Research Article

Adherence to International Guidelines for the Treatment of Uncomplicated Urinary Tract Infections in Lebanon

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Objective. The purpose of this study is to evaluate antibiotic-prescribing practices and adherence to IDSA guidelines for the treatment of uncomplicated urinary tract infections in Lebanon. Methods. This observational prospective study was conducted in 15 community pharmacies in Lebanon over 1 year in adult females. A regimen of nitrofurantoin 100 mg bid for 5 days or fosfomycin 3 grams single dose were considered appropriate. For the bivariate analysis, the chi-square test was used. Results. A total of 376 patients were included in this study. The prescribed antibiotic was appropriate in 35 percent of the patients. Age (more than 50 years) did not significantly affect the appropriateness of the prescribed antibiotic (p = 0.508). The frequency of attacks per year (more than 3) negatively affected the choice of antibiotic (p = 0.025). The dose and duration of the prescribed antibiotic was appropriate in 73 and 58 percent of the patients, respectively, with a significant inappropriate dose and duration with fluoroquinolones as compared to nitrofurantoin and fosfomycin (p < 0.001 for the dose and p = 0.014 for the duration of therapy). Conclusions. In an era of increasing bacterial resistance, interventions that improve physicians’ prescribing practices for uncomplicated urinary tract infections are needed.

1. Introduction

Acute bacterial urinary tract infection (UTI) is one of the most prevalent infections encountered in the outpatient setting [1]. UTIs are very common indications for prescription of antibiotics for otherwise healthy women [2]. In the United States alone, the average of patient visits to health-care providers for uncomplicated UTI was 7 million visits per year between 1996 and 2001 [3]. This high prevalence, coupled with a low risk of progression to severe illness associated with UTIs, merits that more emphasis be geared toward the collateral damage linked with the use of antibiotics for this indication in the community setting [4]. The most recent guidelines on treatment of uncomplicated UTI, published in 2010 by the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID), highlighted the importance of this collateral damage while simultaneously drawing attention to the quintessential role played by local susceptibility data [1].

According to IDSA, first-line therapy for the treatment of uncomplicated UTI consists of trimethoprim-sulfamethoxazole (TMP-SMX) 160 mg/800 mg orally twice daily for 3 days in areas in which the resistance rate of Escherichia coli to TMP-SMX does not exceed 20%, nitrofurantoin 100 mg orally twice daily for 5 days, fosfomycin 3 grams single oral dose, or pivmecillinam 400 mg orally twice daily for 5 days [1]. Fluoroquinolones and β-lactams are recommended as alternative treatments to be prescribed when first-line agents cannot be used [1]. Fluoroquinolones have excellent concentration in the urinary tract, but they have a high propensity for collateral damage and therefore should be reserved for complicated cystitis and pyelonephritis.
The drug choice, dose, and duration of treatment were marked as appropriate or inappropriate; if all three were appropriate, then the overall treatment regimen was considered appropriate. Appropriateness was determined according to IDSA 2010 recommendations; a regimen of nitrofurantoin 100 mg bid for 5 days or fosfomycin 3 grams single dose was considered appropriate [1]. Pivmecillinam is not available in Lebanon and therefore was not considered as a potential regimen. Susceptibility to TMP-SMX for Escherichia coli (E. coli) in Lebanon is around 50%, so an empiric regimen of TMP-SMX was considered inappropriate, unless a culture was obtained that showed that the pathogen was susceptible to TMP-SMX [8]. A dose of 160/800 mg of TMP-SMX for a duration of 3 days was considered appropriate as per IDSA guidelines [1]. An empiric regimen of a fluoroquinolone was considered inappropriate. Dose appropriateness for fluoroquinolones was based on the package insert of the prescribed drug and a 3-days duration of treatment was considerate appropriate [1]. Drug choice was considered inappropriate for all other antibiotics prescribed; dose and duration appropriateness were assessed according to the leaflet information.

