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1 Article

2 **Reconsultation and Antimicrobial Treatment of Urinary Tract**
3 **Infection in Male and Female Patients in General Practice**

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13 Date: 10th June 2016

14 **Abstract:**

15 Current antimicrobial prescribing guidelines indicate that male and female patients with urinary
16 tract infection (UTI) should be treated with same antimicrobials but for different durations. The aim
17 of this study was to explore differences in reconsultations and antimicrobial prescribing for UTI for
18 males and females. A total of 2557 adult suspected UTI patients participating in Supporting the
19 Improvement and Management of Prescribing for urinary tract infection (SIMple) study from 30
20 general practices were analyzed. An antimicrobial was prescribed significantly more often to
21 females (77%) than males (63%). Nitrofurantoin was prescribed more often for females and less for
22 males (58% vs 41%) while fluoroquinolones were more often prescribed for males (11% vs 3%).
23 Overall, reconsultation was 1.4 times higher in females and if the antimicrobial prescribed was not
24 the recommended first-line (nitrofurantoin), reconsultation after empirical prescribing was
25 significantly higher. However, the reconsultation was similar for males and females if the
26 antimicrobial was first-line. When a urine culture was obtained, a positive culture was the most
27 important predictor of reconsultation (Odds ratio 1.8 (95% CI 1.3-2.5)). This suggests, when
28 prescribing empirically, male and female UTI patients should initially be treated with first-line
29 antimicrobials (nitrofurantoin) with different durations (50-100 mg four times daily for three days
30 in females and seven days for males). However, considering culture test before prescribing
31 antimicrobials may improve outcomes.

32 **Keywords:** Urinary tract infection, reconsultation, generala practice, antimicrobial prescribing,
33 treatment, culture test, male and female
34

35 **1. Introduction**

36 Research on urinary tract infections (UTIs) has mainly been focused on women because of the
37 higher incidence and prevalence in women compared to men [1, 2]. Treatment recommendations for
38 UTI differ for males and females, mainly regarding the duration of treatment The Irish antimicrobial
39 guideline for UTI treatment indicates treatment of females and males UTI with same first line
40 antimicrobials (Nitrofurantoin and Trimethoprim) but for different duration (three days vs. seven
41 days).[3]. However, the SIGN guideline UK indicate 7 days first-line (Trimethoprim and
42 Nitrofurantoin) treatment regimen to males with uncomplicated UTI, but the treatment with
43 antimicrobials is not recommended to the females with asymptomatic bacteriuria [4]. One common
44 conception in general practice is that males generally have complicated UTIs, and that therefore

45 treatment recommendations for uncomplicated UTI in women are not appropriate for men. In an
 46 observational study of male veterans treatment outcome (recurrence) was compared with duration
 47 of treatment. This showed that a longer duration of treatment (greater than seven days) was
 48 associated with increased late recurrence (30 days after prior episode), [5]. They also found a link
 49 between longer duration of treatment and the occurrence of *C. difficile* associated diarrhea in
 50 patients. Considering the risks associated with long courses of antimicrobials Trautner suggests in
 51 her commentary, a more judicious use of antimicrobials for UTI in males as there seems to be no
 52 clinical benefit of longer duration of treatment[6] . A German observational study conducted in 2004
 53 in 90 males concluded that UTI in males should not be treated empirically or based on dipstick results
 54 and clinical information. Their study showed that 60% of males had a positive culture, even though
 55 half of them had low colony counts and that the antibiotic prescribed to 36% of the males were not
 56 well targeted. The authors recommend to await urine culture results before a treatment decision is
 57 made [7]. A Dutch study of UTI in males reported that dipstick information in combination with
 58 clinical diagnosis was as accurate as recommended care based on culture results [8]. The subsequent
 59 study comparing uropathogens and their resistance between male and female UTI patients similarly
 60 suggests that given the heterogeneous population of uropathogens causing UTI in males, empiric
 61 treatment should be avoided and treatment should be based on culture results [9]. Differences in
 62 treatment between these studies may be cultural or related to differences in study population and
 63 shows the need for more research to elucidate the epidemiology, diagnosis and treatment of UTI in
 64 males. Also, in the wake of the global spread of antimicrobial resistance, limiting the use of
 65 antimicrobials is essential.

