Antibiotic consumption and time to recovery from uncomplicated urinary tract infection

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Abstract

Background

Randomised trials provide high-quality evidence on the effects of prescribing antibiotics for urinary tract infections (UTI) but may not reflect the effects in those who consume antibiotics. Moreover, they mostly compare different antibiotic types or regimens but rarely included a 'no antibiotic' group.

Aim

To estimate the effect of antibiotic consumption, rather than prescription, on time-to-recovery in women with uncomplicated UTI.

Design and Settings

Secondary analysis of 14-day observational data from a trial of a point of care test for UTI in primary care. Clinicians treated patients using their own judgment providing immediate, delayed, or no antibiotic.

Methods

UTI-symptomatic women who either consumed (n= 333) or did not consume (n= 80) antibiotics during a 14-day follow-up were included. Antibiotic consumption was standardised across participants and grouped into either ≤ 3 or > 3 standardised antibiotic days. To account for confounders, a robust propensity score matching analysis was conducted. Adjusted Kaplan-Meier and Cox proportional hazard models were employed to estimate time-to-recovery and hazard ratios, respectively.

Findings

The adjusted median time-to-recovery was 2 days longer among patients who did not consume antibiotics (9 days; 95% CI 7 – 12) compared to those who did (7 days; 95% CI 7 – 8). We found no difference between those who consumed ≤ 3 (7 days; 95% CI 7 – 8) compared to > 3 standardised antibiotic days (7 days; 95% CI 6 – 9).

Conclusions

Consuming antibiotics was associated with a reduction in self-reported time-to-recovery, but more antibiotics exposure was not associated with faster recovery in this study.

Key words:

Uncomplicated urinary tract infections, general practice, antibiotic consumption, recovery without antibiotics

How this fits in

Limited evidence from randomised trials suggests that, on average prescribing antibiotics improves recovery in women with uncomplicated UTI, and that short (3 days) courses are as effective as longer courses. However, not all antibiotic prescriptions are consumed, and some women recover without antibiotics. Therefore, it is important to explore the relationship between antibiotic consumption and time to recovery. Adjusting for various confounders, we found that women with UTI who consumed antibiotics recovered faster than those who were not prescribed or did not consume antibiotics. We also found no difference in recovery time among those who consumed more antibiotics. However, those who consumed no antibiotics and did not completely recover, reported only mild symptoms by the estimated recovery time for their group.

Introduction

Uncomplicated urinary tract infection (UTI) is common among women, with symptoms lasting 10 days on average.(1, 2) It places a huge burden on individuals and healthcare systems (3-6) and contributes significantly to antibiotic prescribing in the community.

Uncomplicated UTI is treated with empirical antibiotics that vary in type and duration within and across countries.(7, 8) The majority of patients respond adequately to these treatments and some patients choose to not use antibiotics.(9-12) However, the incidence of antibiotic resistant UTI is increasing.(13) Guidelines primarily use evidence from trials which seldom compare antibiotic use with no antibiotic use and rarely take account of antibiotic consumption as opposed to prescribing.(14) We therefore report the effect of antibiotic consumption compared to no antibiotic consumption, and the consumed antibiotic amount, on time to patient-reported recovery.

Methods

We analysed data from the "Point of Care Testing for Urinary Tract Infection in Primary Care" (POETIC) trial.(15, 16) The trial ran from 2012 to 2014 and involved 43 general practices in England, Wales, Spain and Netherlands. Non pregnant, adult female participants had at least one of the main uncomplicated UTI symptoms: dysuria, frequency or urgency were recruited during routine consultation. Patients with pyelonephritis, other severe systemic symptoms, received antibiotics four weeks prior recruitment, on long-term antibiotics or genitourinary tract abnormalities were not recruited.(15) Clinicians treated patients using their own judgement (providing immediate, delayed, or no antibiotic at all) or with the aid of the Flexicult®, which provided results on pathogen and antibiotics sensitivity 24 hours after recruitment, and if necessary treatment was changed accordingly.(15)

Clinicians completed a baseline questionnaire detailing the severity symptoms, history of previous UTI treatments and management chosen. Patients then completed a 14-day diary in which they rated the severity of eleven symptoms (fever, pain in the sides, blood in urine, smelly urine, burning or pain when passing urine [dysuria], urgency, daytime frequency, nighttime frequency, tummy pain, restricted activity and general unwell feeling) on a scale of 0-6 (0= 'not affected' and 6= 'as bad as can be'). Daily consumption of medication and day of recovery (patient answered a direct question on when they have felt completely recovered) were also documented.

