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ORIGINAL RESEARCH

Incidence and Recurrence of Urinary Tract Infections Caused by Uropathogenic *Escherichia coli*: A Retrospective Cohort Study

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Purpose: Urinary tract infections (UTIs) are among the most common bacterial infections, with uropathogenic *Escherichia coli* (UPEC) as the main etiologic agent of uncomplicated UTIs (uUTIs). The prevalence of uUTIs caused by organisms with antimicrobial resistance (AMR) is increasing worldwide, complexifying the disease management and increasing the risk of complications. In efforts to develop new strategies for uUTI prevention, it is imperative to understand factors associated with the occurrence of new episodes.

Patients and Methods: This retrospective cohort study aimed to assess the incidence of uUTIs caused by UPEC (UPEC-uUTIs) or unknown etiology (untested uUTIs) in adults aged ≥18 years receiving care in a San Francisco healthcare system.

Results: During 2014–2019, 1087 UPEC-uUTI and 4106 untested uUTI cases were documented, of which 324 (29.8%; 95% confidence interval: 27.1%–32.6%) and 1030 (25.1%; 95% confidence interval: 23.8%–26.4%) were followed by ≥1 new episode of uUTI within 12 months. In the UPEC-uUTI cohort, male gender, diagnosis of diabetes mellitus, and prior uUTI were risk factors for new episodes of uUTI. At the time of first UPEC-uUTI diagnosis, antimicrobial prescriptions were retrieved for 41.1% of cases. When tested, AMR was most frequently reported for trimethoprim/sulfamethoxazole or trimethoprim/sulfamethoxazole prescribed with other antimicrobials.

Conclusion: Our study provides important information on the incidence and risk of repeated episodes of uUTIs, as well as on AMR related to them.

Keywords: uncomplicated urinary tract infection, urinary tract infection risk factors, antimicrobial resistance, urinary tract infection prevention

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections,[1] with an estimated annual incidence of about 150 million cases worldwide.[2] In 2007, in the United States (US), 0.7% of all outpatient visits were due to UTIs, accounting for 10.5 million outpatient visits.[3] UTIs cause significant morbidity in women, male infants, and older men.[4]

UTIs can be categorized as complicated or uncomplicated (uUTI), the latter affecting otherwise healthy individuals, and classified into lower (confined to the bladder, ie cystitis) and upper (confined to the kidney, eg pyelonephritis) uUTIs.[5] The most common etiologic agent of uUTIs is uropathogenic *Escherichia coli* (UPEC), causing 75%–85% of cases.[6]

An estimated one in three women will experience at least one diagnosed UTI requiring prescription medication by 24 years of age.[7] Antibiotic treatment for UTIs is often empirical,[4,8,9] but can prove ineffective, especially in the treatment of recurrent UTIs, due to antimicrobial resistance (AMR). Globally, in 2019, an estimated 4.95 million deaths were associated with AMR, with *E. coli* being among the primary contributors.[10]

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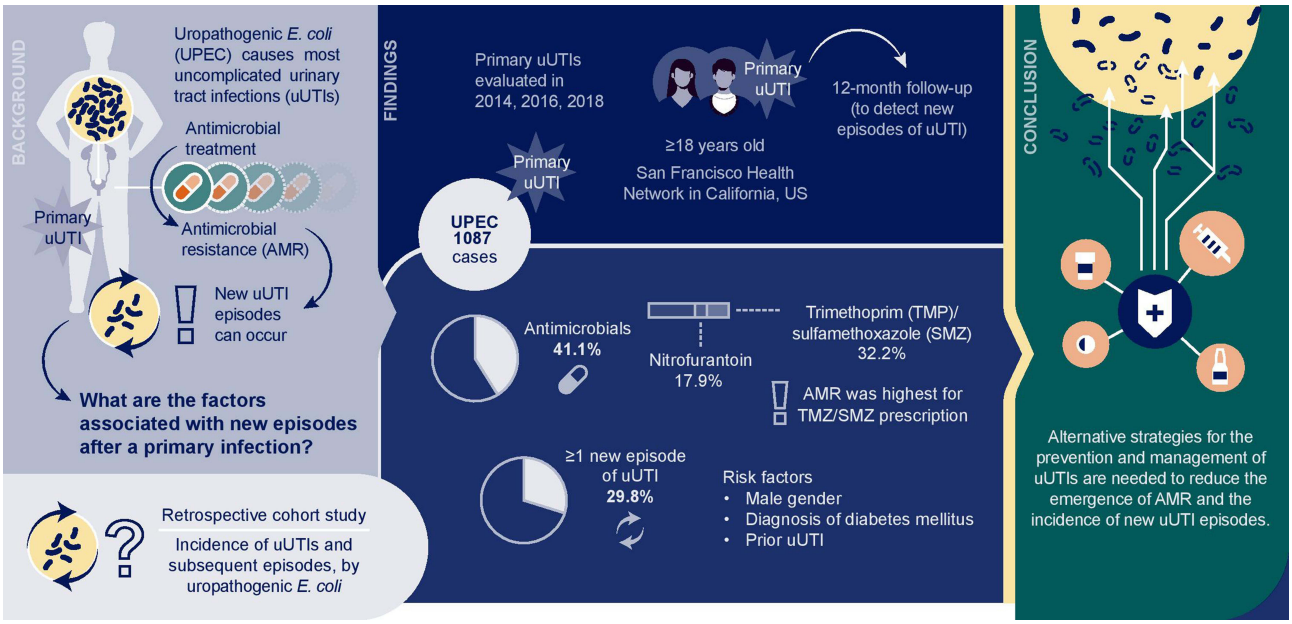
Graphical Abstract



