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MAJOR ARTICLE

Retrospective Cohort Study of the 12-Month Epidemiology, Treatment Patterns, Outcomes, and Health Care Costs Among Adult Patients With Complicated Urinary Tract Infections

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Background. Limited data are available in the United States on the 12-month epidemiology, outpatient (OP) antibiotic treatment patterns, outcomes, and costs associated with complicated urinary tract infections (cUTIs) in adult patients.

Methods. A retrospective observational cohort study of adult patients with incident cUTIs in IBM MarketScan Databases between 2017 and 2019 was performed. Patients were categorized as OP or inpatient (IP) based on initial setting of care for index cUTI and were stratified by age (<65 years vs ≥65 years). OP antibiotic treatment patterns, outcomes, and costs associated with cUTIs among adult patients over a 12-month follow-up period were examined.

Results. During the study period, 95 322 patients met inclusion criteria. Most patients were OPs (84%) and age <65 years (87%). Treatment failure (receipt of new unique OP antibiotic or cUTI-related ED visit/IP admission) occurred in 23% and 34% of OPs aged <65 years and ≥65 years, respectively. Treatment failure was observed in >38% of IPs, irrespective of age. Across both cohorts and age strata, >78% received ≥2 unique OP antibiotics, >34% received ≥4 unique OP antibiotics, >16% received repeat OP antibiotics, and >33% received ≥1 intravenous (IV) OP antibiotics. The mean 12-month cUTI-related total health care costs were $4697 for OPs age <65 years, $8924 for OPs age >65 years, $15 401 for IPs age <65 years, and $17 431 for IPs age ≥65 years.

Conclusions. These findings highlight the substantial 12-month health care burden associated with cUTIs and underscore the need for new outpatient treatment approaches that reduce the persistent or recurrent nature of many cUTIs.

Keywords. burden of illness; complicated urinary tract infections; costs; epidemiology; outcomes.

Complicated urinary tract infections (cUTIs) are one of the most common bacterial infections in both the community and health care settings [1, 2]. Data from a recent US national database study indicated that there are >2.8 million cases of cUTI per year, resulting in annual 30-day total costs of >$6 billion [3]. Oral antibiotics have long been a mainstay of treatment for cUTIs, but use has been compromised by resistance to commonly used oral antibiotics. In the United States, the percentages of *Escherichia coli* in cUTIs, identified as resistant to extended-spectrum cephalosporins, fluoroquinolones, trimethoprim/sulfamethoxazole, or classified as multidrug-resistant (MDR), have dramatically increased in recent years [4–8]. Despite the high incidence and recurrent nature of cUTIs in adults, limited data are available in the United States on the 12-month cUTI-related health care burden. To address the evidence data gap, this study sought to examine the epidemiology, outpatient (OP) antibiotic treatment patterns, outcomes, and costs associated with cUTIs among adult patients over a 12-month follow-up period in a large US administrative claims database containing longitudinal inpatient (IP) and OP patient-level data.

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METHODS

Study Design and Population

A retrospective observational cohort study of adult patients with cUTIs in IBM MarketScan Databases between July 1, 2016, and June 30, 2020, was performed (Supplementary Figure 1). Two IBM MarketScan Research Databases were used in the study: the MarketScan Commercial Claims and Encounters Database and the MarketScan Medicare Supplemental Database (Appendix A). Patients were included if they (1) had ≥1 IP or OP nondiagnostic claim meeting the diagnosis for a cUTI (adapted from the algorithm used in Lodise et al. [9] and Carreno et al. [3]) (Appendix B) between January 1, 2017, and June 30, 2019 (earliest cUTI claim =

index date), (2) were ≥18 years old as of index date, (3) had ≥6 months of continuous enrollment (CE) with medical and pharmacy benefits before the index date, (4) had ≥12 months of CE following the index date or evidence of IP death, and (5) had no evidence of a prior cUTI during the 6-month baseline period.

