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Title

Risk and predictors of hospital admission following primary care consultation for community-onset lower urinary tract infection: a retrospective cohort study using linked primary care, secondary care and microbiology data

Authors

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Abstract

Background

Urinary tract infections (UTIs) are a common indication for antibiotic prescriptions, reductions in which would reduce antimicrobial resistance (AMR). Risk stratification of patients allows reductions to be made safely.

Aim

To identify risk factors for hospital admission following UTI, to inform targeted antibiotic stewardship.

Design and setting

Retrospective cohort study of East London primary care patients.

Method

We used linked primary care, secondary care and microbiology data from 01/04/2012-31/03/2017. Outcomes were urinary infection-related hospital admission (UHA) and all-cause hospital admission (AHA) within 30 days of UTI in primary care. We estimated odds ratios between each variable (demographic characteristics, prior antibiotic exposure and comorbidities) and the outcomes using generalised estimating equations, and fitted a final multivariable model including all variables with a $p$-value $<$ 0.1 on univariable analysis.

Results

UHA occurred in 1336/169524 episodes (0.8%, 95% CI 0.7-0.8), and AHA in 6516/169524 episodes (3.8%, 95% CI 3.8-3.9). On multivariable analysis, increased odds of UHA was seen in patients aged 55-74 (adj OR 1.56) and 75+ years (adj OR 3.44), relative to adults aged 16-34 years. Increased odds of UHA was also associated with chronic kidney disease (CKD, adj OR 1.54), urinary catheters (adj OR 2.17), prior antibiotics (adj OR 1.29), recurrent UTI (adj OR 1.37), faecal incontinence (FI, adj OR 1.49) and diabetes mellitus (DM, adj OR 1.38).

Conclusion
UHA was rare efforts to reduce antibiotic prescribing for suspected UTI should focus on patients aged <55 years without risk factors for complicated UTI, recurrent UTI, DM or FI.

**Keywords**

General Practice, Urinary tract infections, Epidemiology, Antimicrobial Stewardship

**How this fits in**

Reductions in antibiotic prescribing for urinary tract infections (UTIs) would reduce overall antibiotic consumption and AMR. This study using routinely collected primary care, secondary care and microbiology data found that antibiotic stewardship efforts for UTIs should be targeted at younger patients without specific risk factors.

**Introduction**

Urinary tract infections (UTIs) are one of the commonest indications for antibiotic prescriptions in primary and secondary care, and reduction in prescribing for UTI would likely have a significant impact on overall antibiotic consumption and rates of antimicrobial resistance (AMR). Estimates suggest the average person consults their GP 5.5 times per year and that 1-3% of all GP consultations are for UTI symptoms (1,2). In addition to symptomatic relief, fear of complications – pyelonephritis (upper UTI), urinary sepsis and bloodstream infection – is an important driver in antibiotic prescribing for lower UTI (3–5).

Studies suggest that a proportion of uncomplicated UTIs are self-limiting, with up to 50% of women being symptom free without antibiotic treatment at 7 days (6,7). Antibiotic use is also associated with the development of AMR, gastrointestinal side effects and complications such as *Clostridium difficile* colitis (8,9). Delay or avoidance of antibiotic treatment may therefore be preferable in certain patients. Trials in young women have found that approximately 2/3 of patients recover with symptomatic treatment rather than
antibiotics, but that this strategy was associated with a higher symptom burden and, in one of the studies, more cases of pyelonephritis (10,11). Such approaches may reduce antibiotic consumption, but data on patient outcomes is necessary to inform their acceptability and safety. A recent study using electronic health records found the probability of sepsis was higher following consultations for UTI than for respiratory tract or skin infections, and that the risk of sepsis was higher among older adults (12). Other analyses of large datasets using electronic health records have found conflicting results in older adults (13,14).

The aim of our study was to obtain an accurate estimate of the risk of adverse outcomes following lower UTI in primary care in patients aged 16 and over, in order to identify patients in whom antibiotic treatment could be safely delayed or avoided.

**Methods**

A retrospective cohort study using primary care electronic health records linked to secondary care and microbiology data.

**Data source**

We created the cohort using a primary care database of East London general practices, developed and managed by the Clinical Effectiveness Group (CEG), part of Queen Mary University of London. This data was deterministically linked to Secondary Uses Services (SUS, managed by NHS Digital) secondary care data, and to microbiology data (urine and blood cultures) from Barts Health NHS Trust as per the supplementary material.