2.4. Statistical Analysis. Data were entered and analyzed using SPSS, version 23 (BM SPSS Statistics for Windows, IBM Corp., Armonk, NY). A descriptive analysis was carried out using frequency and percentage for nominal and dichotomous variables, and mean and standard deviation for continuous variables. For the bivariate analysis, the chi-square test was used to compare nominal variables between groups. In all cases, a $p$ value < 0.05 was considered statistically significant.

3. Results

3.1. Sample Description. A total of 376 patients were included in this study; Table 1 summarizes the demographic information and the prescribed antibiotics. More than half of the patients (52%) reported only one UTI attack per year, and the mean age was 38 years. 35 patients (9%) reported antibiotic allergy, most commonly associated with penicillin. Most patients (73%) received nonpharmacological treatment, and a urine culture was obtained in 26% of the patients.

3.2. Prescribed Antibiotic. In the 376 patients included, nitrofurantoin was the most frequently prescribed antibiotic ($n = 98$, 26%), followed by ciprofloxacin ($n = 71$, 19%). A total of 146 (39%) patients were prescribed a fluoroquinolone, 19 patients (5%) were prescribed fosfomycin, and 113 (30%) patients were prescribed other medications including amoxicillin/clavulanic acid, cephalosporins, and macrolides.

3.3. Appropriateness: Choice of Antibiotic. One hundred and thirty-one (35%) patients were prescribed an appropriate medication, and 245 (65%) were prescribed an inappropriate medication (Table 2). Age did not significantly affect the
appropriateness of the prescribed antibiotic: 36% of patients under the age of 50 were prescribed appropriate medication versus 31.1% of patients over the age of 50 ($p = 0.508$) (Table 3). The frequency of UTI attacks per year negatively affected the choice of the antibiotic: 23% of patients with 3 attacks or more per year received an appropriate medication versus 37.5% of patients with less than 3 attacks per year ($p = 0.025$) (Table 3).

3.4. Appropriateness: Dose. Two hundred and seventy-six (73%) patients were prescribed the right dose, whereas 100 (27%) patients were prescribed an inappropriate dose (Table 2). Neither age nor frequency of UTI attacks per year affected the appropriateness of the dose prescribed (Table 3). Inappropriate doses were most frequent with fluoroquinolones prescriptions. Only 55% of the prescribed doses of fluoroquinolones were appropriate versus 78% of nitrofurantoin prescriptions, 100% of fosfomycin prescriptions, and 90% of prescriptions for other medications ($p < 0.001$) (Table 3).

3.5. Appropriateness: Duration. The duration of treatment was appropriate for 219 (58%) patients and inappropriate for 157 (42%) patients. Appropriateness of the duration of treatment was not affected by age nor by the frequency of UTI attacks per year (Table 3). Appropriateness of the duration of treatment was significantly affected by the drug choice: 62% of nitrofurantoin and fosfomycin prescriptions had an appropriate duration of therapy, compared to 49% of the fluoroquinolones prescriptions ($p = 0.014$) (Table 3).

3.6. Overall Appropriateness: Regimen (Composite of Drug, Dose, and Duration). Of the 376 patients, 80 (21%) were prescribed an overall appropriate regimen (defined as an appropriate drug, dose, and duration of therapy) and 296 (79%) were prescribed an inappropriate regimen. Age did not affect the overall appropriateness of the regimen prescribed. Patients with 3 UTI attacks or more per year were less likely to receive an appropriate regimen (12%) when compared to patients with a history of less than 3 attacks per year (24%) ($p = 0.30$) (Table 3).

4. Discussion

The Infectious Diseases Society of America updated their 1999 guidelines for the treatment of women with uncomplicated cystitis and pyelonephritis in order to guide health-care professionals on the optimal selection of an antimicrobial agent and its duration of therapy. The 2010 updated guidelines recommend four first-line therapies for uncomplicated cystitis: nitrofurantoin 100 mg orally twice daily for 5 days, trimethoprim-sulfamethoxazole 160 mg/800 mg orally twice daily for 3 days in areas where resistance to *Escherichia coli* does not exceed 20%, fosfomycin 3 grams single oral dose, or pivmecillinam 400 mg orally twice daily for 5 days. Fluoroquinolones and β-lactams remain as second-line agents. In Lebanon, pivmecillinam is not available, and resistance of *Escherichia coli* to TMP-SMX is approximately 50% rendering it an unsuitable empirical treatment for uncomplicated cystitis.

