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Full title

Impact of antibiotic treatment duration on outcomes in older men with suspected urinary tract infection: retrospective cohort study

Running title

Antibiotic duration for UTI in older men

Authors

Haroon Ahmed[1], Daniel Farewell[1], Nick A Francis[1] Shantini Paranjothy[1], Christopher C Butler[2]

Affiliations

[1] Division of Population Medicine, Cardiff University School of Medicine, Cardiff, UK.

[2] Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.

Corresponding author

Haroon Ahmed, Division of Population Medicine, Cardiff University School of Medicine, Neuadd Meirionydd, Heath Park, Cardiff, UK, CF14 4YS. Tel: 0044 2922 510194, Email: ahmedh2@cardiff.ac.uk

Keywords

Urinary tract infection; aged; electronic health records; primary care; men

Key points

- Clinical guidelines recommend at least seven days of antibiotic treatment for urinary tract infection in men, but this is largely based on expert opinion.
- It is not known if shorter durations of antibiotic treatment are as safe or effective as seven days.

- We used linked health data from the UK to estimate the risk of treatment failure, hospitalisation and death in older men presenting to primary care with suspected urinary tract infection, who were prescribed different durations of antibiotic treatment.
- We found that 3-day antibiotic treatment was associated with an increased risk of treatment failure but a reduced risk of acute kidney injury.
- These findings support the need for a definitive randomised trial of short versus standard duration treatment.

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Prior presentation of this work

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Abstract

Purpose

Clinical guidelines recommend at least seven days of antibiotic treatment for older men with urinary tract infection (UTI). There may be potential benefits for patients, health services and antimicrobial stewardship if shorter antibiotic treatment resulted in similar outcomes. We aimed to determine if treatment duration could be reduced by estimating risk of adverse outcomes according to different prescription durations.

Methods

This retrospective cohort study included men aged ≥65 years with a suspected UTI. We compared outcomes in men prescribed 3, 5, 7 and 8-14 days of antibiotic treatment in a multivariable logistic regression analysis, and 3 versus 7 days in a propensity-score matched analysis. Our outcomes were re-consultation and re-prescription (proxy for treatment failure), hospitalisation for UTI, sepsis, or acute kidney injury (AKI), and death.

Results

Of 360,640 men aged ≥65 years, 33,745 (9.4%) had a UTI. Compared to 7-days, men prescribed 3-day treatment had greater odds of re-consultation and re-prescription (adjusted OR 1.48, 95% CI 1.25-1.74) but lower odds of AKI hospitalisation (adjusted OR 0.66, 95% CI 0.45-0.97). We estimated that treating 150 older men with 3-days instead of 7-days of antibiotics could result in four extra re-consultation and re-prescriptions and one less AKI hospitalisation. We estimated annual prescription cost savings at around £2.2 million.

Conclusions

Antibiotic treatment for older men with suspected UTI could be reduced to 3-days, albeit with a small increase in risk of treatment failure. A definitive randomised trial is urgently needed.

Main text

Introduction

Urinary tract infections (UTIs) represent an important cause of morbidity and antibiotic use in older men. Around 20% of all UTIs occur in men.[1] Incidence increases with age from around 3 episodes per 100 person-years in men aged 65-74, to 8-11 episodes per 100 person-years in men aged ≥85.[2, 3]

The optimal duration of antibiotic treatment for UTI in older men is not known.[4] Most clinical guidelines recommend seven days of antibiotic treatment.[5-7] This recommendation is largely based on expert consensus due to the lack of data in this area. Previous randomised trials investigating different antibiotic durations for UTI in men have focussed on febrile [8, 9] or complicated UTI,[10, 11] or men with spinal cord injury,[12] and are not generalizable to the majority of men with community-acquired UTI seen and treated in primary or ambulatory care settings.