66

67 In this study we aim to describe differences between males and females with UTI attending
 68 General Practices with respect to antimicrobial prescribing, and the frequency of reconsultation.

69 2. Results

70 A total of 3561 UTI consultations were recorded over the 15 month period, 372 (10.5% males and
 71 3187 (89.5%) females. There were 2557 (71.8%) index consultations (280/ 2557 males, 2275/2557
 72 females and 2/2557 unknown) and 1004(28.2%) additional consultations with a similar distribution
 73 of males (92/1004) and females (912/1004). The additional consultations were made within 30 days of
 74 the first visit (reconsultation) in the case of 512 (20%) of the index patients. An overview of the index
 75 consultation is presented in Table 1. Males were older than females and were more often patients
 76 holding a medical card.

77

Table 1: Univariate comparisons of the index consultation between males and females

	Male		Female		p-value
	N	%	N	%	
Index consultation	280	11.0	2275	89.0	
Reconsultation	51	18.2	461	20.3	ns
Age in years(mean and SD)	63.6	17.8	52.4	20.9	<0.001
17-25	8	2.9	275	12.0	
26-50	52	18.6	802	35.3	
50-75	134	47.9	814	35.8	
>75	86	30.7	384	16.9	
Medical card	194	69.3	1372	60.3	0.004
Arms					
Intervention arm A	100	35.7	698	30.7	
Intervention arm B	89	31.8	827	36.4	ns
Control arm	91	32.5	750	33.0	
Antimicrobial prescribed	177	63.2	1750	76.9	<0.001
Types of antimicrobial prescribed					
Nitrofurantoin	116	41.4	1328	58.4	<0.001
Trimethoprim	11	3.9	118	5.2	ns