Data inclusion

We included data from patients who were either prescribed an antibiotic immediately, or not at all. Patients with delayed or changed antibiotic because of resistant infection were excluded, to create a clear definition of both exposure and outcome. Patients with missing data for the type, strength and dose of antibiotic used were excluded.

Patients were categorised into two groups: whether they consumed any antibiotic during follow-up or not. A standardised antibiotic consumption unit (standardised antibiotic days) was implemented to allow comparison between different antibiotic strengths and dosing regimens (17-19). Consumption ranged from 0.17 to 14 standardised antibiotic days and patients who consumed antibiotic were categorised into two categories: ≤ 3 and > 3 standardised antibiotic days.

Standardised antibiotic days was calculated as:

$$\frac{\text{antibiotic strength (mg)} \times \text{ total number of consumed doses}}{\text{published defined daily dose (DDD)(19)}}$$

Statistical analysis

Kaplan-Meier survival analysis (20) and Cox proportional hazard models double robust method (21, 22) were used to compare median time-to-recovery and hazard ratio (HR), respectively, between patients who consumed antibiotics and those who did not, and between those who consumed > 3 and ≤ 3 standardised antibiotic days.

Propensity score matching models were used to adjust for confounding factors including the severity scores for baseline symptoms (listed above), analgesic use (ibuprofen, paracetamol, co-codamol, metamizole and tramadol), antifungal use (clotrimazole oral, topical and pessaries and fluconazole), anti-muscarinic use (solifenacin, trospium chloride and mebeverine hydrochloride), age and country. For the analyses where standardised antibiotic days were compared, day 3 symptom scores were added as confounding factors, as this might have also affected patients' decisions to continue taking their antibiotics and it did improve the propensity score balance between the groups (data not shown).

Among many attempted propensity score matching methods, marginal mean weighting through stratification (23) yielded a good balance using the R package "MatchIT".(24) In this method propensity score was estimated using a logistic regression of the antibiotic consumption on the confounding factors listed above. We used all observations from groups and no units were discarded during matching.

A sensitivity analysis was conducted to include UTI treatment history in the calculation of the propensity score. Data analysis was conducted in R version 4.0.5 (2021-03-31).

Results

Antibiotic consumption

The POETIC cohort consisted of 643 patients with full baseline data. The final cohort for this study included 413 (64.2%) patients after exclusion of patients with missing follow-up data (n=116, 18.0%), changed antibiotics (n=73, 11.4%), delayed antibiotics (n=15, 2.3%), and missing data required to calculate the standardised antibiotic consumption (n=26, 4.0%), Figure 1.

80 (19.4%) patients consumed no antibiotics, of whom 75 were not prescribed antibiotics and 5 were prescribed antibiotics but did not consume any. Among those who consumed antibiotics (n=333, 80.6%), nine antibiotics were used: Trimethoprim (n=146, 43.8%), Nitrofurantoin (n=72, 21.6%), Fosfomycin (n=63, 18.9%), Ciprofloxacin (n=13, 3.9%), Norfloxacin (n=13, 3.9%), Amoxicillin Clavulanic (n=9, 2.7%), Amoxicillin (n=8, 2.4%), Cephalexin (n=8, 2.4%) and Cefuroxime (n=1, 0.3%). Among those who consumed ≤ 3 standardised antibiotic days (n=201), 181 (90.0%) patients were prescribed a course of 1-3 days, 17 (8.5%) patients were prescribed a 5- or 7-days course and 3 (1.5%) patients had missing data for prescription duration. Among those who consumed > 3 standardised antibiotic days (n=132), there were 11 (8.3%) patients with 1-3 days prescription and 121 (91.7%) with 4-8 or 10 days prescription.

Potential confounders

The mean age of patients was 48.4 (95% CI, 47.4 – 50.9) years for the entire cohort, and similarly distributed across the antibiotic consumption groups (Table 1). 31.2% (129/413) of patients were from England, 33.4% (138/413) from Wales, 28.3% (117/413) from Spain and 7.0% (29/413) from Netherlands.