Patients meeting all selection criteria were categorized as OP or IP based on the initial setting of care for the index cUTI. Patients were classified as OP if the first cUTI diagnosis during the study period was in an OP setting and there was evidence of receipt of antibiotic treatment within ±3 days of the index cUTI diagnosis date or subsequent IP admission for a cUTI within 3 days of the index cUTI diagnosis. Patients were classified as IP if the index cUTI diagnosis was in the emergency department (ED) or observational unit with subsequent hospital admission or during a hospital admission. Patients within each cohort were stratified a priori by age (<65 years vs ≥65 years) given the distinctive differences in insurance coverage (ie, Commercial vs Medicare Supplemental) and anticipated variations in baseline characteristics and outcomes between the 2 age groups.

Baseline Characteristics in the 6-Month Pre-index cUTI Period

Demographics collected during the 6-month pre-index cUTI period included age, sex, US Census Bureau geographic region, place of residence (urban vs rural), and payer type (commercial vs Medicare Supplemental). Baseline clinical characteristics measured during the 6-month pre-index cUTI period included the Deyo-Charlson Comorbidity Index (CCI; overall score and components of CCI) [10] and the following clinical conditions: bacteremia, cancer, chronic kidney disease, diabetes, infective endocarditis, pregnancy, renal failure, sepsis, systemic inflammatory response syndrome (SIRS), urinary stones, and uncomplicated UTI [11]. Collected urinary tract procedures and surgeries included cystoscopy, cystectomy, cystolithalopaxy, cystourethrogram, lithotripsy, nephrolithotomy, prostate biopsy, retrograde pyelogram, transurethral resection of the prostate, transurethral resection of the bladder, ureteroscopy, urethroplasty, and urodynamics.

Outcomes in the 12-Month Postindex cUTI Period

Outcomes assessed in the 12-month postindex cUTI period within each study cohort included treatment failure, cUTI-related admissions in the OP cohort, 30-day cUTI-related readmissions, number of unique cUTI episodes, and recurrences. The definition of failure was objectively defined based on the initial setting of care. For the OP cohort, a patient was considered to have initial treatment failure if 1 of the following occurred within 30 days of the index cUTI date: (1) evidence of a new antibiotic prescription or ED visit/IP admission with a cUTI diagnosis 7–30 days after the index cUTI date or (2) cUTI-related ED or IP admission 7–30 days from the index cUTI day. For the IP cohort, a patient was considered to have failed treatment if (1) there was evidence of a new antibiotic prescription 7–30 days postdischarge or (2) there was a 30-day cUTI-related readmission postdischarge. A subsequent cUTI episode was defined as occurrence of a cUTI >30 days after the last cUTI-related claim for the prior cUTI [3]. Recurrence was defined as either ≥3 unique cUTI episodes in a 12-month period or ≥2 unique cUTI episodes in a 6-month period at least 30 days apart [2, 12, 13].

Outpatient Antibiotic Treatment in the 12-Month Postindex cUTI Period

All oral and intravenous (IV) antibiotics received in the 12-month postindex cUTI period in the OP setting were collected. Antibiotics received in the ED were included when tabulating antibiotics received in the OP setting. Antibiotics received in the IP setting were not captured in the MarketScan Commercial and Medicare Supplemental Databases. Within each cohort and age group, the number (%) of patients receiving 1, 2, 3, or ≥4 unique antibiotics (overall, oral, and IV) was recorded. The most used oral and IV antibiotics were also documented across the study cohort strata. For each cUTI episode during the 12-month postindex cUTI period, the total duration of OP antibiotic treatment, the number and type of antibiotics received, the frequency of refills and repeat antibiotic use (ie, same antibiotic was prescribed in prior episode), and the most common treatment sequences were tabulated. For patients with ≥2 cUTI episodes in the 12-month follow-up period, the gap time between episodes and frequency of repeat antibiotic use (ie, same antibiotic was prescribed in a prior episode) were documented. Antibiotics received from the pharmacy benefit were based on National Drug Code (NDC) codes, while outpatient infusions were based on both Level I [current procedural terminology (CPT)] and II (J-codes) healthcare common procedure coding system (HCPCS) codes.