As recent data on new uUTI episodes after index infections are limited in the literature, this retrospective study aimed to assess the epidemiology of uUTIs, primarily focusing on the burden of UPEC-uUTIs. We aimed to assess the proportion of uUTIs caused by UPEC, the incidence proportion of UPEC-uUTIs with ≥1 new episode of uUTI within 12 months after the reference primary infection, as well as the risk factors associated with experiencing repeated uUTI episodes, in a US medical institution. When available, the prescription of antimicrobial treatment and the outcome of the antimicrobial susceptibility testing (AST) were assessed for UPEC-uUTIs.

Materials and Methods

Study Design, Patient Population, and Data Collection

This was a retrospective cohort study with data from male and female individuals aged ≥18 years with a uUTI, attending outpatient services from the San Francisco Health Network, in California, US. Data were extracted from electronic health records, including laboratory, outpatient clinic, and emergency department databases, for uUTI cases from 2014 to 2019 by the University of California, San Francisco Clinical and Translational Science Institute data abstraction services. Laboratory databases provided information on confirmed UPEC-uUTIs. We defined confirmed UPEC-uUTIs as first diagnoses of microbiologically confirmed UPEC-uUTI cases in an evaluable calendar year (ie 2014, 2016, and 2018); the first diagnosis was referred to as the reference primary infection. Outpatient clinic and emergency department data provided information on untested uUTIs, defined as first diagnoses of uUTIs that were not microbiologically tested in an evaluable calendar year (see Supplementary Table S1 for the list of ICD-9 and ICD-10 codes). Laboratory data, including urine culture and AST results, were linked to patient diagnoses (ICD-9 and ICD-10 codes) and demographic characteristic data. The microbiology laboratory performed AST with Microscan and disk diffusion tests, reporting resistance based on Clinical Laboratory Standards Institute breakpoint standards.[11]

To allow for a 12-month follow-up, all reference primary uUTI episodes were detected in the 2014, 2016 and 2018 cohorts, with follow-up periods during 2014–2015, 2016–2017 and 2018–2019 (ie follow-up years), respectively, and starting on the day of diagnosis of the reference primary infection (Figure 1). For each participant enrolled in the three yearly cohorts, any uUTI episode reported during the 12-month follow-up was considered a new episode of uUTI if it occurred ≥14 days after the last diagnosis of an uUTI event.