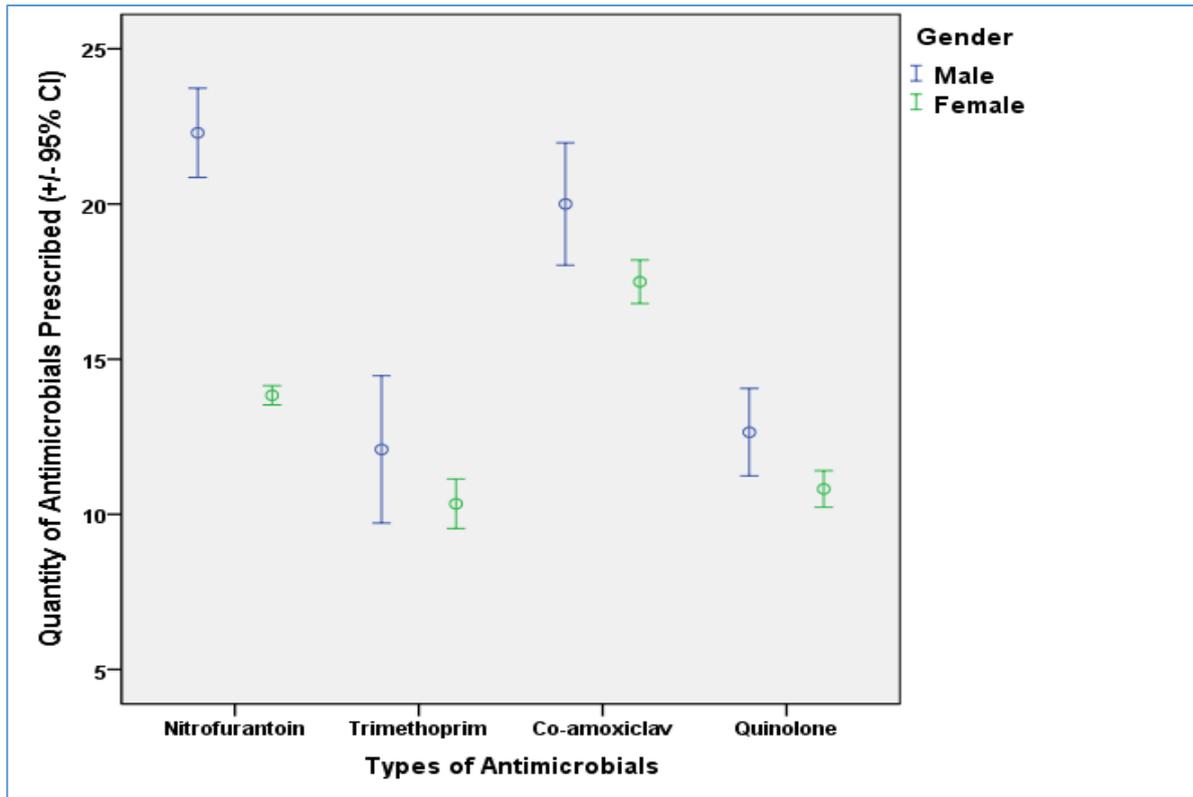
Fluoroquinolone	31	11.1	71	3.1	<0.001
Co-amoxiclav	14	5.0	140	6.2	ns
Amoxicillin	3	1.1	43	1.9	ns
Duration of treatment (median, min-max) where antimicrobial was prescribed	7	1-14	3	1-28	<0.001
Duration of treatment (days) for types of antimicrobial prescribed (median, min-max)					
Nitrofurantoin	7	1-10	3	1-28	<0.001
Trimethoprim	5	1-14	5	1-14	0.002
Fluoroquinolone	5	1-10	5	1-10	ns
Co amoxiclav	7	1-7	7	1-15	ns
Urine sample obtained	135	48.2	1150	50.5	ns
Positive culture	49	36.3	522	45.4	0.04
Resistance to any tested antimicrobial	33	73.3	268	56.3	0.02
Types of bacteria (among +ve culture)					
<i>E.coli/coliform</i>	40	14.3	442	19.4	0.03
<i>Proteus spp.</i>	2	3.3	17	2.4	ns
<i>Staphylococcus</i>	0		28		
Other	7		35		

78 *ns= not significant*

79 2.1 Antimicrobial prescribing

80 Overall, an antimicrobial was prescribed to 75% of patients at the index consultation and this
 81 was significantly higher for females (77%) compared to males (63% (Table 1)). When prescribed an
 82 antimicrobial, most received nitrofurantoin (75%) while 7% received trimethoprim and 5% received
 83 a fluoroquinolone (not shown in table). Females were prescribed nitrofurantoin (58% vs 41%)
 84 significantly more often while males received fluoroquinolones more often compared to females (11%
 85 vs 3.1%). No significant differences were observed for the other antimicrobials. Duration of treatment,
 86 measured as the duration of the dose dispensed, was significantly higher for males compared to
 87 females. (Table 1) The median duration of treatment for nitrofurantoin was significantly higher for
 88 males compared to females; seven days for males (median quantity 28/4 times daily (QDS)) and three
 89 days for females (median quantity 12, QDS) (Fig 1). There were no difference in duration in
 90 prescribing fluoroquinolones and co-amoxiclav between male and female (Table 1).