Similar studies evaluating antibiotic prescribing practices for uncomplicated cystitis in the United States reveal a low adherence to the guidelines and an increase in the use of fluoroquinolones for this indication [6, 15]. Fluoroquinolones, mainly ciprofloxacin and levofloxacin, have a broad spectrum of activity against uropathogens, and have been shown to be highly efficacious in 3-day regimens. They also possess moderate activity against enterococcus, a Gram-positive organism often complicating UTIs [16]. Moreover, fluoroquinolones possess favourable pharmacokinetics including high concentrations in the urinary tract, good oral bioavailability, and good renal excretion. However, these drugs have been associated with MRSA infections and an increase in the resistance of difficult-to-treat Gram-negative bacilli such as *Pseudomonas aeruginosa* [7]. Several case

Table 1: Baseline demographics.

| Demographics          | Number of patients | Percentage |
|-----------------------|--------------------|------------|
| Age                   |                    |            |
| 18–30                 | 117                | 31         |
| 30–40                 | 114                | 30         |
| 40–50                 | 84                 | 22         |
| 50–60                 | 39                 | 10         |
| >60                   | 22                 | 6          |
| Number of UTI per year|                    |            |
| 1                     | 194                | 52         |
| 2                     | 113                | 30         |
| ≥3                    | 69                 | 18         |

| Prescribed antibiotic |                |            |
|-----------------------|----------------|------------|
| Fluoroquinolones      | 146            | 39         |
| Nitrofurantoin        | 98             | 26         |
| TMP-SMX               | 52             | 14         |
| Cephalosporin         | 40             | 11         |
| Fosfomycin            | 19             | 5          |
| Amoxicillin/clavulanate| 12             | 3          |
| Other β-lactams       | 5              | 1          |
| Other antibiotics     | 4              | 1          |

| Allergy                |                |            |
| Penicillin            | 28             | 7          |
| TMP-SMX               | 4              | 1          |
| Nitrofurantoin        | 1              | 0          |
| Fluoroquinolones      | 1              | 0          |
| Tetracyclines         | 1              | 0          |
| No allergy            | 341            | 91         |

| Nonpharmacological treatment | | |
| Yes                     | 276            | 73         |
| No                      | 100            | 27         |

| Culture obtained      |                |            |
| Yes                    | 97             | 26         |
| No                     | 279            | 74         |
studies have shown a significant association between prior levofloxacin or ciprofloxacin use and the emergence of resistance of as a single oral dose, increasing patient compliance, and the resistance of Escherichia coli to fosfomycin is very low in Lebanon [19]. Additionally, resistance to fosfomycin observed in clinical studies appears to be considerably lower than the resistance seen in in-vitro data [20]. In urinary tract infections in particular, the development of resistance is low because of the increased drug concentration in the acidic urinary pH. This is possibly due to the low adherence of fosfomycin-resistant mutants to epithelial cells. The lower resistance pattern to fosfomycin seen in clinical trials can also be attributed to the reduced growth and virulence of the mutant strains compared to the parent strains. This was shown to be mainly true not only for *Escherichia coli*, but also for *Klebsiella pneumoniae* and *Proteus mirabilis*.

Grigoryan and Zoorab examined data from two private family medicine faculty clinics from 2011 to 2014 [21]. They assessed the choice of antibiotic and the duration of treatment administered for acute uncomplicated UTI. Fluoroquinolones were the most commonly prescribed antibiotics (51.6% of visits), followed by nitrofurantoin (33.5%), TMP/SMX (12%), and other antibiotics (3.2%). Regarding the duration of treatment, 71% of the prescriptions for fluoroquinolones, 82% of the prescriptions for TMP/SMX, and 76% of the prescriptions for nitrofurantoin were given for a duration that exceeded the guidelines’ recommendations [21].