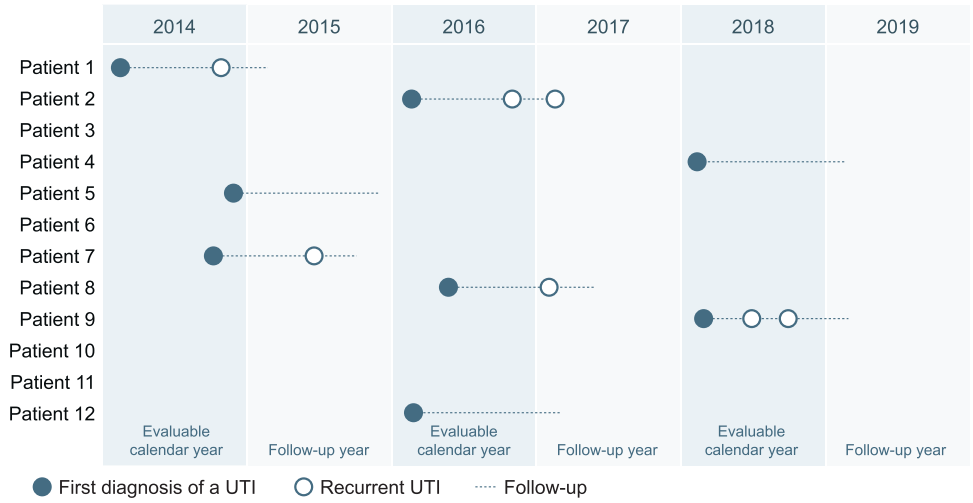


Figure 1 Study design.
Notes: The study was conducted in adults attending outpatient services from the San Francisco Health Network, in California, United States, during 2014–2019. For each patient, reference primary uUTI events (dark points), collected during evaluable calendar years, were the beginning of a follow-up period of 12 months (dotted horizontal lines). All uUTI events emerging during follow-up (white points) were collected and considered new episodes if they occurred ≥14 days after the last diagnosis of an uUTI event.
Abbreviation: UTI, urinary tract infection.

The study was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences ethical guidelines, as well as all other applicable laws and regulations. The study complied with the applicable data protection and privacy regulations. Ethics approval was granted by the University of California San Francisco Institutional Review Board, which waived informed consent for the study.

Statistical Analyses

Cohorts were composed by uUTI cases (UPEC or untested) during the evaluable calendar years (2014, 2016, and 2018). Patients in a cohort could also enter the cohort of another evaluable calendar year.

As primary study objectives, we assessed: 1) the number of UPEC-uUTIs that had ≥1 new episode of uUTI diagnosed within 12 months after the reference primary infection, 2) their incidence proportion (with 95% confidence intervals [CIs]), 3) the time to first new episode of uUTI, and 4) the number and proportion of patients having 0, 1, 2, 3, 4, and ≥5 new episodes of uUTI within 12 months after the reference primary uUTI. Two-sided exact 95% CIs were computed using the Clopper–Pearson method.[12] The time to the first new episode of uUTI was expressed using descriptive statistics (mean with standard deviation [SD] or median with range).

Secondary objectives were to assess the same for untested uUTI cases. Finally, prescription of antimicrobial treatment and the AST outcome were assessed for UPEC-uUTIs.

Several possible risk factors were considered for each analysis, including gender, age category, presence of diabetes mellitus, obesity, menopause, and prior UTI events. We used Cox regression on the time between the reference primary UPEC-uUTI and first onset of a new episode of uUTI to determine a minimal set of individual characteristics that can be used to identify cases at the highest risk of being followed by a new episode; the backward selection method was used with a minimum significance level of 0.1 for removing an explanatory variable from the model. In the Cox regression model, the 51–64 year category was used as reference for the age category variable.

A sensitivity analysis was conducted to evaluate the incidence proportion of new episodes of uUTI, defined as any uUTI reported at least 30 days after the previous uUTI and within 12 months after the reference primary infection, in UPEC-uUTI and untested uUTI cases.

Analyses were conducted using SAS Drug Development 9.4 (SAS Institute Inc., Cary, NC, US).

Results

Cohort Description

Overall, 8227 reference primary uUTI cases were identified, of which 1087 (13.2%) were UPEC-uUTI cases and 4106 (49.9%) were untested uUTIs. The remaining 3034 (36.9%) cases were non-UPEC-uUTI cases. Two main analysis cohorts were created: the UPEC-uUTI cohort and the untested uUTI cohort. Most UPEC-uUTI cases were reported in women (86.8%), in the age category >50 years (54.6%), and in participants without a prior UTI event (86.9%) (Table 1).