At baseline, mean symptom severity scores were generally slightly higher among those who consumed antibiotics compared to those who did not (Table 1), but these differences were less clear among antibiotic consumption levels of ≤ 3 or > 3 standardised antibiotic days.

UTI treatment within the past year was received by 181/274 (66.1%) and 39/55 (70.9%) patients among those who did and did not consume antibiotics, respectively (Table 1). There were 108/165 (65.5%) and 73/109 (67.0%) patients with UTI treatment history among those who consumed ≤ 3 and > 3 standardised antibiotic days, respectively.

Only small proportions of the study cohort consumed over-the-counter analgesics, antifungals and antimuscarinics at some point in the follow-up. However, there was a lower proportion of women taking

antifungal (1.8% vs 2.5%), anti-muscarinic (0.9% vs 1.3%) or analgesics (4.5% vs 10%) among those who consumed antibiotics compared to those who did not. These proportions were similar across the standardised antibiotic days groups (Table 1).

UTI microbiological culture results were known to clinicians following the initial management decision was made, thus it was not included as a confounder. However, we summarise its proportions among antibiotic consumption groups in Table 1 to provide clinically relevant information about the study cohort (Table 1).

Time to recovery

331 (80.1%) participants reported complete symptom recovery during the follow-up. Only 2 (0.5%) reporting not being recovered by day 14, but 80 (19.4%) had missing recovery data therefore their recovery time was censored. Among those who consumed no antibiotics (n=80), 50 (62.5%) patients reported recovery during the follow-up, while 281 (84.4%) reported recovery among those who consumed antibiotics (n=333).

The overall estimated median time at which 50% of the cohort reported feeling recovered was 8.0 (95% CI 7.5 – 8.5) days. Following adequate propensity score balancing (Figure 2), the adjusted estimated median time-to-recovery was 2 days longer among participants with no antibiotic consumption (9 days, 95% CI 7 – 12) compared to those who consumed antibiotics (7 days, 95% CI 7 – 8; Log rank test $P < 0.001$), Figure 3A. Those who consumed no antibiotics and not recovered by day 9 (48/80, 60%) had only mild to moderate average symptom severity scores for the rest of the period (Supplementary Figure 1). The adjusted HR for recovery was 1.72 (95% CI 1.19 – 2.47) for those who consumed antibiotics compared to those who did not (Table 2).

The adjusted median time-to-recovery among those who consumed ≤ 3 and > 3 standardised antibiotic days was similar (7 days for both) with wider 95% CI among the latter (95% CI 6 – 9) compared to the former group (95% CI 7 – 8, Log-rank $p = 0.026$), Figure 3B. This analysis was then repeated excluding those who recovered prior to or on day 3 to emulate a target trial with similar recovery baseline. Similarly, we found no difference in the adjusted median time-to-recovery (both groups were 8 days; 95% CI 7 – 9, log rank test = 0.086) nor a significant HR (0.90; 95% CI 0.68 – 1.20) for those who consumed > 3 compared to those who consumed ≤ 3 standardised antibiotic days (Table 2).

Sensitivity analysis

Patients reported on whether they had received UTI treatment within the last year (n=220) or not (n=109) were included in a sensitivity analysis where this important confounding factor was adjusted for. Both the

estimated median time to recovery (Figure 3C) and HR (Table 2) increased among those who did not take antibiotics compared to the main analysis.

Similar to the main analysis, the estimated time to recovery was slightly longer among those who consumed >3 compared to those who consumed ≤ 3 standardised antibiotic days (Figure 3D). The HR for recovery also did not deviate from the main analysis (Table 2).

Discussion

Summary

We found that antibiotic consumption reduced time to recovery from UTI symptoms by 2 days (for a 14-day follow up) compared to not taking antibiotics, after matching by baseline characteristics and use of other medication. However, when considering history of UTI treatment as a confounder, recovery could be as much as 7 days longer in those who consumed no antibiotics. We found no substantial difference in time to recovery among those who consumed more antibiotics, which was supported by the Cox model HR and target trial analysis.