Consultations for lower UTI were identified through Read codes, antibiotic prescriptions for and positive urine cultures with relevant uropathogens. We used a modified version of the Read code lists used in previous similar studies (13,14), Supplementary Table S2. As first-line antibiotics used to treat lower UTI are frequently unlinked to a diagnostic code, we also identified UTI consultations through prescriptions for nitrofurantoin, trimethoprim, fosfomycin and pivmecillinam (15). Relevant uropathogens are shown in Supplementary Table S3. UK guidelines recommend only sending urine cultures in certain situations including complicated UTI, treatment failure or where antibiotic resistance is suspected. In
order to exclude patients with upper UTI we therefore excluded any consultations where a Read code for upper UTI was recorded within +/- 3 days of a positive urine culture, Supplementary Table S4.

We identified distinct episodes of UTI using a 30-day washout period, with any consultations within that period considered part of the same episode. Any consultations outside the washout period were considered a new episode. Any consultation occurring within the washout period was considered an ongoing episode and excluded from the analysis, Supplementary Figure S1. Patients could have more than one episode during the study period.

**Population**

Patients aged 16 years or older registered at the approximately 100 GP surgeries across Tower Hamlets and Newham, London, who consulted their GP for UTI between 01/04/2012-31/03/2017 were eligible for inclusion. We excluded the following patients:

- no data available for sex, age, index of multiple deprivation (IMD) score
- registered for less than 12 months prior to their first episode (to allow for identification of comorbidities)
- less than 30 days follow up data (unless death occurred within that period)
- admitted to hospital on the day of their episode
- discharged from hospital in the 30 days prior

Patients could have multiple episodes of UTI, and entered the cohort at the start of their first episode. They left the cohort at the earliest of these dates: death, change of practice or end of the study period.

**Putative risk factors**

We examined a number of risk factors (see supplementary material for rationale and definitions) as variables in our analysis, including:

- demographics: age, sex, ethnicity, IMD quintile (obtained by linking individual patient’s postcode to Lower layer Super Output Area)
- non-treatment with antibiotics within +/- 7 days
- risk factors for complicated UTI: structural abnormalities, chronic kidney disease (CKD), urinary catheterisation
- recurrent UTI
- comorbidities: cancer, diabetes mellitus (DM), heart failure, hypertension, urinary incontinence (UI), faecal incontinence (FI) and obesity
- antibiotics in the last 6 months (supplementary material)
- season of the year

Outcomes

The primary outcome was urinary infection-related hospital admission (UHA) in the 30 days from the start of an episode. This definition included ICD-10 codes related to UTI (upper UTI, sepsis and bloodstream infection, Supplementary Table S9), and urine and blood cultures positive for relevant organisms within 2 days of hospital admission. The secondary outcome was all-cause hospital admission (AHA) in the 30 days following an episode.

Statistical analyses

We used descriptive statistics to summarise the clinical and demographic characteristics. We summarized continuous variables using median and interquartile range (IQR), and categorical variables using absolute numbers and proportions. We estimated crude associations (odds ratios [ORs]) between each included variable (risk factor) and the outcomes using generalised estimating equations (GEEs) with a logit link and an exchangeable correlation structure to account for multiple episodes per patient. We used Huber-White sandwich estimators to calculate 95% confidence intervals (95% CI). We fitted a final multivariable adjusted model using GEEs, including all predictors with a *p*-value < 0.1 in the univariable analysis. We included age as a categorical variable in the multivariable model, as this was felt most informative for primary care prescribing decisions.

Because older patients may be more likely to be treated with antibiotics due to concerns around progression to sepsis, we looked for an interaction between antibiotic treatment within +/-7 days and age on the outcome of UHA. We ran a model including an interaction term between age and antibiotic treatment, looking for a significant Wald *p* value for the
interaction coefficients. We used the Quasi Information Criterion (uQIC) to assess the model fit, using a difference in uQIC of $\geq 10$ to signify a statistically significant improvement (where a lower number indicates a better fit). All data cleaning and analyses were performed using the statistical software R version 3.6.1 for Windows. Generalized estimating equations were fitted using `geepack` (version 1.2-1).