UPEC-uUTIs

During the entire study period, 324 (29.8%; 95% CI: 27.1%–32.6%) reference primary UPEC-uUTIs were followed by ≥1 new episode of uUTI within 12 months (Table 2). Incidence proportions for ≥1 new episode of uUTI after the

Table 1 Number and Proportion of uUTI Cases in Each Cohort, by Demographic Characteristics and Risk Factors, San Francisco, United States, 2014–2019

Variable	UPEC-uUTI Cases N=1087		Untested uUTI Cases N=4106	
	No.	%	No.	%
Cohort for each evaluable year				
2014	302	27.8	1626	39.6
2016	369	33.9	1238	30.2
2018	416	38.3	1242	30.2
Gender				
Male	143	13.2	879	21.4
Female	944	86.8	3227	78.6
Age category[a]				
18–50 years	494	45.4	2022	49.2
51–64 years	309	28.4	970	23.6
≥65 years	284	26.1	1114	27.1
>50 years	593	54.6	2084	50.8
Presence of diabetes mellitus[a]				
Yes	360	33.1	1263	30.8
No	727	66.9	2843	69.2
Presence of obesity[a,b]				
Yes	325	29.9	1050	25.6
No	570	52.4	2092	50.9
Missing	192	17.7	964	23.5
Presence of menopause[a]				
Yes	157	14.4	406	9.9
No	787	72.4	2821	68.7
Not applicable	143	13.2	879	21.4

(*Continued*)

Table 1 (Continued).

Variable	UPEC-uUTI Cases N=1087		Untested uUTI Cases N=4106	
	No.	%	No.	%
Prior UTI event[c]				
Yes	142	13.1	769	18.7
No	945	86.9	3337	81.3

Notes: [a]At the time of the reference primary infection. [b]Obesity was defined as having a body mass index ≥30 kg/m^2. [c]A prior UTI event was defined as a uUTI episode diagnosed up to 12 months before the reference primary infection for patients ≥18 years of age, and before turning 18 for patients aged 18 years.
Abbreviations: N, number of cases in each cohort; UPEC, uropathogenic *E. coli*; UTI, urinary tract infection; uUTI, uncomplicated urinary tract infection.

Table 2 Incidence Proportion of Reference Primary UPEC-uUTI Cases Followed by New Episodes of uUTI, by Demographic Characteristics and Risk Factors, San Francisco, United States, 2014–2019

Variable	n	Incidence Proportion (%; 95% CI)
Overall cohort	324	29.8 (27.1–32.6)
Cohort for each evaluable year		
2014	97	32.1 (26.9–37.7)
2016	117	31.7 (27.0–36.7)
2018	110	26.4 (22.3–31.0)
Gender		
Male	50	35.0 (27.2–43.4)
Female	274	29.0 (26.1–32.0)
Age category[a]		
18–50 years	120	24.3 (20.6–28.3)
51–64 years	105	34.0 (28.7–39.6)
≥65 years	99	34.9 (29.3–40.7)
>50 years	204	34.4 (30.6–38.4)
Presence of diabetes mellitus[a]		
Yes	152	42.2 (37.1–47.5)
No	172	23.7 (20.6–26.9)
Presence of obesity[a, b]		
Yes	123	37.8 (32.6–43.4)
No	178	31.2 (27.4–35.2)
Presence of menopause		
Yes	74	47.1 (39.1–55.2)
No	200	25.4 (22.4–28.6)

(*Continued*)

Table 2 (Continued).

Variable	n	Incidence Proportion (%; 95% CI)
Prior UTI event[a, c]		
Yes	73	51.4 (42.9–59.9)
No	251	26.6 (23.8–29.5)

Notes: [a]At the time of the reference primary infection. [b]Obesity was defined as having a body mass index ≥30 kg/m$^{2.}$ [c]A prior UTI event was defined as a uUTI episode diagnosed up to 12 months before the reference primary infection for patients ≥18 years of age, and before turning 18 for patients aged 18 years.

Abbreviations: CI, confidence interval; n, number of cases with ≥1 new uUTI episode; UPEC, uropathogenic *E. coli*; UTI, urinary tract infection; uUTI, uncomplicated urinary tract infection.

reference primary infection were similar in the first two evaluable calendar years and slightly decreased in the third: 32.1% (95% CI: 26.9%–37.7%), 31.7% (95% CI: 27.0%–36.7%), and 26.4% (95% CI: 22.3%–31.0%) in 2014, 2016, and 2018, respectively. Incidence proportions were lower in younger aged participants: 24.3%, 34.0%, and 34.9%, for participants aged 18–50 years, 51–64 years, ≥65 years, respectively.