Strengths and limitations:

Non-adherence is a recognised issue in community infection management (25, 26) which weakens conclusions from prescription data. To our knowledge, only one other study (12) explicitly explored recovery from UTI using antibiotic consumption rather than prescription data. Our study included most of the antibiotics used to treat uncomplicated UTI, and we standardised variable antibiotic exposure (type, dose and strength) by calculating a standardised antibiotic consumption. A further strength of this study is the use of propensity score matching based on the initial symptoms to estimate effects on time to recovery. This approach helps correct for indication bias, where those with more severe symptoms are more likely to be prescribed and consume antibiotics. We further conducted sensitivity analyses using UTI treatment history as a potential confounder. UTI history is an important factor which affects clinicians' decisions to prescribe and patients' decisions to consume antibiotics. However, this information was missing from 84 patients: hence the use of sensitivity analysis. The results highlighted the importance of this confounder and suggest that it should be included in future studies.

The main limitation of this study is the risk of residual confounding from unmeasured confounders such as comorbidities and the current UTI symptoms duration which might affect antibiotic-prescribing decisions but were not recorded in the POETIC study. However, the POETIC study did not include patients with UTI symptoms for longer than two weeks. Moreover, we recognise that the 2 days longer time to recovery among

those who consumed no antibiotic might be longer if longer follow up was considered, however, the survival analysis median time to recovery as opposed to the mean will not be affected by extremely longer recovery durations. POETIC trial included a follow up at 3 months about UTI recurrence, but we did not consider it for this study as we are interested in the immediate recovery from uncomplicated UTI infection. Although antimuscarinic, antifungal and analgesic use was adjusted for, we used binary indicators and did not consider the amount, duration or time point these were consumed, as this information was not collected. We used data from a randomised trial of a point of care test that could potentially affect antibiotic prescribing. However, the test results were not available to clinicians until approximately 24 hours after the initial consultation, the intervention had little overall effect on antibiotic use,(16) and patients who were prescribed a new or different antibiotic after the initial consultation were excluded in the current analysis. Therefore, we think the trial intervention is unlikely to have biased our findings. The exclusion of patients who changed antibiotics was also to clarify the definition of both exposure and recovery time, for example antibiotics might be changed because of evidence of resistance, which could affect outcomes. A relatively small number of patients fell into this category, and we feel that their exclusion is unlikely to have biased our findings. Finally, we used antibiotic consumption provided by patients, which may not be as accurate as medication adherence monitoring containers or measurement of antibiotic levels in blood or urine.(27)

Comparison with existing literature

A recent Cochrane review on antibiotics efficacy for UTI commented on the lack of data to evaluate time to symptomatic recovery.(28) In addition, the evidence from placebo-controlled trials is scarce, only three such trials reported symptom duration in a review on the natural course of uncomplicated UTI in women up to November 2019.(29) Their results showed that complete symptom recovery could occur in 18% (up to 3 days) to 54% (up to 6 weeks) of the placebo arm, with most improvement occurring in the first 9 days. This is consistent with our finding, estimating that 50% of those who did not consume antibiotics would recover completely by day 9.

Moreover, antibiotics were found to be superior to no-antibiotic management strategies, such as painkillers, for uncomplicated UTI in women. While ~40% of women recovered by day 4 with ibuprofen, ~70% recovered with pivmecillinam.(30) With higher dose of ibuprofen ~70% of women recovered by day 7 compared to 82% for fosfomycin.(12) In addition, recovery time prolonged with diclofenac (4 days) compared to norfloxacin (2 days).(31) No-antibiotic management may be suitable for women with mild to moderate symptoms, with caution about potential risk of pyelonephritis.(12, 30, 31)

Implications for research and practice

Our study found an association between antibiotic consumption and shorter time-to-recovery in women with uncomplicated UTI in primary care which is consistent with evidence from trials suggesting net overall benefit from antibiotics.(14) However, many women with UTI symptoms make a good recovery without antibiotic treatment and only mild symptoms remain (Supplementary Figure 1). They may choose to delay antibiotic treatment and/or consider alternative treatments for their symptoms.(10, 32) Our results may help informing such a shared decision-making approach if patients were aware of the likelihood of recovering within 14 day without antibiotics. These strategies particularly useful in younger patients and in those with lower risk for pyelonephritis (10, 31, 33) and could lead to a reduction in antibiotic use and risk of resistance.(26) Attention should focus on trying to identify these women, particularly it is possible that some of them do not have bacterial infections (only 34% of the study group had culture-confirmed bacterial pathogen), or that their immunity are able to self-limit the infection. There is also a need for further studies quantifying the risk and predictors of complications associated with UTI managed with and without antibiotics.