**Results**

A total of 169524 UTI episodes (in 86561 patients) were included in the study, Figure 1. The majority (132094/169524; 77.9%) of episodes occurred in female patients, and the median age was 43 years (IQR 31-60), Supplementary Table S1. Factors associated with antibiotic treatment within +/- 7 days of the episode were female sex, older age, increased socioeconomic deprivation, prior antibiotic treatment, risk factors for complicated UTI and all other comorbidities examined, Supplementary Table S1.

UHA occurred in 1336/169524 episodes (0.8%, 95% CI 0.7-0.8). On multivariable analysis adjusting for age, sex, antibiotic treatment and all variables associated with the outcome on univariable analysis, the factor most strongly associated with UHA was older age, Figure 2. Age groups 55-74 years and 75+ years had increased odds of UHA as compared to age 16-34 years, with adjusted odds ratios of 1.49 (95% CI 1.21-1.84) and 3.24 (95% CI 2.57-4.08) respectively, Table 1.

Recurrent UTI (adj OR 1.33, 95% CI 1.16-1.53), CKD (adj OR 1.55, 95% CI 1.31-1.84) and urinary catheters (adj OR 2.01, 95% CI 1.53-2.66) were associated with increased odds of UHA, Table 1. Of other comorbidities examined, only FI and DM were associated with increased odds of UHA, with adjusted odds ratios of 1.47 (95% CI 1.12-1.93) and 1.37 (95% CI 1.19-1.58) respectively. Prior antibiotics were also associated with increased odds of UHA, with adjusted odds ratios of 1.23 (95% CI 1.08-1.4) for 1-2 courses and 1.38 (95% CI 1.15-1.65) for $\geq 3$ courses as compared to none.

AHA occurred in 6516/169524 episodes (3.8%, 95% CI 3.8-3.9). On multivariable analysis adjusting for age, sex, antibiotic treatment and all variables associated with the outcome
on multivariable analysis, factors associated with increased odds of AHA included older age, increased socioeconomic deprivation, prior antibiotic exposure, risk factors for complicated UTI and all co-morbidities examined apart from recurrent UTI, Table 2 and Figure 3.

Discussion

Summary

In this study of 169524 primary care lower UTI episodes in 86561 patients using routinely collected data, 3.8% of patients were admitted to hospital for any cause in the following 30 days and 0.8% were admitted for a UTI-related diagnosis. UHA-specific risk factors included age >55 years, recurrent UTI, urinary catheters, CKD, prior antibiotic treatment, FI and DM. The majority of episodes (77.9%) occurred in female patients, but there was no association between female sex and UHA.

Strengths and limitations

The strengths of our study include the assessment of microbiological and clinical outcomes to determine the proportion of admissions directly attributable to UTI, rather than simply assessing all-cause admission which is potentially misleading. We used a novel database including a large cohort of patients with individual level data on primary care consultations, antibiotic prescriptions, hospital admissions and microbiology data, allowing investigation of risk factors for adverse outcomes in a way not previously done. Recognising that coding for clinical consultations is not always complete, we used a wide range of indicators to capture episodes.

The limitations of our study are common to many studies using routinely collected data, with data collected in short consultations with a focus on clinical care. We used UTI-specific antibiotics to identify consultations. Whilst nitrofurantoin, pivmecillinam and fosfomycin are not used for other indications, trimethoprim may rarely be used to treat respiratory tract or skin and soft tissue infections, and we may have misclassified consultations for another infection as one for UTI. Positive urine cultures may have represented asymptomatic bacteriuria, however positive urine cultures accounted for only 5% of the included
consultations (Figure 1). Furthermore, UK guidance is to only send a urine culture from primary care in cases where complicated infection is suspected so most urine cultures should be from patients who are symptomatic.

We aimed to include only community-onset cases but did not captured attendances or prescriptions from urgent care centres, A&E (without admission) or outpatient clinics. A proportion of included episodes may therefore have been healthcare-associated. We did not specifically exclude patients with a Read code for a suspected sexually-transmitted infection (STI), so it is possible that symptoms were due to STI rather than UTI. However, Read codes included: "Urine culture" (62%), "Suspected UTI (22%), "Urinary tract infection, site not specified" (8%) and "Recurrent UTI" (3%). Additionally, none of the antibiotics used to identify consultations are used to treat STIs in the UK. In the UK, the majority of STIs are managed in sexual health clinics and a study of conditions treated with antibiotics in primary care in England found that only 6.7% of genitourinary conditions were genital in origin(15).