Antimicrobial stewardship policies and guidelines recommend prescribing the minimum duration of antibiotic treatment required for clinical resolution.[13, 14] Two recent studies indicate that antibiotic treatment duration for UTI in older men could be reduced. First, a retrospective study of UK health records found that around 20% of older men presenting to primary care with a UTI were prescribed <7 days of antibiotics, suggesting that some clinicians may already be prescribing shorter treatment to selected men.[2] Second, an observational study found no difference in the rate of clinical recurrence between US male Veterans with UTI prescribed long course (>7 days) versus short course treatment (≤7 days).[15] However, this study used outpatient data only and therefore may have missed men who were subsequently hospitalised with UTI-related emergencies, such as sepsis or acute kidney injury.

We therefore used anonymised linked health records that spanned primary care, secondary care and death registry data, to estimate risk of adverse outcomes in older men prescribed different durations of antibiotic treatment for UTI in primary care. Our aim was to assess whether short course treatment was associated with an increased risk of adverse events to determine the potential for safe and effective reduction of antibiotic treatment duration.

Patients and Methods

Data Source

We used the Clinical Practice Research Datalink (CPRD), an electronic database of anonymised primary care records, covering 11.3 million patients from 674 general practices across the UK.[16] Approximately 7% of the UK population are included and patients are broadly representative of the wider UK population in terms of age, gender and ethnicity. The CPRD holds data on demographics, clinical encounters and diagnoses (coded using Read codes), drug prescriptions, laboratory tests and referrals to specialists. Data are available once the primary care records have met a series of quality checks on completeness and reliability and the CPRD deems them to be of a required standard for research purposes. Linked hospital and death registration data are available for patients from approximately 50% of contributing English practices. Hospital diagnoses and causes of death are recorded using version 10 of the International Classification of Disease (ICD-10).

The CPRD Independent Scientific Advisory Committee approved the study protocol (protocol number 17_250). Further ethical approval was not required as the proposed research was within the remit of the CPRD's broad National Research Ethics Service approval. We used the Reporting of Studies Conducted using Observational

Routinely-collected Health Data (RECORD) statement and checklist to guide study reporting.[17]

Design and participants

This was a retrospective cohort study using linked health record data. Men were eligible for inclusion if, between 1st January 2010 and 31st December 2016, their data were of the quality required by CPRD, they were ≥65 years old, were registered with a practice that had consented to linkage to hospital and death registry data, and had a primary care record of an incident UTI. Follow-up began from the latest of, study start date (1st January 2010), patient's 65th birthday, six months after they registered with the practice (to avoid including historical UTIs recorded at registration), or the date their practice met the CPRD data quality requirements. Follow-up ended on the earliest of study end date (31st December 2016), the day the patient died or transferred out of the practice (i.e. last date of CPRD data collection), or 28 days after an incident UTI event. We excluded men who were temporary residents, or had gaps in their data coverage. We defined 'incident' as an event occurring in a man without a UTI-related Read code or trimethoprim or nitrofurantoin prescription in the preceding 90 days. We defined UTI as the presence of a symptom code (e.g., "dysuria") or diagnostic code (e.g., "cystitis") relevant to UTI (codes available in Supplementary Appendix 1), and a same-day prescription code indicating prescribing of a relevant antibiotic. We restricted the analyses to the first incident UTI identified during a patient's follow-up period.

Exposure

We used prescription data for daily dosing and total quantity prescribed to calculate duration of antibiotic prescriptions as a proxy for duration of treatment. We excluded

prescriptions with durations >14 days as it is unlikely that these were prescribed for an acute UTI, and more likely that they reflected treatment for prostatitis. We also excluded prescription durations of 1, 2, 4, and 6 days, as together these represented <1% of all calculated durations and were potentially unreliable. The final exposure groups were 3, 5, 7 and 8-14 days.

Outcomes

We assessed the impact of antibiotic prescription duration on:

1. Re-consultation for urinary symptoms and a same-day antibiotic prescription within 14 days following the incident UTI, as a proxy for treatment non-response, ascertained through Read and prescription codes recorded in primary care records.
2. Hospitalisation for UTI, sepsis, or acute kidney injury (AKI) within 14 days following the incident UTI ascertained from ICD-10 codes recorded in linked hospital admission data for the first episode of a hospital admission, i.e., the episode most likely responsible for the admission.
3. Death within 28 days following the incident UTI using linked death registration data.

