystitis. Fosfomycin was not prescribed in any visit captured in our study. Age, presence of diabetes, race, and insurance status were not significantly associated with

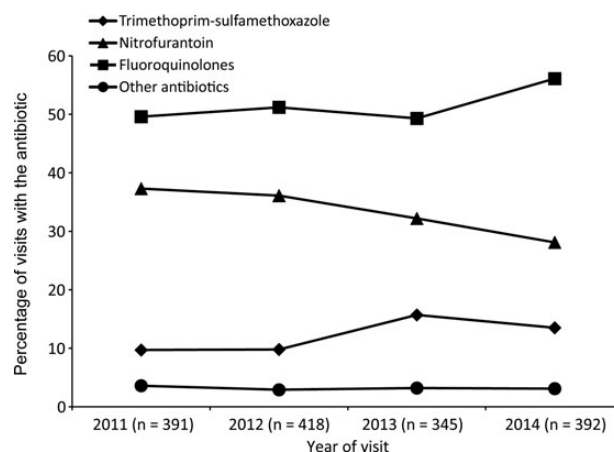


Figure 2. Prescribing trends in the period of 2011–2014. Shown are yearly percentages of visits in which the antibiotics were prescribed. The categories sum to more than 100% because 5 visits involved 2 antibiotics. Fluoroquinolones include 774 (97%) visits with ciprofloxacin and 24 (3%) with levofloxacin. Other antibiotics include 20 (41%) visits with amoxicillin-clavulanate, 24 (49%) other β -lactams, 3 visits with methenamine, 1 with clindamycin, and 1 with azithromycin.

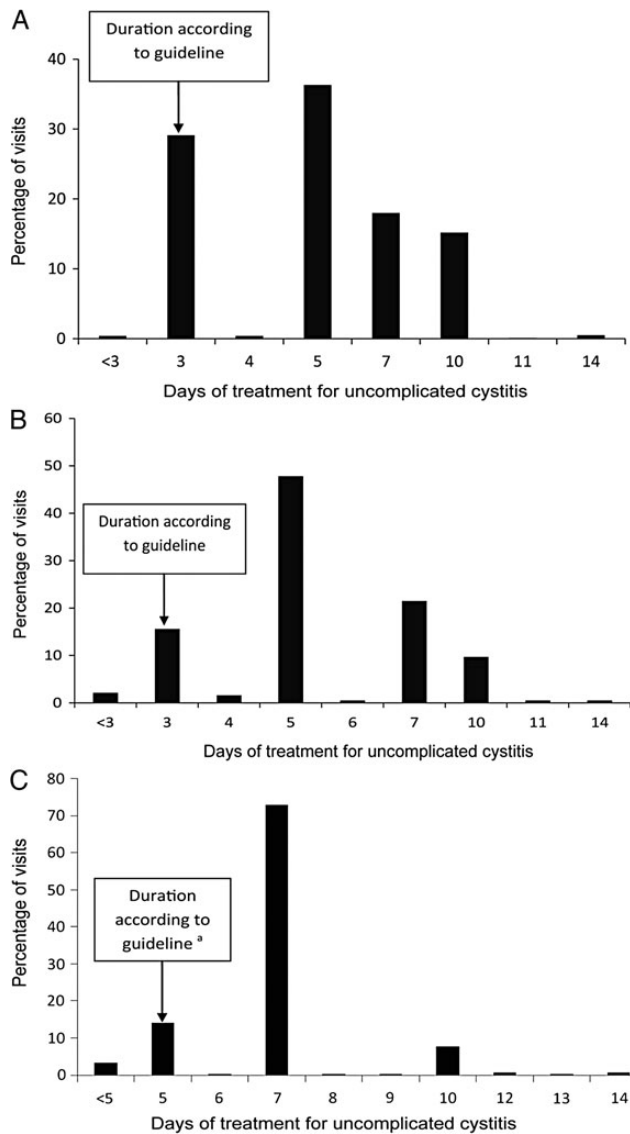


Figure 3. (A) Duration of treatment for ciprofloxacin and levofloxacin. (B) Duration of treatment for trimethoprim-sulfamethoxazol. (C) Duration of treatment for nitrofurantoin. ^aThe recommended duration of therapy for nitrofurantoin has been reduced to 5 days compared with the previous 1999 Infectious Diseases Society of America guideline, based on a clinical trial showing effectiveness with a shorter duration of therapy [8].

prescribing of any particular agent in the logistic regression analyses.