Health Care Resource Utilization and Costs in the 12-Month Postindex cUTI Period

All-cause and cUTI-specific health care resource utilization and costs were collected during the 12-month follow-up period. An encounter for a particular type of service was considered cUTI-related in the presence of the following: (1) IP admissions with a primary diagnosis of cUTI, (2) OP claims with a diagnosis of cUTI in any position or an HCPCS code for an antibiotic, and (3) cUTI-specific pharmacy claims. All-cause and cUTI-related costs over the 12-month follow-up period were tabulated based on the amount paid to the payer (Appendix A). Health care costs were based on paid amounts of adjudicated claims, including insurer and health plan payments as well as patient cost-sharing in the form of copayment, deductible, and coinsurance. Costs for services provided under capitated arrangements were estimated using payment proxies based on paid claims at the procedure level using the MarketScan Commercial and Medicare Supplemental Databases. Arithmetic mean (SD) costs were presented, as this is the most informative measure to guide health care policy decision-making and presenting cost data [14]. All-cause and cUTI-related health care resource utilization and costs were reported for patients with an encounter in the following service categories: IP, OP, and OP pharmacy. For OP health care resource utilization, the proportion of patients and associated costs among patients with an encounter for the following types of OP services were recorded: ED visit, office visit, telehealth visit, laboratory service, and other. Other OP services reflected those not captured in ED, OP office, or OP lab service categories and included OP parenteral therapy (OPAT) at a physician office or infusion suite, home health care, OP surgery, long-term care facility, physical therapy, radiology, durable medical equipment, and other. Among OPAT patients, the mean average costs of 14 days of OPAT were determined. All dollar estimates were inflated to 2020 dollars using the Medical Care Component of the Consumer Price Index (CPI).

RESULTS

During the 2-year study period, 95 322 patients met the study criteria (Supplementary Table 1). The initial setting of care was OP for 84% (n = 79 715) of the study population. Among included patients, 86.4% were from the MarketScan Commercial Database, and 13.6% were from the MarketScan Medicare Supplemental Database. Among both cohorts, the majority (>77%) were <65 years of age. Baseline demographics and clinical characteristics in the 6-month pre-index cUTI period are shown in Table 1. Patients in the IP cohort had a higher proportion of males, a higher comorbidity burden at baseline, and greater proportions of other select clinical conditions and procedures, as compared with patients in the OP cohort. For patients age <65 years, the majority were female, while most cUTIs in patients age ≥65 years were observed in males. Patients age <65 years had fewer comorbidities and a lower proportion of select clinical conditions and procedures relative to patients ≥65 years of age.

The proportions of patients with treatment failure, cUTI ED visits/IP admissions (OP cohort), 30-day cUTI-related readmissions, cUTI episodes ≥2/3, and recurrence in the 12-month postindex cUTI period are shown in Figure 1. Among OPs age <65 years, 23% had treatment failure (mostly due to receipt of a new, unique antibiotic prescription), 7% had a cUTI-related IP admission, and 12% of the OP cohort with a cUTI-related admission had a 30-day cUTI-related readmission. Among OPs age ≥65 years, 34% had treatment failure, 16% had a cUTI-related IP admission, and 26% of patients with a cUTI-related admission had a 30-day cUTI-related readmission. Treatment failure was observed in >37% of the IP cohort, irrespective of age. Of these, 9% of IPs age <65 years had a 30-day readmission while 25% of IPs age ≥65 years had a 30-day readmission. The proportions of OPs age <65 years, OPs age ≥65 years, IPs age <65 years, and IPs age ≥65 years with ≥2 episodes/recurrence were as follows: 6%, 15%, 12%, and 17%.