Statistical Analyses

We used primary care demographic and clinical codes to describe baseline characteristics for patients by prescription duration. Firstly, we assessed the impact of different prescription durations by calculating odds ratios (OR) and 95% confidence intervals (CI) for the risk of each outcome in those prescribed 7-day treatment, compared to those prescribed 3, 5 or 8-14 days treatment. We adjusted for potential confounders of the association between antibiotic duration and outcome, including the

choice of antibiotic, age, Index of Multiple Deprivation score quintile, Charlson comorbidity score, polypharmacy (defined as records indicating ≥5 long-term medications per month in the year prior to the incident UTI), and the presence or absence of a record indicating diabetes, dementia, coronary heart disease, stroke, cancer, heart failure, renal disease, benign prostatic hyperplasia, and prostate cancer.

Secondly, we compared outcomes in men prescribed 3-day versus 7-day treatment using propensity score matching to improve balance of baseline covariates across the two treatment groups. We chose 7 days as the reference standard as it is currently the recommended treatment duration for male UTI in the UK, and 3 days as the comparator as it is a potentially acceptable and feasible shorter duration of treatment, given that 3-day treatment is widely used to treat UTI in women. Men were matched on a range of demographic and clinical variables related to their propensity to receive a 7-day prescription. We used nearest neighbour matching with no replacement and matched each patient with a 3-day prescription to three patients with a 7-day prescription. We assessed balance in measured baseline covariates between matched groups by visually inspecting jitter plots and histograms of covariate distribution before and after matching, and by calculating standardised mean differences for covariates between groups. We regarded standardised mean differences of <0.1 as reflecting adequate balance.[18, 19]

We used mixed effects models in both analyses to account for clustering by general practice. We repeated the analyses restricting to men prescribed trimethoprim, the most commonly used antibiotic for UTI in the UK during the study period. Finally, we calculated E-values to estimate the minimum effect size required by an unmeasured confounder to fully explain away any statistically significant associations.[20] All statistical tests were 2-sided with $p<0.05$ considered statistically significant but an

effect size of 10% considered clinically significant. Analyses were conducted in R version 3.2.1.

Results

From a cohort of 360,640 men aged 65 and over with a median follow-up of 4.9 years (Interquartile range (IQR), 3.1-6.4), we identified 33,745 (9.4%) with an incident UTI treated with a relevant antibiotic (Figure 1). Of these, we were able to assign an antibiotic prescription duration to 32,593 (96.6%) incident UTIs. The median age at the time of incident UTI was 77 years (IQR, 70 - 83). In total, 1966 (6.0%) men were prescribed amoxicillin, 2002 (6.1%) ciprofloxacin, 2060 (6.3%) cefalexin, 2143 (6.6%) co-amoxiclav, 5724 (17.6%) nitrofurantoin, and 18,698 (57.4%) trimethoprim. Guideline concordant 7-day treatment was prescribed to 20,729 (63.6%) men, 3-day treatment to 2498 (7.7%), 5-day treatment to 6254 (19.2%), and 8-14 days to 3112 (9.5%). Practices varied in their prescribing of the different antibiotic durations. Of all antibiotic prescriptions for UTI in older men, the median proportion prescribed 3-day treatment was 5.1% (IQR, 1.8-10.8), 5-day treatment was 14.6% (IQR, 7.7-25.4), 7-day treatment was 65.4% (IQR, 53.1-76.2), and >7day treatment was 8.3% (IQR, 3.8-14.8). Baseline comorbidities were broadly similar across the different treatment duration groups (Table 1).

Outcomes according to treatment duration

A total of 2007 (6.2%) men re-consulted and received another antibiotic prescription within 14 days following the incident UTI. Compared to 7-day prescriptions, there was a graded association between prescription duration and odds of re-consultation and re-prescription with adjusted ORs of 1.48 (95% CI 1.25-1.74) for 3-day prescriptions, 1.18 (95% CI 1.04-1.33) for 5-day prescriptions, and 0.80 (95% CI 0.67-0.96) for 8-14

240 day prescriptions (Table 2). The re-prescribed antibiotics were made up of a lower
241 proportion of trimethoprim, similar proportion of amoxicillin, and greater proportions of
242 the other antibiotics (Supplementary Table 1).