91 **Figure 1: Types of antimicrobial prescribing based on script quantity by gender**



92

93

94

95 2.2 Urine Culture

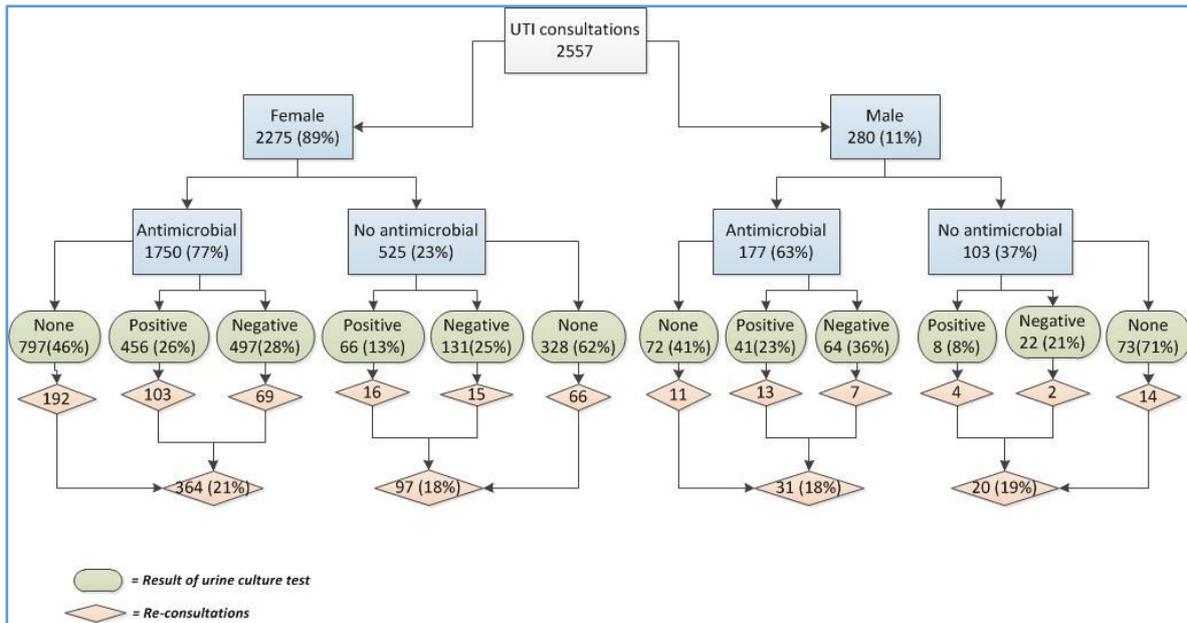
96 A urine sample was obtained during 1286 or 50% of the index consultations. Samples were
 97 submitted from 135 (48%) of males and 1150 (51%) of females (Table 1). A lower percentage of
 98 samples from male patients 'showed a positive culture compared to female urine samples (36% vs
 99 45%). The percentage breakdown of species identified in the positive culture results by male and
 100 female is shown in table 1.

101

102 Of the 49 male patients who had a positive culture, 41 received an antimicrobial, generally
 103 nitrofurantoin (66%). Of the patients who received an antimicrobial, 13 had a subsequent
 104 reconsultation of whom one may have been related to non-susceptibility of the organism to the
 105 antimicrobial prescribed (i.e. nitrofurantoin was prescribed for *Proteus* spp.). Of the 522 females with
 106 positive cultures, 456 received an antimicrobial, of which 76% received nitrofurantoin. Of the
 107 subsequent 129 reconsultations, seven may have been due to non-susceptibility of the organism to
 108 the prescribed antimicrobials (one *Proteus* spp. where nitrofurantoin was prescribed, six organisms
 109 identified with resistance against the antimicrobial that was prescribed) (Fig 2 flow chart).