The proportion of male patients who were not treated was high, which was surprising given that UTIs in male patients are considered complicated and will usually warrant treatment. It is possible that a significant proportion of the male consultations were catheter urine specimens, which the GP did not treat as they felt a catheter-associated UTI (CAUTI) was clinically unlikely. We identified very few Read codes for catheter-associated UTI (CAUTI), there is no ICD code for CAUTI and urine cultures frequently do not specify the specimen type. We attempted to mitigate this by identifying urinary catheters through prescriptions for devices and accessories recorded in the 6 months preceding the episode, but we will not have captured all CAUTIs. As CAUTI is one of the commonest healthcare associated infections, this highlights the importance of improving coding of catheter use in primary care. It is also possible that a proportion of men had dysuria which the GP thought was an STI, so a urine culture was sent for completeness and the patient was referred to a sexual health clinic for treatment.

Whilst we attempted to include a number of confounding variables, we acknowledge the risk of residual confounding. Non-treatment within +/-7 days was associated with reduced odds of UHA. This is surprising and suggests that the effect of confounding by indication in
our study may be stronger than the protective effect of antibiotics in treated patients. There were systematic differences between treated and non-treated patients, with non-treated patients younger, less co-morbid and with less prior antibiotic exposure than treated, and this result may simply reflect healthier patients. On examining the data for an interaction between age and antibiotic treatment, no interaction was found (data not shown).

There is evidence that asymptomatic bacteriuria and symptomatic UTI in pregnancy is associated with increased risk of pyelonephritis (16). We identified very few codes related to UTI in pregnancy and were unable to examine this as a risk factor. The population represented is an urban, ethnically diverse and socioeconomically deprived cohort, and the results may not be generalisable to other settings.

**Comparison with existing literature**

We found that whilst the 16-34 and 35-54 years age groups had the largest proportion of episodes (33.1% and 35.1% respectively), they did not have greater risk of UHA. This concords with surveillance data on *Escherichia coli* bacteraemia (ECB), where incidence in adults increases with age and is highest in patients aged ≥85 years (17,18). It is also supported by the results of a cohort study using electronic health records of all patients at 706 general practices, with 66.2 million person-years of follow up from 2002-2017 and 35244 first episodes of sepsis, where the risk of sepsis following a consultation for infection was highly age dependent. While the number needed to treat (NNT) to avoid an episode of sepsis was 6517 (95% CI 4779-9522) for men and 13926 (95% CI 10044-21273) for women aged 25-34, it was 262 (95% CI 236-293) for men and 385 (95% CI 352-421) for women aged >85 years(12). We found no association between socioeconomic deprivation and UHA, which conflicts with other studies in UTI and other infections(14,19). High levels of deprivation in our cohort may have affected these results for the rare outcome of UHA. This may also be related to our ability to identify admissions for UTI-specific diagnoses, since odds of AHA was associated with increasing socioeconomic deprivation.

Trials have examined the safety of withholding antibiotics for UTI in younger women (10,11,20). Current PHE guidelines recommend a “watch and wait” approach with a backup antibiotic for likely UTI in non-pregnant women aged <65, without a history of recurrent UTI
or a urinary catheter(21). We found that CKD, DM and FI were also associated with increased odds of UHA. A matched cohort study in primary care using CPRD data linked to Hospital Episodes Statistics (HES) data in 242349 matched pairs of patients found that patients with CKD had higher relative risk of hospital admission with UTI than patients without. On multivariable analysis adjusted for ethnicity, socioeconomic status, smoking status, body mass index and a number of comorbidities, they found an adjusted hazard ratio of 1.27 (95% CI 1.23-1.32) in patients ≤75 years and 1.71 (95% CI 1.61-1.81) in patients >75 years (22). A number of studies have shown DM to be a risk factor for asymptomatic bacteriuria, symptomatic UTI, pyelonephritis and ECB(23–28). Faecal incontinence is associated with increased risk of UTI due to colonisation of the urethra with faecal flora, but we have not identified any studies looking specifically at the association with adverse outcomes.