Incidence proportion was higher in males (35.0% versus 29.0% in females), participants with diabetes mellitus (42.2% versus 23.7% in participants without diabetes), participants with obesity (37.8% versus 31.2% in participants without obesity), women in menopause (47.1% versus 25.4% in women not in menopause), and in cases with a prior uUTI event (51.4% versus 26.6% in participants without such an event).

Using Cox regression on the time between the reference primary UPEC-uUTI and first onset of a new episode of uUTI, we identified three risk factors for new episodes after the reference primary infection: being male (hazard ratio [HR]: 1.39; 95% CI: 1.01–1.89; P=0.0417), having a diagnosis of diabetes mellitus (HR: 1.68; 95% CI: 1.33–2.11; P<0.0001), and having a record of a prior uUTI event (HR: 2.10; 95% CI: 1.60–2.75; P<0.0001).

For the 324 UPEC-uUTI cases with ≥1 new episode of uUTI after the reference primary infection, the mean time to first uUTI within 12 months was 103.6 (SD=90.9) days and the median time was 67.0 (range: 15.0–362.0) days. For the three evaluable calendar years, the mean time to the first episode of uUTI after the reference primary infection ranged from 95.2 (in 2016) to 109.9 days (in 2018) and the median time ranged from 50.0 (in 2016) to 82.0 days (in 2014).

For UPEC-uUTI episodes, 70.2% of reference primary infection cases were not followed by a new episode of uUTI, and 19.1%, 5.6%, 2.8%, 1.2% and 1.1% were followed by 1, 2, 3, 4 and ≥5 new episodes of uUTI, respectively. The relative proportions of UPEC-uUTI cases with 0, 1, 2, 3, 4, and ≥5 new uUTI episodes were similar in each evaluable year (Table 3).

Table 3 Proportion of Reference Primary UPEC-uUTI Cases Followed by 0, 1, 2, 3, 4, and ≥5 New Episodes of uUTI, by Demographic Characteristics and Risk Factors, San Francisco, United States, 2014–2019

Variable	N	Number (%) of New Episodes of uUTI					
		0	1	2	3	4	≥5
Overall cohort	1087	763 (70.2)	208 (19.1)	61 (5.6)	30 (2.8)	13 (1.2)	12 (1.1)
Cohort for each evaluable year							
2014	302	205 (67.9)	71 (23.5)	15 (5.0)	7 (2.3)	1 (0.3)	3 (1.0)
2016	369	252 (68.3)	69 (18.7)	22 (6.0)	13 (3.5)	8 (2.2)	5 (1.4)
2018	416	306 (73.6)	68 (16.3)	24 (5.8)	10 (2.4)	4 (1.0)	4 (1.0)

(*Continued*)

Table 3 (Continued).

Variable	N	Number (%) of New Episodes of uUTI					
		0	1	2	3	4	≥5
Gender							
Male	143	93 (65.0)	33 (23.1)	7 (4.9)	≤5[a]	≤5	≤5
Female	944	670 (71.0)	175 (18.5)	54 (5.7)	25 (2.6)	10 (1.1)	10 (1.1)
Age category[b]							
18–50 years	494	374 (75.7)	77 (15.6)	25 (5.1)	12 (2.4)	≤5	≤5
51–64 years	309	204 (66.0)	67 (21.7)	21 (6.8)	8 (2.6)	≤5	6 (1.9)
≥65 years	284	185 (65.1)	64 (22.5)	15 (5.3)	10 (3.5)	6 (2.1)	≤5
>50 years	593	389 (65.6)	131 (22.1)	36 (6.1)	18 (3.0)	9 (1.5)	10 (1.7)
Presence of diabetes mellitus[b]							
Yes	360	208 (57.8)	95 (26.4)	26 (7.2)	18 (5.0)	7 (1.9)	6 (1.7)
No	727	555 (76.3)	113 (15.5)	35 (4.8)	12 (1.7)	6 (0.8)	6 (0.8)
Presence of obesity[b,c]							
Yes	325	202 (62.2)	80 (24.6)	19 (5.8)	16 (4.9)	≤5	≤5
No	570	392 (68.8)	107 (18.8)	40 (7.0)	14 (2.5)	9 (1.6)	8 (1.4)
Presence of menopause[b]							
Yes	157	83 (52.9)	41 (26.1)	13 (8.3)	9 (5.7)	≤5	6 (3.8)
No	787	587 (74.6)	134 (17.0)	41 (5.2)	16 (2.0)	≤5	≤5
Prior UTI event[b,d]							
Yes	142	69 (48.6)	33 (23.2)	10 (7.0)	17 (12.0)	≤5	11 (7.7)
No	945	694 (73.4)	175 (18.5)	51 (5.4)	13 (1.4)	11 (1.2)	≤5

Notes: [a]Results were not reported where individual cell count was ≤5 (to maintain confidentiality). [b]At the time of the reference primary infection. [c]Obesity was defined as having a body mass index ≥30 kg/m^2. [d]A prior UTI event was defined as a uUTI episode diagnosed up to 12 months before the reference primary infection for patients ≥18 years of age, and before turning 18 for patients aged 18 years.