110

111 **Figure 2: Flow chart reconsultations according to gender, antimicrobial treatment and culture**
 112 **results**



113

114 **2.3 Reconsultation**

115 A logistic regression analysis with outcome reconsultation, showed females to have a higher
 116 occurrence of reconsultation compared to males after correction for confounding factors (age, medical
 117 card status and whether an antimicrobial was prescribed) (Table 2). However, no significance
 118 differences were observed in reconsultation between males and female when an antimicrobial was
 119 first-line (nitrofurantoin) (Fig 3 flow chart). When an antimicrobial was prescribed empirically and
 120 this was not nitrofurantoin, the odds of reconsultation were higher (OR 1.56, 95% CI (1.1-2.0)). There
 121 was no difference in reconsultations when quinolones were prescribed empirically, but the odds of
 122 reconsultation was significantly higher when trimethoprim was prescribed (OR 2.0 95% CI (1.3-3.1))
 123 (not shown in table). However, neither gender nor antimicrobial prescribing was significant in a
 124 model in which culture test results were included. In the subset of patients in whom urine culture
 125 was performed the positive culture test was associated with reconsultation (OR = 1.8, 95% CI 1.3-2.5)
 126 (not shown in table).

127

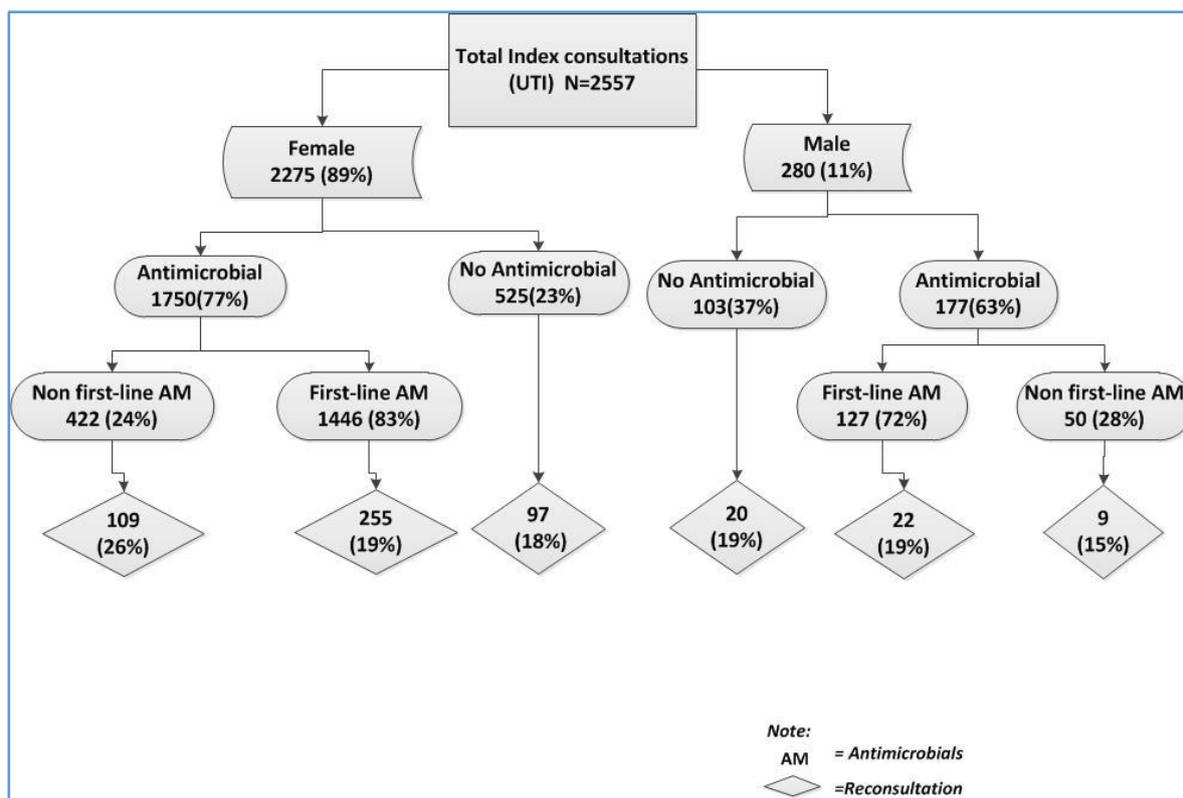
Table 2: Logistic regression of re-consultation for UTI