OP antibiotics received in the 12-month period following the cUTI index date in the 2 cohorts are shown in Figure 2. Across both cohorts and age strata, >78% received ≥2 unique OP antibiotics, >34% received ≥4 unique OP antibiotics. Within each cUTI cohort, receipt of unique OP antibiotics was similar between patients age <65 years vs ≥65 years. Regardless of age, receipt of an oral OP antibiotic was frequent across both cohorts within the initial setting of care, with ∼70% of patients receiving ≥2 oral antibiotics. The 5 most used oral antibiotics in rank order for both cohorts during the 12-month postindex cUTI period were ciprofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, cephalexin, and amoxicillin-clavulanate. In the OP cohort, 49% of patients <65 years of age and 36% of patients ≥65 years of age received ≥1 OP IV antibiotic. For the IP cohort, 40% of patients age <65 years received at least 1 OP IV antibiotic, while 33% of patients ≥65 years of age received ≥1 OP IV antibiotic. Among the OP IV antibiotics, ceftriaxone (32%) and cefazolin (10%) were most used. All other IV OP antibiotics were administered in <5% of the study population, irrespective of the initial setting of care and age strata. Repeat receipt of the same OP antibiotic was observed in 16%, 25%, 19%, and 16% of OPs age <65 years, OPs age ≥65 years, IPs age <65 years, and IPs age ≥65 years, respectively. The most common repeat OP antibiotics among the overall study population were ciprofloxacin (20%), IV ceftriaxone (18%), trimethoprim-sulfamethoxazole (9%), nitrofurantoin (8%), and cephalexin (6%).

A breakdown of OP antibiotic use per cUTI episode by cUTI initial setting of care and age category is shown in Supplementary Table 2. For the index cUTI episode, nearly 50% received ≥2 OP antibiotics, 14% received the same antibiotic twice (ie, the same antibiotic was prescribed in a prior episode), and the average treatment duration was 13 days. Among the 8% of patients with 2 cUTI episodes, the mean gap time between cUTI episodes 1 and 2 was 71 days and the average duration of treatment for the second cUTI episode was 15 days. For the second cUTI episode, 41% of patients received ≥2 OP antibiotics and 41% of patients in the study population received the same OP antibiotic in episodes 1 and 2. For the 3% of patients with 3 cUTI episodes, the mean gap time between cUTI episodes 2 and 3 was 54 days and the average duration of treatment for cUTI episode 3 was 16 days. Over 40% of patients received ≥2 OP antibiotics for their third cUTI episode, 17% received the same antibiotic twice (ie, the same antibiotic was prescribed in a prior episode), and 54% received the same OP antibiotic in episodes 2 and 3.

All-cause and cUTI-related costs during the 12-month follow-up period are shown in Figure 3 and Supplementary Table 3. Average 12-month all-cause total health care costs for