We found that antibiotic treatment in the last 6 months was associated with increased odds of UHA. Antibiotic exposure has been associated with increased odds of antibiotic resistance and therefore potential treatment failure, as well as risk of ECB(23,29). A cohort study of 425 women aged 18-40 years at a staff-model health management organisation in the USA found the relative risk of developing a UTI was 6.40 (95% CI 2.43-16.84, p < 0.001) for women who had received antibiotics for UTI in the previous 15-28 days as compared to those that had not, and 3.82 (95% CI 1.95-7.45, p < 0.001) for those who had received antibiotic therapy for a non-UTI indication(30).

**Implications for research and/or practice**

Our findings suggest that UHA following lower UTI is rare, and there may be scope for reduction in antibiotic prescribing. Studies trialling avoidance or delay of antibiotic treatment may be safely targeted at low risk groups including patients aged <55 years, without risk factors for complicated UTI, a history of recurrent UTI or prior antibiotic exposure, and without the comorbidities of DM or FI. Research is needed into the acceptability of such strategies, as avoidance of hospitalisation is likely not to be the only consideration in prescribing decisions.
Funding

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Ethics approval

The NHS Health Research Authority toolkit ([http://www.hra-decisiontools.org.uk/ethics/](http://www.hra-decisiontools.org.uk/ethics/)) identified that Research Ethics Approval was not required for this study as all data was pseudonymised and presented in aggregate form. HRA approval was received on 25/01/18 (IRAS project ID 226836; REC reference 18/HRA/0502).

Competing interests

The authors have no competing interests to declare.

Acknowledgements

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References


Risk factors for adverse outcomes tables and figures

Figure 1. Flowchart of creation of cohort
Figure 2. Forest plot of multivariable analysis of odds of urinary infection-related hospital admission (UHA)

Figure 3. Forest plot of multivariable analysis of odds of all-cause hospital admission (AHA)
Table 1. Multivariable analysis of odds of urinary infection-related hospital admission (UHA)

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Season

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<td>Winter</td>
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Table 2. Multivariable analysis of odds of all-cause hospital admission (AHA)

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<tr>
<td>Female</td>
<td>0.73 (0.68-0.77)</td>
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Age (categorical)

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<tr>
<td>75</td>
<td>3.47 (3.09-3.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IMD quintile

<table>
<thead>
<tr>
<th>IMD quintile</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (least deprived)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.48 (0.86-2.58)</td>
<td>0.16</td>
</tr>
<tr>
<td>3</td>
<td>1.93 (1.14-3.26)</td>
<td>0.015</td>
</tr>
<tr>
<td>4</td>
<td>1.93 (1.15-3.22)</td>
<td>0.012</td>
</tr>
<tr>
<td>5 (most deprived)</td>
<td>2.02 (1.21-3.37)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.75 (0.68-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>0.83 (0.78-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed &amp; other</td>
<td>0.81 (0.68-0.97)</td>
<td>0.025</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.84 (0.69-1.02)</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Treatment within +/- 7 days
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not treated</td>
<td>0.84 (0.79-0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Risk factors for cUTI**

- Absence of risk factor: 1
- Structural abnormalities: 1.29 (1.19-1.41) <0.001
- CKD: 1.35 (1.24-1.47) <0.001
- Urinary catheter: 1.64 (1.4-1.91) <0.001

**Antibiotics last 6m**

- 0 courses: 1
- 1-2 courses: 1.26 (1.19-1.34) <0.001
- ≥3 courses: 1.52 (1.4-1.66) <0.001

**Other risk factors**

- Absence of risk factor: 1
- Recurrent UTI: 1.03 (0.96-1.1) 0.404
- UI: 1.24 (1.15-1.33) <0.001
- FI: 1.27 (1.09-1.47) 0.002
- Obesity: 1.19 (1.02-1.39) 0.025
- Heart failure: 1.37 (1.21-1.56) <0.001
- Hypertension: 1.13 (1.06-1.21) <0.001
- Cancer: 1.39 (1.26-1.54) <0.001
- DM: 1.26 (1.17-1.34) <0.001

**Season**

- Spring: 1
- Summer: 1.04 (0.97-1.12) 0.239
- Autumn: 1.05 (0.98-1.13) 0.144
- Winter: 1.03 (0.96-1.11) 0.421