	OR	95% CI	p-value
Gender			
Male	reference		
Female	1.4	1.0-1.9	0.04
Age			
	1.02	1.0-1.02	<0.001
Medical card			
No	reference		
Yes	1.7	1.3-2.1	<0.001
Prescribed antimicrobials			
No	reference		
Yes	1.2	0.96-1.5	0.1
Intervention			
Control (arm C)	reference		
Intervention (arm A and B)	0.6	0.5-0.8	<0.001

128

129 **Figure 3: Flow chart reconsultation according to gender and first-line treatment of antimicrobials**

130



131

132 **3. Discussion**

133 A urine sample was only available for approximately 50% of the patients. Even though there is
 134 no indication that patients without culture results have better or worse outcomes, it is unclear as to
 135 why no urine sample was obtained from the other half of the UTI patients. Studies indicate that
 136 empiric antimicrobial treatment without urine culture is appropriate for uncomplicated UTI in
 137 primary care however for males a urine culture rather than empiric treatment is recommended [5, 6,
 138 8]. Conversely, the Scottish Intercollegiate Guidelines Network (SIGN) recommends both urine
 139 culture and empiric treatment to all male with symptoms of UTI [10].

140 Males were less often prescribed an antimicrobial empirically but if an antimicrobial was
 141 prescribed the duration of treatment was generally longer and the antimicrobial prescribed was more
 142 likely to be a fluoroquinolone. Cultures from males were less likely to be positive and re consultations
 143 were less common. However, for both males and females reconsultation was less common when
 144 nitrofurantoin was prescribed compared with prescription of any other antimicrobial or compared
 145 with no antimicrobial prescription. A study conducted in Germany also supports following local
 146 (first-line) antimicrobial guidelines for both males and females when prescribing empirically [7].

147 Conventional practice with respect to management of UTI has emphasized empiric
 148 antimicrobial prescribing at first consultation. This is challenged by an emerging body of evidence
 149 that symptomatic treatment and delayed antimicrobial use for UTI in females is safe and allows
 150 spontaneous resolution in a high proportion of cases. Our study points to differences between males
 151 and females presenting with features suggestive of UTI with respect to the likelihood of a positive
 152 culture, management decisions and frequency of reconsultation. Given these differences it is
 153 important that studies reassess conventional practice with respect to UTI and address both male and
 154 female patients independently.

155 The data used in this study were obtained through a remote electronic download from the
 156 general practice patient management software through the Irish Primary Care Research Network
 157 (IPCRN) and are therefore reliable and complete. However, no detailed information was available
 158 from any other UTI related consultation, only 'suspected UTI' (U71) was recorded. If the GP

159 considered a male presentation of suspected UTI as complicated or if the consultation was not
160 recorded as U71, no data was downloaded. Also, whether patients were referred to an urologist or
161 other specialist for further investigation and management is not recorded. Similarly, no symptoms
162 nor any further diagnostic information, such as dipstick results or other predictive indicators were
163 recorded in the GP patient management software as this was an observational study of patient
164 records.

165 4. Materials and Methods

166 This is a secondary data analysis of Supporting the Improvement and Management of
167 Prescribing for Urinary tract infection (SIMPlE) study. [11]. The study was conducted in 30 general
168 practices in the west of Ireland, for a period of 15 months to improve the quality of antimicrobial
169 prescribing for UTIs in general practice. GPs were requested to code all consultations (U71) with
170 patients with suspected UTI. Remote, electronic data collection was initiated from the practice's
171 patient management software through the Irish Primary Care Research Network (IPCRN)[12], a
172 national research network of general practices. At the start of the study, all practices received a
173 workshop on consultation coding after which practices were allocated to intervention (arm A and B)
174 and control groups (arm C). The intervention arm A received a workshop on appropriate prescribing
175 for UTI supported by practice specific audit reports and the intervention arm B received workshop
176 on delayed prescribing including the intervention package in arm A. There was no any specific
177 intervention delivered to intervention arms in relation to management of UTI in males.
178