Table 1. Baseline Demographic and Clinical Characteristics

	Index cUTI OP Age <65		Index cUTI OP Age ≥65		Index cUTI IP Age <65		Index cUTI IP Age ≥65	
	(n = 70 385)		(n = 9330)		(n = 12 157)		(n = 3460)	
Age, mean (SD), y	43.5	(13.8)	76.7	(7.7)	46.7	(13.5)	78.3	(8.1)
Sex, No. (%)								
Male	16 938	(24.1)	5496	(58.9)	3962	(32.6)	1787	(51.6)
Female	53 447	(75.9)	3834	(41.1)	8195	(67.4)	1673	(48.4)
Geographic region, No. (%)								
Northeast	9311	(13.2)	2388	(25.6)	1910	(15.7)	841	(24.3)
North Central	14 349	(20.4)	2850	(30.5)	2650	(21.8)	1225	(35.4)
South	35 579	(50.5)	2834	(30.4)	6162	(50.7)	1007	(29.1)
West	11 002	(15.6)	1241	(13.3)	1401	(11.5)	378	(10.9)
Unknown	144	(0.2)	17	(0.2)	34	(0.3)	9	(0.3)
Population density, No. (%)								
Urban	61 147	(86.9)	8164	(87.5)	10 720	(88.2)	3060	(88.4)
Rural	9146	(13.0)	1135	(12.2)	1420	(11.7)	387	(11.2)
Unknown	92	(0.1)	31	(0.3)	17	(0.1)	13	(0.4)
Payer, No. (%)								
Commercial	70 262	(99.8)	0	(0.0)	12 107	(99.6)	0	(0.0)
Medicare Supplemental	123	(0.2)	9330	(100)	50	(0.4)	3460	(100)
Comorbidities								
Deyo-CCI, mean (SD)	0.49	(1.17)	1.90	(2.21)	1.12	(1.94)	2.28	(2.45)
Components of the Deyo-CCI, No. (%)								
Cerebrovascular disease	956	(1.4)	1088	(11.7)	441	(3.6)	488	(14.1)
Chronic pulmonary disease	5576	(7.9)	1554	(16.7)	1186	(9.8)	601	(17.4)
Congestive heart failure	557	(0.8)	825	(8.8)	389	(3.2)	452	(13.1)
Dementia	67	(0.1)	384	(4.1)	50	(0.4)	273	(7.9)
Diabetes	7686	(10.9)	2538	(27.2)	2437	(20.0)	1065	(30.8)
Mild/moderate	7686	(10.9)	2538	(27.2)	2437	(20.0)	1065	(30.8)
Severe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hemiplegia/paraplegia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HIV/AIDS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Liver disease	246	(0.3)	45	(0.5)	109	(0.9)	30	(0.9)
Mild	246	(0.3)	45	(0.5)	109	(0.9)	30	(0.9)
Moderate/severe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malignancy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metastatic solid tumor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial infarction	395	(0.6)	326	(3.5)	177	(1.5)	148	(4.3)
Peptic ulcer disease	304	(0.4)	76	(0.8)	110	(0.9)	31	(0.9)
Peripheral vascular disease	556	(0.8)	774	(8.3)	262	(2.2)	357	(10.3)
Renal disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rheumatologic disease	1204	(1.7)	251	(2.7)	331	(2.7)	112	(3.2)
Clinical conditions, No. (%)								
Bacteremia	123	(0.2)	68	(0.7)	133	(1.1)	38	(1.1)
Cancer	2562	(3.6)	1678	(18.0)	898	(7.4)	578	(16.7)
Chronic kidney disease	1571	(2.2)	1139	(12.2)	916	(7.5)	579	(16.7)
Endocarditis	55	(0.1)	27	(0.3)	34	(0.3)	14	(0.4)
Pregnancy	1847	(2.6)	1	(0.0)	632	(5.2)	3	(0.1)
Renal failure	721	(1.0)	524	(5.6)	675	(5.6)	281	(8.1)
Sepsis	604	(0.9)	294	(3.2)	542	(4.5)	178	(5.1)
Systemic inflammatory response syndrome	64	(0.1)	18	(0.2)	66	(0.5)	19	(0.5)
Urinary stones	5890	(8.4)	765	(8.2)	1017	(8.4)	183	(5.3)
Uncomplicated UTI	14 145	(20.1)	2312	(24.8)	2299	(18.9)	666	(19.2)
UTI procedures and surgeries, No. (%)								
Cystectomy	36	(0.1)	14	(0.2)	32	(0.3)	6	(0.2)
Cystolitholapaxy	53	(0.1)	34	(0.4)	13	(0.1)	4	(0.1)
Cystoscopy	3761	(5.3)	1339	(14.4)	702	(5.8)	244	(7.1)

Table 1. Continued

	Index cUTI OP Age <65		Index cUTI OP Age ≥65		Index cUTI IP Age <65		Index cUTI IP Age ≥65	
	(n = 70 385)		(n = 9330)		(n = 12 157)		(n = 3460)	
Cystourethrogram	216	(0.3)	40	(0.4)	60	(0.5)	8	(0.2)
Lithotripsy	490	(0.7)	53	(0.6)	108	(0.9)	12	(0.3)
Nephrolithotomy	40	(0.1)	6	(0.1)	28	(0.2)	1	(0.0)
Prostate biopsy	300	(0.4)	105	(1.1)	114	(0.9)	28	(0.8)
Retrograde pyelogram	13	(0.0)	2	(0.0)	4	(0.0)	0	(0.0)
Transurethral resection of the bladder	144	(0.2)	144	(1.5)	32	(0.3)	23	(0.7)
Transurethral resection of the prostate	221	(0.3)	124	(1.3)	31	(0.3)	17	(0.5)
Ureteroscopy	113	(0.2)	16	(0.2)	46	(0.4)	7	(0.2)
Urethroplasty	22	(0.0)	2	(0.0)	1	(0.0)	1	(0.0)
Urodynamics	3525	(5.0)	1595	(17.1)	400	(3.3)	295	(8.5)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CCI, Charlson Comorbidity Index; cUTI, complicated urinary tract infection; IP, inpatient; OP, outpatient; UTI, urinary tract infection.