Funding

This secondary analysis was supported by Cardiff University Intercalated BSc in Population Medicine Program 2018/2019

Ethical approval

POETIC was approved in the UK by the Research Ethics Committee for Wales (now known as Wales REC3) (reference: 12/WA/0394), Jordi Gol i Gurina Ethics Committee in Barcelona (reference: AC13/01), and the Medical Research Ethics Committee of UMC Utrecht (reference: 13/304) in the Netherlands. The use of data for future studies concerning UTI diagnosis and management was consented for during the POETIC study. All patients' data were completely anonymised for the current study research team.

Competing interests

NF reports grants from European Union FP7, during the conduct of the study; personal fees and non-financial support from Abbott and GSK, outside the submitted work. CL reports grants from Abbott Diagnostics, outside the submitted work. All other authors declare no competing interests.

Acknowledgments

This research was partially supported by the Division of Population of Medicine, Cardiff University. We thank Dr Rhian Daniel, Reader in Medical Statistics, Cardiff University for the very useful discussion and advice on statistical analysis.

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Table 1: Baseline characteristics of the study group

	Antibiotic consumption groups			
			Within antibiotic consumption	
	Not consumed (n= 80*)	**Consumed** (n=333*)	≤ 3 standardised antibiotic days (n=201*)	> 3 standardised antibiotic days (n=132*)
Age Mean and 95% CI	47.1 (43.1 – 51.1)	48.7 (46.7 – 50.6)	47.4 (44.8 – 50.0)	50.7 (47.7 – 53.6)
Country n (%) within antibiotic consumption				
Netherlands	7 (8.7)	22 (6.6)	2 (1)	20 (15.2)
England	26 (32.5)	103 (30.9)	78 (38.8)	25 (18.9)
Wales	20 (25.0)	118 (35.5)	60 (29.9)	58 (43.9)
Spain	27 (33.8)	90 (27.0)	61 (30.3)	29 (22.0)
Severity of the initial symptoms Mean and 95% CI of score (0-6)				
Urgency	3.01 (2.57 – 3.45)	3.54 (3.35 – 3.73)	3.56 (3.31 – 3.81)	3.52 (3.22 – 3.82)
Dysuria	2.79 (2.34 – 3.25)	3.10 (2.89 – 3.32)	3.16 (2.89 – 3.44)	3.01 (2.67 –3.35)
Daytime frequency	3.46 (3.07 – 3.85)	3.66 (3.48 – 3.85)	3.63 (3.38 – 3.88)	3.72 (3.43 – 4.00)
Night-time frequency	2.64 (2.18 – 3.10)	3.00 (2.79 – 3.21)	3.01 (2.73 – 3.29)	2.98 (2.68 – 3.29)
Smelly urine	1.58 (1.16 – 2.00)	1.90 (1.68 – 2.11)	1.82 (1.55 – 2.09)	2.02 (1.66 – 2.38)
Pain in the side	1.37 (0.95 – 1.79)	1.29 (1.10 – 1.48)	1.22 (0.98 – 1.47)	1.39 (1.07 – 1.70)
Tummy pain	1.74 (1.33-2.15)	2.00 (1.80 – 2.20)	2.01 (1.74 – 2.28)	1.98 (1.67 – 2.30)
Fever	0.46 (0.20 – 0.72)	0.80 (0.65 – 0.96)	0.84 (0.64 – 1.04)	0.75 (0.50 – 0.99)
Blood in urine	0.41 (0.16 – 0.65)	0.70 (0.55 – 0.86)	0.73 (0.53 – 0.94)	0.66 (0.43 – 0.90)
Restricted activities	1.41 (1.02 – 1.80)	1.55 (1.34 – 1.75)	1.52 (1.25 – 1.78)	1.59 (1.26 – 1.92)
Generally Unwell	1.74 (1.32 – 2.16)	2.14 (1.95 – 2.34)	2.13 (1.88 – 2.38)	2.17 (1.85 –2.49)
UTI treatment within the past year n (%) within antibiotic consumption				
No	16 (29.1)	93 (33.9)	57 (34.5)	36 (33.0)