179 From June 2013 to August 2014, data was collected on all adult patients with suspected UTI in
180 the 30 general practices. No specific guidance was given regarding the diagnosis of UTI to interfere
181 as little as possible with daily clinical care. GPs were encouraged to submit a urine sample from all
182 suspected UTI patients.
183 The IPCRN provided data on patients' age, gender, medical card status, consultation date, type of
184 prescription and treatment (Anatomical Therapeutic Chemical (ATC) code). A medical card provides
185 the holder with free healthcare and medication. Entitlement to a medical card is based on income and
186 age - 97% of those aged 70 and older and about one-third of the population under 70 have a medical
187 card [13].

188 Ethical approval for the SIMPlE study was obtained from the Irish College of General
189 Practitioners (ICGP).

191 UTI and Urine culture

192 A UTI episode was defined as a clinical consultation for which a U71 consultation code was
193 entered. For each of these patients, information on previous and subsequent consultations as well as
194 antimicrobial therapy was extracted. Urine culture results and antimicrobial susceptibility profiles of
195 isolates were also extracted. Standard microbiological methods were used for detection and
196 identification of pathogens. UTI was considered laboratory confirmed when bacterial growth was
197 >10⁵ pure culture/ml was detected. Susceptibility to amoxicillin, co-amoxyclov, trimethoprim,
198 ciprofloxacin, nitrofurantoin and cefpodoxime was performed by EUCAST disc diffusion and
199 interpreted according to EUCAST guidelines[14].
200

201 Reconsultation

202 The first UTI episode was classified as the index consultation and reconsultation was identified
203 as a further consultation within 30 days of the first visit for the same reason (UTI).
204

205 Empirical prescribing

206 At the time of the study, nitrofurantoin and trimethoprim were recommended first-line
207 treatment for males and females according to national guidelines. However, the guidelines
208 recommends use of these first-line antimicrobials when resistance levels among common pathogens
209 is below a threshold of 20% [15]. As trimethoprim resistance in E. coli in this region has been greater

210 than 20% for some years this means that effectively nitrofurantoin is the only first-line treatment
211 recommended [16]. According to current national guidelines, the first-line recommended agent is for
212 different durations; seven days in males and three days in females. Fluoroquinolones (such as
213 ciprofloxacin) were considered a reserve antimicrobial and should only be prescribed after culture
214 results and susceptibility is known [3]. For the purpose of analysis, the dose dispensed (12 tablet four
215 times daily equal to duration of 3 days) was considered as the duration of the treatment according to
216 the recommended daily dose.

217

218 **Statistical analysis**

219 The presented secondary analyses are performed with data generated during the SIMPlE study.
220 An overview of patients is presented according to gender. General demographic profiles of the
221 patients in relation to antimicrobial prescribing are presented in percentages as well as means and
222 medians of age. A binary logistic regression model was applied and results were presented as odds
223 ratio (OR) and associated 95% confidence interval (CI). Interactions were tested and omitted from the
224 models if not significant. Overall statistical analysis was performed with IBM SPSS v21.0. Flow
225 diagrams and figures presented in the paper were produced using Microsoft Visio 2010 and Microsoft
226 Excel.

227 **4. Conclusions**

228 After allowing for differences in prescribing (first-line, non first-line or no antimicrobial), no
229 significance differences were observed in reconsultation among male and female UTI patients. When
230 prescribing antimicrobial treatment for UTI empirically, first-line treatment (nitrofurantoin) should
231 be the preferred choice for both males and females.

232

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237 **Author Contributions:** MT performed the statistical analysis and wrote the draft manuscript. AV conceived and
238 managed the study and provided statistical support. MT, AV and SD were involved in drafting the final
239 manuscript. MC and AM thoroughly revised the paper. All authors read and approved the final manuscript.

240 **Conflicts of Interest:** The authors declare that they have no competing interest.

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