Abbreviations: N, number of UPEC-uUTI cases in the evaluable calendar years and in a given category; %, percentage of UPEC-uUTI cases with 0, 1, 2, 3, 4, and ≥5 new episodes of uUTI after reference primary infection in a given category; UPEC-uUTI, uropathogenic *E. coli*-uncomplicated urinary tract infection.

When considering a 30-day interval between two distinct UPEC-uUTI episodes, 275 (24.9%; 95% CI: 22.4%–27.5%) reference primary infection cases were followed by ≥1 new episode of uUTI within 12 months. The incidence proportions ranged between 23.3% (95% CI: 19.4%–27.7%) in 2018 and 26.6% (95% CI: 21.8%–31.9%) in 2014. The incidence proportions per age category were 20.9%, 29.1%, 27.1%, and 28.2% for individuals aged 18–50 years, 51–64 years, ≥65 years, and >50 years of age, respectively. Incidence proportions were higher in participants with diabetes mellitus (35.8% versus 19.5% in participants without diabetes), participants with obesity (33.7% versus 25.7% in participants without obesity), women in menopause (42.5% versus 20.4% in women not in menopause), and cases with a prior UTI event (44.9% versus 21.8% without a prior UTI event) (Supplementary Table S2).

Untested uUTIs

The total number of untested uUTI cases was 4106, with 1626 in 2014, 1238 in 2016, and 1242 in 2018. Most cases with untested uUTIs were in participants aged >50 years (50.8%) and without a prior UTI event (81.3%) (Table 1).

Overall, 1030 (25.1%; 95% CI: 23.8%–26.4%) reference primary untested uUTIs were followed by ≥1 new episode of uUTI within 12 months. The incidence proportions ranged between 22.2% (95% CI: 20.2%–24.3%) in 2014 and 27.9% (95% CI: 25.5%–30.5%) in 2018 (Table 4).

Table 4 Incidence Proportion of Reference Primary Untested uUTI Cases Followed by New Episodes of uUTI, by Demographic Characteristics and Risk Factors, San Francisco, United States, 2014–2019

Variable	n	Incidence Proportion (%; 95% CI)
Overall cohort	1030	25.1 (23.8–26.4)
Cohort for each evaluable year		
2014	361	22.2 (20.2–24.3)
2016	322	26.0 (23.6–28.5)
2018	347	27.9 (25.5–30.5)
Gender		
Male	240	27.3 (24.4–30.4)
Female	790	24.5 (23.0–26.0)
Age category[a]		
18–50 years	408	20.2 (18.4–22.0)
51–64 years	289	29.8 (26.9–32.8)
≥65 years	333	29.9 (27.2–32.7)
>50 years	622	29.8 (27.9–31.9)
Presence of diabetes mellitus[a]		
Yes	398	31.5 (29.0–34.2)
No	632	22.2 (20.7–23.8)
Presence of obesity[a, b]		
Yes	288	27.4 (24.7–30.2)
No	622	29.7 (27.8–31.7)
Presence of menopause[a]		
Yes	154	37.9 (33.2–42.8)
No	636	22.5 (21.0–24.1)
Prior UTI event[a, c]		
Yes	376	48.9 (45.3–52.5)
No	654	19.6 (18.3–21.0)

Notes: [a]At the time of the reference primary infection. [b]Obesity was defined as having a body mass index ≥30 kg/m^{2}. [c]A prior UTI event was defined as a uUTI episode diagnosed up to 12 months before the reference primary infection for patients ≥18 years of age, and before turning 18 for patients aged 18 years.

Abbreviations: CI, confidence interval; n, number of cases with ≥1 new uUTI episode; UTI, urinary tract infection; uUTI, uncomplicated urinary tract infection.