243 A total of 817 (2.5%) men were hospitalised for UTI, 89 (0.3%) hospitalised for sepsis,
244 and 449 (1.4%) hospitalised for AKI within 14 days following the incident UTI. There
245 were no significant associations between antibiotic prescription duration and
246 hospitalisation for UTI or sepsis. Compared to 7-days, 3 and 8-14 day prescriptions
247 were associated with reduced odds of hospitalisation for AKI (adjusted OR for 3-days,
248 0.66, 95% CI 0.45-0.97, adjusted OR for 8-14 days, 0.63, 95% CI 0.40-0.99). A total
249 of 419 (1.3%) men died within 28 days of the incident UTI. There were no significant
250 associations between antibiotic prescription duration and odds of death.

251 **Propensity score matched comparison of 7-day versus 3-day therapy**

252 We matched 2392 men prescribed 3-day treatment to 7182 men prescribed 7-day
253 treatment. Inspection of jitter plots and histograms suggested matching had improved
254 balance of covariates across the two groups. Standardised mean differences were all
255 less than 0.1 (Table 3). 3-day prescriptions were associated with increased odds of
256 re-consultation and re-prescription (OR 1.52, 95% CI 1.25-1.85) and reduced odds of
257 hospitalisation for AKI (OR 0.62, 95% CI 0.42-0.93) (Table 4).

258 Using the propensity score matched event rates and ORs in table 4, we estimate that
259 treating 150 older men with 3-day instead of 7-day treatment, could result in four extra
260 re-consultation and re-prescriptions (numbers needed to harm = 37) and one less AKI
261 hospital admission (numbers needed to treat = 148).[22] Our previous study showed
262 that around 7% of a sample of roughly 400,000 men ≥65 were prescribed an antibiotic
263 in primary care for UTI in 2014.[2] Current UK population estimates suggest there are

around 5.2 million men aged ≥65.[23] A 7% annual UTI rate equates to around 364,000 UTI events. Based on current prescribing costs reported in the British National Formulary (3-day trimethoprim = £3.60, 7-day trimethoprim = £10.00, 7-day nitrofurantoin = £9.50), if all men were prescribed 3-days of trimethoprim instead of 7 days, and men who re-consulted were prescribed 7 days of nitrofurantoin, the UK health service could save around £2.2 million a year.

Sensitivity analyses

We repeated the analyses restricting to men who received trimethoprim and found that all ORs were consistent with our main analyses. We calculated E-values for the two significant associations in our propensity-score matched analysis. The E-value was 2.4 for re-consultation and re-prescription, and 2.6 for AKI hospitalisation, suggesting any unmeasured confounder would require an OR of at least 2.4 for its association with antibiotic prescription duration and outcome, independent of measured confounders, to explain away the observed associations.

Discussion

We showed, for the first time, that in older men presenting to primary care with a UTI, 3-day antibiotic treatment was associated with a 52% increase in odds of re-consultation and re-prescription that may indicate treatment failure or recurrent infection, but was not associated with increased odds of UTI-related hospitalisation or death. We also showed for the first time, an association between 3-day treatment and a 38% reduction in the odds of hospitalisation for AKI.

Results in context

A retrospective observational study of 33,336 index UTIs in US male Veterans found no difference in recurrence rates at 30 days between short and long duration antibiotic

288 treatment.[15] Similar to our study, patients did not require microbiological confirmation
289 of UTI and were included if they had a relevant diagnostic code and antibiotic
290 prescription. However, this study defined 'short duration' as ≤7 days, and 77% of the
291 short duration group received 7-day treatment. Thus, their comparison was ≤7 days
292 versus >7 days, and explains the discrepancy between our finding of increased odds
293 of re-consulting and receiving another antibiotic prescription in short duration (3 or 5-
294 day) versus long duration (7-day) treatment.