Yes	39 (70.9)	181 (66.1)	108 (65.5)	73 (67.0)
Antifungal use[3]				
n (%) within antibiotic consumption				
No	78 (97.5)	327 (98.2)	197 (98.0)	130 (98.2)
Yes	2 (2.5)	6 (1.8)	4 (2.0)	2 (1.5)
Antimuscarinic use[4]				
n (%)				
No	79 (98.7)	330 (99.1)	199 (99.0)	131 (99.2)
Yes	1 (1.3)	3 (0.9)	2 (1.0)	1 (0.8)
Analgesic use[5]				
n (%) within antibiotic consumption				
No	72 (90.0)	318 (95.5)	192 (95.5)	126 (95.5)
Yes	8 (10.0)	15 (4.5)	9 (4.5)	6 (4.5)
UTI confirmed by culture[6]				
n (%) within antibiotic consumption				
No	55 (74.3)	206 (63.6)	131 (66.8)	75 (58.6)
Yes	19 (25.7)	118 (36.4)	65 (33.2)	53 (41.4)

[1] Defined Daily Dose
[2] Propensity score: the probability of antibiotic consumption given the severity score of the initial symptoms and the history of previous UTI treatment.
[3] Antifungal: Clotrimazole pessaries, fluconazole, canesten combi and canesten thrush cream
[4] Antimuscarinic: Vesicare, flortros, mebeverine hydrochloride
[5] Analgesics: Ibuprofen, paracetamol, solpadol, metamizole, tramadol and co-codamol
[6] Culture for UTI diagnosis was done after antibiotic prescription
[*] If any of patient's characteristics contained missing observation it was not included in percentage calculations.
For UTI treatment within the past year and UTI microbiology results there were 84 and 15 missing data points, respectively.

Table 2 Adjusted hazard ratio of recovery among antibiotic consumption levels compared to no antibiotic consumption

	Hazard Ratio	95% CI[1]	
		Lower	Upper
Main analysis			
Antibiotic consumption[2]			
None (n=80)		Referent	
Any (n=333)	1.72	1.19	2.47
≤ 3 days (n=201)		Referent	
> 3 days (n=132)	0.90	0.68	1.20
Sensitivity analysis[3]			
None (n=55)		Referent	
Any (n=274)	2.65	1.50	4.69
≤ 3 days (n=161)		Referent	
> 3 days (n=102)	0.79	0.58	1.09

[1] 95% Confidence intervals
[2] Antibiotic consumption calculated as number of standardised antibiotic days
[3] Sensitivity analysis included history of UTI episodes within the past year among the confounders contributed to the propensity score matching.

Figure 1: Flow chart showing application of the exclusion criteria

Figure 2: Covariate balance assessment. *The figure shows the absolute standardized mean difference (SMD) in the sample before (grey circle) and after (black circle) propensity score adjustment. SMD is the difference in means of each covariate between antibiotic consumption groups standardized by the pooled standard deviation across both groups. SMDs < 0.1 is recommended for prognostically important covariates, however, higher values are acceptable if double robust method is used as we have implemented in our Cox proportional hazard models.*[22] *Panel A shows covariate balance for those consumed any antibiotics vs those who did not, while panel B is for covariate balance for those consumed ≤ 3 vs > 3 standardised antibiotic days. Panels C and D are for the corresponding sensitivity analyses based on the addition of UTI history.*

Figure 3: Propensity score-adjusted survival curves. *Figure A shows the estimated time-to-recovery in patients who consumed antibiotics versus those who did not. Figure B shows the estimated time-to-recovery among those who consumed ≤ 3 standardised antibiotic days compared to those who consumed > 3 standardised antibiotic days. Figures A and B show the main analyses, while figures C and D show the sensitivity analyses utilizing UTI treatment history. Survival curves were compared using log rank test. Vertical lines from the survival curves demonstrate the median time to recovery.*