Figure 3 shows the distribution of the duration of therapy for FQs (Figure 3A), TMP/SMX (Figure 3B), and nitrofurantoin (Figure 3C) for all visits with uncomplicated cystitis. For ciprofloxacin and levofloxacin, 29% of all visits led to a prescription with guideline adherent duration of therapy (3 days), whereas 71% had longer than guideline recommended duration. For TMP/SMX, only 16% of all visits had guideline recommended duration of 3 days, whereas 82% had longer than guideline recommended duration. Only 14% of all visits were adherent with

Table 2. Multiple Linear Regression Analysis of Predictors of Antibiotic Treatment Duration^a

Predictors	β^b (95% Confidence Interval) ^c	<i>P</i> Value
Age (years)	0.009 (.002–.016)	.008
Presence of diabetes	0.45 (.08–.81)	.017
Antibiotic		
Trimethoprim-sulfamethoxazole	Referent	
Fluoroquinolones ^d	–0.036 (–.37 to .30)	0.83
Nitrofurantoin	1.33 (.98–1.68)	<.001
Other antibiotics ^e	1.70 (1.04–2.35)	<.001

^a Race and insurance status were not significant.

^b Regression coefficient.

^c Confidence interval; positive beta coefficient shows that the mean value of the outcome (treatment duration) increases with the presence of the risk factor (if dichotomous, eg diabetes) or as independent continuous variable increases (ie, age). Negative beta coefficient shows that the mean value of the outcome decreases with the presence of risk factor (if dichotomous) or as the independent continuous variable increases.

^d Includes ciprofloxacin and levofloxacin.

^e Includes amoxicillin-clavulanate, other β -lactams, methenamine, clindamycin, and azithromycin.

the 5-day recommended duration of therapy for nitrofurantoin according to the 2010 IDSA guidelines, whereas 73% had 7-day duration recommended by the 1999 IDSA guidelines. Older age and presence of diabetes were significantly associated with longer duration of therapy in the multiple linear regression analysis adjusted for the type of antibiotic (Table 2).

DISCUSSION

Our study demonstrates discrepancies between the 2010 IDSA guidelines and clinical practice, a situation commonly observed for many types of guidelines [9]. Throughout the study period, FQs were the most common antibiotic prescribed, despite the recommendation that FQs should not be used as a first-line treatment for uncomplicated cystitis and should be “saved” for the treatment of more serious infections [4]. Nitrofurantoin was the second most commonly used antibiotic; however, there was a significant trend toward decreasing nitrofurantoin use in the period from 2011 to 2014. In contrast, there was a significant trend toward increasing use of TMP-SMX, a recommended first-line agent. Despite being recommended as a first-line agent by the IDSA guidelines [4], and available at local pharmacies, fosfomycin was not prescribed in our study. No patient or visit characteristics predicted prescribing of specific antibiotics (FQs, TMP-SMX, and nitrofurantoin), suggesting that the provider’s choice of these antibiotics is not driven by the patient characteristics we studied. The rate of concordance with the guidelines concerning the duration of treatment was also low for FQs, TMP-SMX, and nitrofurantoin, with most prescriptions

having longer than guideline-recommended duration. Older age and presence of diabetes were independent predictors of longer treatment duration.

Our findings are in line with previous studies showing low concordance with the updated 2010 IDSA guidelines for acute cystitis in an internal medicine clinic [5] and emergency department [6] in the United States. Before the introduction of updated guidelines, concordance with the previous 1999 IDSA guidelines was also low in older studies, because FQs were overprescribed for uncomplicated cystitis in primary care [10–14]. Concordance with treatment guidelines for UTI in primary care varies in other countries [15]. For example, concordance with guidelines for antibiotic selection was high in general practice in Norway with only 6% of FQ prescriptions [16]. In Spain, first-choice antibiotics were administered as empiric treatment in only 18% of women with uncomplicated UTI [17].