295 Our finding of an association between 3-day antibiotic treatment and reduced odds of
296 AKI could be explained by trimethoprim prescribing. Trimethoprim is associated with
297 hyperkalaemia and AKI in older adults. [21] In our unmatched multivariable logistic
298 regression analysis, the risk of AKI was reduced in the group with the shortest
299 exposure to trimethoprim (3-day treatment) and the group with the lowest proportion
300 of trimethoprim use (8-14 day group, 16.8% prescribed trimethoprim versus 60% in
301 the 7-day group). In our propensity-score matched analysis, 85% of men in the 3 and
302 the 7-day treatment groups were prescribed trimethoprim, but there was again a
303 reduced risk of AKI in the 3-day group, supporting an association between shorter
304 trimethoprim exposure and reduced risk of AKI.

305 Few randomised trials have investigated the potential for shorter duration of antibiotic
306 treatment in men with UTI, and those that have focussed on more severe UTI. A
307 Swedish trial of 114 men with febrile UTI showed similar clinical and microbiological
308 cure rates between 14-day and 28-day antibiotic treatment.[9] A randomised placebo
309 controlled non-inferiority trial recruited men with febrile UTI from Dutch primary care
310 and emergency departments, and showed 7-day antibiotic treatment was inferior to
311 14-day treatment in terms of clinical cure rates 10-18 days post UTI.[8] In contrast, a US
312 trial of men and women (39% men) with complicated UTI or acute pyelonephritis

showed no difference in outcomes between those receiving 5-day versus 10-day antibiotic treatment.[10] However, these trials recruited men with more severe UTI than that normally seen in a primary care setting. To the best of our knowledge, no trials have investigated the effect of short duration antibiotic treatment for men presenting to primary care with symptoms suggestive of UTI, but without fever or other signs of ascending infection.

Strengths and weaknesses of this study

We used data from a general practice database that is broadly representative of the UK population.[16] Cohort entry was dependent on presentation and empirical treatment of UTI in primary care, and thus reduced indication bias. We also reduced indication bias by matching patients on their propensity to receive a 7-day prescription, and achieving adequate balance of covariates across treatment groups.

Our study has important limitations. We attempted to capture patients presenting with UTI but had no microbiological data to support this. However, whilst a limitation, this is also more representative of clinical practice. Our estimates are based on *prescription* duration and may overestimate actual antibiotic consumption. Despite careful selection of codes used to identify eligible men, differential use of codes amongst clinicians means we may have included some men who had more complicated UTI or pyelonephritis. Our finding of an increase in the rate of UTI-related re-consultation and re-prescription among men prescribed 3-day treatment may be due to planned follow-up for those prescribed shorter courses. Furthermore, whilst some of these events may represent 'treatment failure', others may reflect different expectations about the speed of symptom resolution. Finally, despite our design, differential coding, indication bias and residual confounding may still have affected our

findings. However, our E-values suggest residual confounders would need relatively strong associations between antibiotic duration and outcomes to alter the conclusions from our effect estimates.

Conclusions

Our findings suggest it may be possible to safely reduce the duration of antibiotic treatment to 3 days for older men presenting to primary care with a UTI. For patients, shorter duration treatment could mean better adherence and less side effects. Other potential benefits may include a reduction in AKI-related hospitalisations, antibiotic burden, and prescription costs. Potential harms include a possible increased risk of treatment failure. A definitive randomised trial is needed to compare short versus standard treatment duration of a specific antibiotic for UTI in men.

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Transparency declaration

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Tables

Table 1. Baseline characteristics according to antibiotic prescription duration. Values are numbers (%) unless otherwise stated.