Using Cox regression on the time between reference primary untested uUTI and first new untested uUTI event, we identified two risk factors: older age (HR: 0.73; 95% CI: 0.62–0.85; $P<0.0001$ for the 18–50 versus the 51–64 years of age) and having a record of a prior uUTI event in the medical history (HR: 2.61; 95% CI: 2.28–2.98; $P<0.0001$).

For the 1030 untested uUTI cases with ≥1 new episode of uUTI after the reference primary infection, the mean time to first uUTI within 12 months was 111.2 (SD=93.0) days, while the median time to first recurrence was 78 (range: 15–364) days.

Overall, 74.9% of untested uUTI reference primary cases were not followed by a new episode of uUTI, and 14.7%, 5.0%, 2.4%, 1.4%, and 1.7% of cases were followed by 1, 2, 3, 4, and ≥5 new episodes of uUTI, respectively.

When considering a 30-day interval between two distinct uUTI episodes, 866 (21.5%; 95% CI: 20.2%–22.8%) reference primary infection cases were followed by ≥1 new episode of uUTI within 12 months.

Prescription of Antimicrobials and AST for UPEC-uUTIs

Antimicrobial treatment prescriptions for the reference primary UPEC-uUTI were retrieved for 41.1% of cases. The proportion of cases with prescribed antimicrobial treatment was 52.2%, 59.5%, and 63.6% for the first, second, and third new episode of uUTI, respectively, after the reference primary infection. Trimethoprim (TMP)/sulfamethoxazole (SMZ) (in 32.2% of cases) and nitrofurantoin (in 17.9% of cases) were the most frequently prescribed antimicrobials for the reference primary infection; TMP/SMZ (in 23.1% of cases) was more commonly prescribed for the first new episode of uUTI after the reference primary infection (Supplementary Table S3).

When tested, AMR to the class of antibiotics taken for the reference primary UPEC-uUTI was most frequently reported for TMP/SMZ (for 44 cases) or TMP/SMZ in combination with other antimicrobials (for 27 cases) (Supplementary Table S4).

Discussion

This retrospective cohort study assessed the prevalence of UPEC- and untested uUTIs, both reference primary infections and new episodes of uUTI after the reference primary infection, to provide a comprehensive overview on the incidence of these infections of the urinary tract, irrespective of patient gender. Although UTIs in males are generally classified as complicated,[13,14] the events included in the database for male patients were diagnoses of simple acute cystitis.

We found that 13.2% of individuals with uUTIs receiving care in a public healthcare system in San Francisco were culture tested and diagnosed with UPEC-uUTIs between 2014 and 2019, with most UPEC-uUTI cases reported in females (86.8%) and in the age category >50 years of age (54.6%).

While most literature reports focus on the incidence of recurrent UTIs, usually defined as ≥2 UTI episodes in six months or ≥3 episodes in one year, in this study, we evaluated the occurrence of any repeated episodes within one year from primary infection, to include all possible UTI events. The overall risk of experiencing an episode of uUTI within 12 months after the reference primary infection in the UPEC-uUTI cohort was 29.8%, which is consistent with reports from other studies.[5] Understanding the risk factors associated with experiencing repeated uUTI episodes can help tailor prophylactic strategies. We found that male gender, diagnosis of diabetes mellitus, and a prior uUTI event were associated with an increased risk of experiencing new episodes of uUTI within 12 months after a primary infection. When assessing the clinical history of a patient presenting with a UTI, these factors should be carefully explored.

Our finding that male gender is associated with increased risk of new episodes of uUTI may seem surprising seeing that female gender is a known risk for UTIs.[9] However, the difference between genders in UTI prevalence has been reported to change over time[15] and to decrease in older adults until they become almost equivalent,[16,17] due to factors like menopause, prostate gland disorders and the related instrumentation involving the urinary tract (males) which can favor UTIs.[18] More than half of the adults enrolled in our study were >50 years and almost one-third were ≥65 years of age. UTIs are common in patients with diabetes mellitus and are more frequently associated with serious complications compared to the general population.[19] In addition to glucosuria, which enables bacterial growth,[20] other factors such as impaired granulocyte function, changes in the humoral, cellular and innate immunity, age, diabetic nephropathy, poor metabolic control, and neuropathy leading to incomplete bladder voiding may contribute to the higher risk of UTI in this population.[19,21] Recently, Mohanty et al showed that high glucose concentrations induce lower levels of psoriasin, an

antimicrobial peptide, and impair urothelial barrier function, thereby contributing to impaired host defenses against *E. coli* UTIs.[21]