Our study suggests that publication of the 2010 updated guidelines may not have changed prescribing practices for uncomplicated cystitis. We found an increasing trend for TMP-SMX, which suggests that high use of quinolones was not in response to rising sulfa resistance. We were surprised to find a decreasing trend for nitrofurantoin, which is exclusively used for UTI and has preserved in vitro efficacy for *Escherichia coli* over many years of use [4, 18]. Nitrofurantoin may have been less popular as a treatment option, because it is considered unsuitable for patients with reduced estimated glomerular filtration rate (eGFR) [19]. However, this recommendation has recently been questioned [19, 20]. In a recent database study, women with low and high eGFRs experienced similar rates of treatment failure with nitrofurantoin, suggesting that physicians may not need to avoid its use in patients with decreased renal function [20]. Fosfomycin is another UTI-specific first-choice antibiotic with high in vitro activity over many years of use in many countries, but it was not prescribed in our study [4, 21, 22]. Although fosfomycin is available in US pharmacies and is approved by the US Food and Drug Administration, providers in our clinic are not yet prescribing it. Primary care providers still have a strong preference for prescribing FQs, although the rate of resistance among *E coli* to the FQs (approximately 20%) is approximately 10-fold higher than to fosfomycin (1%–2%) [18], and FQs may be potentially harmful in the elderly [23].

We also found that most prescriptions for TMP-SMX, nitrofurantoin, and FQs had longer than recommended treatment duration, which may lead to increased risk of resistance, avoidable side effects, waste of resources, and high costs. Physicians may be unaware of the evidence supporting shorter treatment duration for UTI than for many other infectious diseases [24]. Older women and women with diabetes were more likely to receive longer treatment. This finding is not surprising because the optimal treatment duration is not well defined for older adults [7] and women with diabetes [2]. A review of 15 studies in older women showed no difference in short-term

clinical failure between short-course (3–6 days) and long-course (7–14 days) antibiotic treatment [25]. In a Dutch observational study, women with diabetes had a higher recurrence rate despite receiving a longer course of treatment in comparison with nondiabetic women [26]. Thus, neither of these studies supports a longer duration of treatment in older women or those with diabetes.

Prior research has shown that lack of awareness of the guidelines, limited familiarity with guideline contents, and cognitive biases significantly inhibit adoption of clinical guidelines [27–29]. Previously published reasons for low concordance with the guidelines for antibiotic selection in primary care include lack of awareness of the IDSA guidelines, [10] physicians' familiarity with certain antibiotics, [10] physicians' preference of certain agents over others based on their clinical experiences, [10, 30] concern for patient satisfaction [30], and fear of infectious complications [30]. The lack of adherence concerning guidelines in family practitioners may be due in part to the difficulty of keeping up with new recommendations for many different diseases [31].

Interventional studies have addressed the issue of reducing inappropriate FQ therapy for uncomplicated cystitis [6, 32]. Significant improvements in antibiotic prescribing patterns for UTIs were observed in a French study using a multimodal approach [32]. In that study, general practitioners attended training sessions that provided didactic lectures, actual clinical examples, and information on antibiotic prescribing and resistance [32]. In a before and after study in an emergency department, a stewardship intervention that included implementation of an electronic order set followed by a period of audit and feedback was associated with a sustained improvement in adherence to uncomplicated UTI guidelines [6]. In a Swiss cluster-randomized trial in primary care, implementing guidelines, coupled with individual feedback on antibiotic prescribing behavior, resulted in an increase in the use of TMP-SMX for uncomplicated cystitis [33]. Quality improvement programs that encourage clinicians to do more for patients rather than less are typically more successful [34, 35]. Our results show that we need to develop focused strategies to improve adherence to guidelines for both the choice of drug and duration of therapy for uncomplicated cystitis in primary care. Optimum empirical regimens should be based not only on regimen tolerability but also current local resistance prevalence of uropathogens.

The limitation of our study is that it was conducted in 2 private family medicine clinics with predominantly white population with private insurance. This may not be representative of the overall US population. Another limitation is that the adherence to guidelines was measured using a database study and not a manual chart review, thus we cannot assess the rationale for providers' choice of certain antibiotics, nor can we measure the patient symptoms documented only in free text that may have influenced antibiotic prescribing decisions. However, recent evidence shows that the correlation between self-reported UTI symptoms and healthcare providers' documentation is low [36].

CONCLUSIONS

Our study demonstrated low adherence to the updated IDSA guideline for both the choice of drug and duration of therapy for uncomplicated cystitis in primary care. Identifying barriers to guideline adherence and designing interventions to decrease overuse of FQs will help preserve the clinical activity of these important antimicrobials.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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