	Antibiotic prescription duration			
	3 days	**5 days**	**7 days**	**8-14 days**
Number (%) of prescriptions	2498 (7.7)	6254 (19.2)	20729 (63.6)	3112 (9.5)
Mean (SD) age	77.4 (8.0)	77.7 (8.1)	76.9 (7.9)	76.7 (7.8)
Antibiotic choice				
Amoxicillin	12 (0.5)	512 (8.2)	1392 (6.7)	50 (1.6)
Cefalexin	60 (2.4)	262 (4.2)	1133 (5.5)	605 (19.4)
Ciprofloxacin	38 (1.5)	852 (13.6)	649 (3.1)	463 (14.9)
Co-amoxiclav	13 (0.5)	195 (3.1)	1843 (8.9)	92 (3.0)
Nitrofurantoin	241 (9.6)	802 (12.8)	3301 (15.9)	1380 (44.3)
Trimethoprim	2134 (85.0)	3631 (58.1)	12411 (59.9)	522 (16.8)
Index of multiple deprivation decile				
1 or 2 (least deprived)	527 (21.1)	1670 (26.7)	5217 (25.2)	890 (28.6)
3 or 4	552 (22.1)	1494 (23.9)	5016 (24.2)	764 (24.6)
5 or 6	599 (24.0)	1398 (22.4)	4568 (22.0)	655 (21.0)
7 or 8	427 (17.1)	945 (15.1)	3437 (16.6)	466 (15.0)
9 or 10 (most deprived)	393 (15.7)	747 (11.9)	2491 (12.0)	337 (10.8)
Housebound	101 (4.0)	251 (4.0)	641 (3.1)	107 (3.4)
Respiratory disease	478 (19.1)	1159 (18.5)	3934 (19.0)	629 (20.2)
Cardiac failure	178 (7.1)	438 (7.0)	1365 (6.6)	202 (6.5)
Dementia	160 (6.4)	399 (6.4)	1080 (5.2)	158 (5.1)
Peripheral vascular disease	218 (8.7)	573 (9.2)	1695 (8.2)	248 (8.0)
Renal disease	620 (24.8)	1560 (24.9)	4758 (23.0)	755 (24.3)
Rheumatoid arthritis	47 (1.9)	105 (1.7)	374 (1.8)	53 (1.7)
Cancer	486 (19.5)	1306 (20.9)	4225 (20.4)	689 (22.1)
Stroke	320 (12.8)	856 (13.7)	2542 (12.3)	370 (11.9)
Diabetes	576 (23.1)	1411 (22.6)	4659 (22.5)	677 (21.8)
Liver disease	17 (0.7)	36 (0.6)	122 (0.6)	23 (0.7)
Ischaemic heart disease	674 (27.0)	1622 (25.9)	5347 (25.8)	811 (26.1)
Urinary catheter	182 (7.3)	626 (10.0)	1783 (8.6)	325 (10.4)
Urinary incontinence	184 (7.4)	496 (7.9)	1393 (6.7)	225 (7.2)
Polypharmacy	1048 (42.0)	2462 (39.4)	7859 (37.9)	1123 (36.1)
Benign prostatic hyperplasia	760 (30.4)	1953 (31.2)	6341 (30.6)	1033 (33.2)
Prostate cancer	213 (8.5)	626 (10.0)	2071 (10.0)	331 (10.6)
eGFR				
60-90	1569 (62.8)	3909 (62.5)	13573 (65.5)	2016 (64.8)
45-59	514 (20.6)	1269 (20.3)	4101 (19.8)	600 (19.3)
30-44	223 (8.9)	563 (9.0)	1735 (8.4)	280 (9.0)
15-29	69 (2.8)	201 (3.2)	478 (2.3)	93 (3.0)
<15	19 (0.8)	48 (0.8)	74 (0.4)	11 (0.4)
missing	104 (4.2)	264 (4.2)	768 (3.7)	112 (3.6)

Charlson score				
0	657 (26.3)	1594 (25.5)	5819 (28.1)	836 (26.9)
1	484 (19.4)	1254 (20.1)	4067 (19.6)	579 (18.6)
2	512 (20.5)	1230 (19.7)	3958 (19.1)	613 (19.7)
3	334 (13.4)	902 (14.4)	2881 (13.9)	450 (14.5)
4	219 (8.8)	522 (8.3)	1759 (8.5)	258 (8.3)
5	141 (5.6)	351 (5.6)	1131 (5.5)	189 (6.1)
≥6	151 (6.0)	401 (6.4)	1114 (5.4)	187 (6.0)

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Table 2. Adjusted ORs and 95% CIs for each outcome by antibiotic prescription duration.