Among risk factors identified in our study, the incidence proportion of new episodes of uUTI within 12 months following the reference primary infection in individuals with a prior UTI was almost twice as high as in individuals without a prior UTI event, and the median time to the next episode was 67 days. Although one of the strongest predictors of UTI recurrence is a history of prior UTI, the biological reasons remain unclear. According to recent hypotheses, the exposure of bladder epithelial cells to UPEC may lead to long-lasting epigenetic modifications, thereby sensitizing the host for recurrent infections.[22] Several other studies showed that UPEC can accumulate in dormant intracellular reservoirs in the urothelium[23] and then escape to promote recurrent UTIs.[24]

In this study, antimicrobial prescriptions were retrieved for 41.1% of patients with a reference primary infection, with TMP/SMZ and nitrofurantoin being the most frequently prescribed. The proportion of patients who were prescribed antimicrobials also increased with each subsequent episode of uUTI after the reference primary infection. Moreover, AMR was most reported for TMP/SMZ alone or in combination with other antimicrobials. These findings are not surprising as a urine culture is not always obtained on presentation of a patient with uUTI, and antimicrobial treatment is usually started empirically for lower uUTIs, if at all.[9] In addition, Ahn et al showed that a high proportion of female patients with UTIs caused by extended-spectrum beta-lactamase-producing *E. coli* experienced recurrences with the same resistant bacteria.[25]

There is no uniform approach for the prevention of new episodes of UTI after a primary infection. Prolonged prophylactic antibiotic use is controversial, considering the contribution of *E. coli* infections to the overall AMR burden[10] and the potential alteration of the patient's commensal microbiota leading to secondary infections.[26] Currently, available alternative options include long-term use of antibiotics or non-antimicrobial prophylactic measures, ranging from behavioral changes related to the avoidance of spermicide-based contraceptives to dietary measures (eg adequate hydration and the use of ascorbic acid), phytotherapy using cranberry-based products, probiotics, D-mannose, estrogens, and immunostimulants.[27] However, these alternative methods lack a solid scientific basis and, in most cases, strong confirmatory evidence of efficacy. Alternative strategies for the treatment and prevention of UTIs, including vaccination, are warranted to reduce the emergence and spread of resistant UPEC strains. This particularly applies to individuals at increased risk of developing new uUTI episodes after their primary infection.

This study has several strengths and some limitations. Its main strength is the diverse patient population included in the study. Indeed, the results on frequency of primary and subsequent uUTI episodes as well as their risk factors are consistent with the internationally published literature. Moreover, the study also assessed the prescription of antimicrobials and the development of AMR for frequently used antimicrobial combinations. The main limitation of this single-center epidemiology study is the likely underestimation of UPEC-uUTI cases as only a limited proportion of clinical uUTI cases are microbiologically tested, largely reflecting clinical practice. The number of confirmed UPEC-uUTI cases may therefore constitute a biased sample. This limitation was partially addressed by carrying out separate analyses for UPEC-uUTIs and untested uUTIs. Another limitation is the nature of the data used. The use of medical record data may explain the low percentage of patients retrieved with antibiotic prescriptions as medical records may not be complete or fully available (eg incomplete data entry or patient treated in another facility).

Assessment of the burden of non-UPEC-uUTIs and their antimicrobial susceptibility as well as the collection of additional AMR data may help guide future treatment guidelines and research.

Conclusions

Our study provides important information on the incidence and risk of repeated episodes of uUTIs, as well as on AMR related to them. Our findings highlight the need to identify alternative interventions to reduce the risk of new episodes of uUTI after a primary infection, especially in the context of non-modifiable risk factors, and to limit the burden of AMR against commonly used antimicrobials.

Abbreviations

AMR, antimicrobial resistance; AST, antimicrobial susceptibility testing; CI, confidence interval; HR, hazard ratio; SD, standard deviation; SMZ, sulfamethoxazole; TMP, trimethoprim; UPEC, uropathogenic *Escherichia coli*; US, United States; UTI, urinary tract infection; uUTI, uncomplicated urinary tract infection.

Data Sharing Statement

Anonymized individual participant data and study documents can be provided upon request from www.clinicalstudydatarequest.com.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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