Another cross-sectional study, involving 61 patients, gathered data from July 2011 to June 2012 in a university-based internal medicine clinic [3]. According to this study, the overall concordance for the entire regimen with the IDSA 2010 updated guidelines was 34%. TMP/SMX was the most frequently prescribed antibiotic (45.3%), followed by ciprofloxacin (28.3%) and nitrofurantoin (24.5%). Interestingly, more than half of the patients prescribed TMP/SMX received a regimen in complete concordance with the guidelines, as opposed to none of the patients prescribed ciprofloxacin [3].

Our findings are in line with previous studies showing low adherence to the IDSA 2010 guidelines for the treatment of uncomplicated cystitis. Moreover, studies published before the update also showed low adherence to the 1999 version of the IDSA guidelines, suggesting that the updated guidelines may not have significantly altered prescribing practices [7].

Also, in Lebanon, it should be noted that fluoroquinolones are relatively more expensive than other available treatment options such as nitrofurantoin and fosfomycin. The increase in the use of fluoroquinolones not only confers a risk of increased cost and collateral damage, but also poses an increased risk of serious adverse effects.

The low adherence to the IDSA guidelines could be due to a lack of awareness to the recommendations, physicians’ familiarity and preference for certain antibiotics based on their clinical experience, and concern for infectious complications. It may also be due in part to the difficulty of keeping up with new recommendations for many different diseases.

To our knowledge, this is the first study to evaluate antibiotic-prescribing practices and adherence to IDSA guidelines for the treatment of uncomplicated UTI in Lebanon. Nevertheless, the study has several limitations. First, it is observational in nature so the cause-effect relationship between elements could not be ensured. Second,

### Table 2: Appropriateness of treatment.

|                | Appropriate | Nonappropriate |
|----------------|-------------|---------------|
| Regimen        | 80 (21%)    | 296 (79%)     |
| Drug           | 131 (33%)   | 245 (65%)     |
| Dose           | 276 (73%)   | 100 (27%)     |
| Duration       | 219 (58%)   | 157 (42%)     |
convenience samples of only fifteen Lebanese community pharmacies were included in the study. However, patients were recruited from different geographical areas and for a one-year period which could dilute this limitation and make the sample representative. Finally, there was no follow-up of patients after filling in their prescriptions which could have provided more information about the antibiotic’s efficacy and safety.

5. Conclusions

This study demonstrates a high prevalence of inappropriate use of antibiotics for the treatment of outpatient uncomplicated urinary tract infections in Lebanon. This is mainly attributable to inappropriate indication, dose, and/or duration of therapy with fluoroquinolones. In an era of increasing bacterial resistance and dwindling antimicrobial choices for Gram-negative infections, interventions that improve physicians’ prescribing practices through education on appropriate therapy for uncomplicated UTIs are needed.

Ethical Approval

This study was approved by the Lebanese American University Institutional Review Board, and the study was performed in accordance with the Declaration of Helsinki.

Disclosure

This study was presented at the 25th Annual Congress of the Lebanese Order of Pharmacists.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

All authors read and approved the final manuscript and are accountable for all aspects of the work.

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| Table 3: Bivariate analysis. |
|-----------------------------|
| Age                        | Appropriate antibiotic | Appropriate dose | Appropriate duration | Appropriate overall regimen |
| <50 years                  | 112 (35.6%)            | 232 (73.7%)     | 183 (58.1%)         | 66 (21.0%)                  |
| >50 years                  | 19 (31.1%)             | 44 (72.1%)      | 36 (59%)            | 14 (23.0%)                  |
| Frequency of attacks       |                           |     |                     |                              |
| <3/year                    | 115 (37.5%)            | 226 (73.6%)     | 180 (58.6%)         | 72 (23.5%)                  |
| ≥3/year                    | 16 (23.2%)             | 50 (72.5%)      | 39 (56.5%)          | 8 (11.6%)                   |
| Choice of medication       |                           |     |                     |                              |
| Nitrofurantoin             | N/A                    | 76 (77.6%)      | 58 (59.2%)          | N/A                         |
| Fosfomycin                 | N/A                    | 19 (100%)       | 15 (78.9%)          | N/A                         |
| Fluoroquinolones           | N/A                    | 80 (54.8%)      | 72 (49.3%)          | N/A                         |
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