Re-consultation and re-prescription within 14 days	Number of prescriptions	Number (%) of events	Crude OR	Adjusted OR (95% CI)	p-value
7 days [reference]	20729	1225 (5.9)	1	1	
3 days	2498	198 (7.9)	1.37	1.48 (1.25 - 1.74)	<0.001
5 days	6254	416 (6.7)	1.13	1.18 (1.04 - 1.33)	0.009
8-14 days	3112	168 (5.4)	0.91	0.80 (0.67 - 0.96)	0.020
Hospitalised for UTI within 14 days					
7 days [reference]	20729	543 (2.6)	1	1	
3 days	2498	61 (2.4)	0.93	0.87 (0.66 - 1.15)	0.331
5 days	6254	147 (2.4)	0.89	0.82 (0.67 - 1.01)	0.063
8-14 days	3112	66 (2.1)	0.81	0.81 (0.61 - 1.08)	0.152
Hospitalised for sepsis within 14 days					
7 days [reference]	20729	53 (0.3)	1	1	
3 days	2498	4 (0.2)	0.63	0.63 (0.22 - 1.75)	0.366
5 days	6254	13 (0.2)	0.81	0.63 (0.34 - 1.19)	0.159
8-14 days	3112	9 (0.3)	1.13	0.85 (0.38 - 1.90)	0.700
Hospitalised for AKI within 14 days					
7 days [reference]	20729	307 (1.5)	1	1	
3 days	2498	30 (1.2)	0.82	0.66 (0.45 - 0.97)	0.033
5 days	6254	88 (1.4)	0.97	0.84 (0.66 - 1.08)	0.182
8-14 days	3112	24 (0.8)	0.53	0.63 (0.40 - 0.99)	0.047
Death within 28 days					
7 days [reference]	20729	252 (1.2)	1	1	
3 days	2498	37 (1.5)	1.22	1.12 (0.78 - 1.61)	0.522
5 days	6254	89 (1.4)	1.17	1.01 (0.78 - 1.31)	0.917
8-14 days	3112	41 (1.3)	1.08	1.21 (0.83 - 1.78)	0.316

Table 3. Baseline characteristics before and after propensity-score matching of men prescribed three versus seven days of antibiotics. Values are numbers (%) unless otherwise stated. *SMD = standardised mean difference

	Before matching			After matching		
	3 days	**7 days**	**SMD***	**3 days**	**7 days**	**SMD***
Number (%) of prescriptions	2498 (7.7)	20729 (63.6)		2394 (25.0)	7182 (75.0)	
Mean (SD) age	77.4 (8.0)	76.9 (7.9)	0.071	77.5 (8.0)	77.4 (8.0)	0.008
Antibiotic choice						
Amoxicillin	12 (0.5)	1392 (6.7)	-0.887	12 (0.5)	39 (0.5)	-0.006
Cefalexin	60 (2.4)	1133 (5.5)	-0.202	57 (2.4)	166 (2.3)	0.005
Ciprofloxacin	38 (1.5)	649 (3.1)	-0.127	38 (1.6)	109 (1.5)	0.006
Co-amoxiclav	13 (0.5)	1843 (8.9)	-1.141	13 (0.5)	36 (0.5)	0.006
Nitrofurantoin	241 (9.6)	3301 (16.0)	-0.217	231 (9.6)	703 (9.8)	-0.005
Trimethoprim	2134 (85.4)	12411 (60.0)	0.727	2043 (85.3)	6129 (85.3)	0.000
IMD decile						
1 or 2 (least deprived)	527 (21.1)	5217 (25.2)		498 (20.8)	1497 (20.8)	
3 or 4	552 (22.1)	5016 (24.2)		529 (22.1)	1545 (21.5)	
5 or 6	599 (24.0)	4568 (22.0)		578 (24.1)	1703 (23.7)	
7 or 8	427 (17.1)	3437 (16.6)		408 (17.0)	1368 (19.0)	
9 or 10 (most deprived)	393 (15.7)	2491 (12.0)	0.147	381 (15.9)	1069 (14.9)	0.000
Housebound	101 (4.0)	641 (3.1)	0.052	100 (4.2)	296 (4.1)	0.003
Respiratory disease	478 (19.1)	3934 (19.0)	0.002	460 (19.2)	1371 (19.1)	0.003
Cardiac failure	178 (7.1)	1365 (6.6)	0.025	178 (7.4)	527 (7.3)	0.004
Dementia	160 (6.4)	1080 (5.2)	0.044	151 (6.3)	469 (6.5)	-0.009
Peripheral vascular disease	218 (8.7)	1695 (8.2)	0.018	213 (8.9)	622 (8.7)	0.008
Renal disease	620 (24.8)	4758 (23.0)	0.047	618 (25.8)	1764 (24.6)	0.029
Rheumatoid arthritis	47 (1.9)	374 (1.8)	-0.002	44 (1.8)	129 (1.8)	0.003
Cancer	486 (19.5)	4225 (20.4)	-0.022	476 (19.9)	1408 (19.6)	0.007
Stroke	320 (12.8)	2542 (12.3)	0.023	319 (13.3)	935 (13.0)	0.009
Diabetes	576 (23.1)	4659 (22.5)	0.020	576 (24.1)	1692 (23.6)	0.012
Liver disease	17 (0.7)	122 (0.6)	0.016	17 (0.7)	51 (0.7)	0.000
Ischaemic heart disease	674 (27.0)	5347 (25.8)	0.028	667 (27.9)	1983 (27.6)	0.006
Urinary catheter	182 (7.3)	1783 (8.6)	-0.053	174 (7.3)	498 (6.9)	0.013
Urinary incontinence	184 (7.4)	1393 (6.7)	0.018	175 (7.3)	512 (7.1)	0.007
Polypharmacy	1048 (42.0)	7859 (37.9)	0.086	1033 (43.1)	3080 (42.9)	0.005
Prostatic hyperplasia	760 (30.4)	6341 (30.6)	-0.006	743 (31.0)	2138 (29.8)	0.027
Prostate cancer	213 (8.5)	2071 (10.0)	-0.056	207 (8.6)	618 (8.6)	0.002
eGFR						
60-90	1569 (62.8)	13573 (65.5)		1569 (65.5)	4740 (66)	
45-59	514 (20.6)	4101 (19.8)		514 (21.5)	1558 (21.7)	
30-44	223 (8.9)	1735 (8.4)		223 (9.3)	685 (9.5)	
15-29	69 (2.8)	478 (2.3)		69 (2.9)	172 (2.4)	
<15	19 (0.8)	74 (0.4)		19 (0.8)	27 (0.4)	
missing	104 (4.2)	768 (3.7)	0.064	0 (0)	0 (0)	0.029
Charlson score						
0	657 (26.3)	5819 (28.1)		594 (24.8)	1894 (26.4)	
1	484 (19.4)	4067 (19.6)		463 (19.3)	1385 (19.3)	
2	512 (20.5)	3958 (19.1)		499 (20.8)	1423 (19.8)	
3	334 (13.4)	2881 (13.9)		328 (13.7)	1003 (14)	
4	219 (8.8)	1759 (8.5)		218 (9.1)	623 (8.7)	
5	141 (5.6)	1131 (5.5)		141 (5.9)	425 (5.9)	
≥6	151 (6.0)	1114 (5.4)	0.045	151 (6.3)	429 (6.0)	0.027

Table 4. Odds ratios and 95% CIs for each outcome in men matched on their propensity to receive a seven-day antibiotic prescription.

	7 day prescriptions	**3 day prescriptions**		
Outcome	**Number (%) of events**	**Number (%) of events**	**OR (95% CI)***	**p-value**
Re-consultation and re-prescription within 14 days	399 (5.6)	192 (8.0)	1.52 (1.25 - 1.85)	<0.001
Hospitalised for UTI within 14 days	209 (2.9)	59 (2.5)	0.81 (0.61 - 1.09)	0.179
Hospitalised for sepsis within 14 days	18 (0.3)	4 (0.2)	0.60 (0.20 - 1.75)	0.350
Hospitalised for AKI within 14 days	131 (1.8)	29 (1.2)	0.62 (0.42 - 0.93)	0.021
Death within 28 days	96 (1.3)	36 (1.5)	1.07 (0.73 - 1.57)	0.729

*Reference = 7 day prescription

Figure legends

Figure 1. Flow of men from initial identification in the database to final cohort.

Figures

Figure 1.