OPs age <65 years, OPs age ≥65 years, IPs age <65 years, and IPs age ≥65 years were $23 825, $48 711, $80 063, and $90 072, respectively. The average 12-month cUTI-related total health care costs were $4697 for OPs age <65 years, $8924 for OPs age >65 years, $15 401 for IPs age <65 years, and $17 431 for IPs age ≥65 years. Mean cUTI-related patient out-of-pocket total health care costs were $539, $244, $1022, and $312 for OPs age <65 years, OPs age ≥65 years, IPs age <65 years, and IPs age ≥65 years, respectively. Twelve-month all-cause and cUTI-related costs by service categories (IP, OP, and OP pharmacy) among patients with encounters in the service category are shown in Figure 4. The breakdown of all-cause and cUTI-related OP 12-month costs by OP service categories (ED, office visit, telehealth visit, laboratory services, and other) among patients with encounters for that OP service category is shown in Supplementary Figures 2 and 3. Among the 74 012 patients with other OP cUTI-related services, 38 659 (52%) received OPAT (cUTI-specific IV antibiotic in a physician office or IV infusion suite) and 1341 (1.8%) received a cUTI-specific IV antibiotic at home (home health). Among patients who received OPAT, the average 14-day OPAT costs were $2184, $2553, $3471, and $2673 for OPs age <65 years, OPs age ≥65 years, IPs age <65 years, and IPs age ≥65 years, respectively. Mean 14-day costs for home health were slightly higher than OPAT, at $3009, $2990, $2621, and $1885 for OPs age <65 years, OPs age ≥65 years, IPs age <65 years, and IPs age ≥65 years, respectively. Of note, mean costs were biased high due to some patients with high costs, and mean costs were more consistent with the 75th percentile costs than the median (50th percentile) costs.

DISCUSSION

There were several notable findings in this 12-month longitudinal study of adult patients with incident cUTIs. While UTIs are generally considered to be self-limiting and easily managed infections [15], 12-month costs associated with cUTIs were substantial, with the cUTI-related mean cost ranging from $4697 for OPs age <65 years to $17 431 for IPs age ≥65 years. Patient out-of-pocket costs were also found to be considerable, especially for patients with hospital IP admissions. However, patient out-of-pocket costs were less than costs reported in other studies [16, 17], reflecting the commercially insured status of the study population. IP admissions were the most substantial component in all initial settings of care and age strata. The observed costs associated with cUTI-related IP care in this study are consistent with recent reports [3, 18, 19] and highlight the need for health care systems to develop well-defined criteria for hospital admissions, as data demonstrate that UTI-related admissions can be reduced through the use of structured institutional site-of-care clinical pathways [20–24]. The second major contributor to 12-month cUTI-related costs was OP medical costs, largely attributed to costs associated with ED visits and administering OPAT at a physician office or infusion suite. Outpatient pharmacy costs comprised a relatively small proportion of the total cUTI-related costs, and this was not surprising given that most OP cUTI antibiotics are available as generics.

Treatment failure was a frequent event. Among OPs, ~1 in 4 patients age <65 years met the treatment failure criteria, while ~1 in 3 patients age ≥65 years were treatment failures. Treatment failure was even higher among patients in the IP cohort, with an incidence of 38% and 46% in patients age <65 years and ≥65 years, respectively. Our treatment failure findings align with 2 studies [3, 19] that assessed the short-term outcomes (ie, 30- or 90-day postindex cUTI) of patients with cUTIs and highlight the acute refractory nature of managing cUTIs in the OP setting. The overall 12-month incidence of recurrence was also found to be moderately high (~8%), especially among IPs, irrespective of age (13%), and OPs age ≥65 years

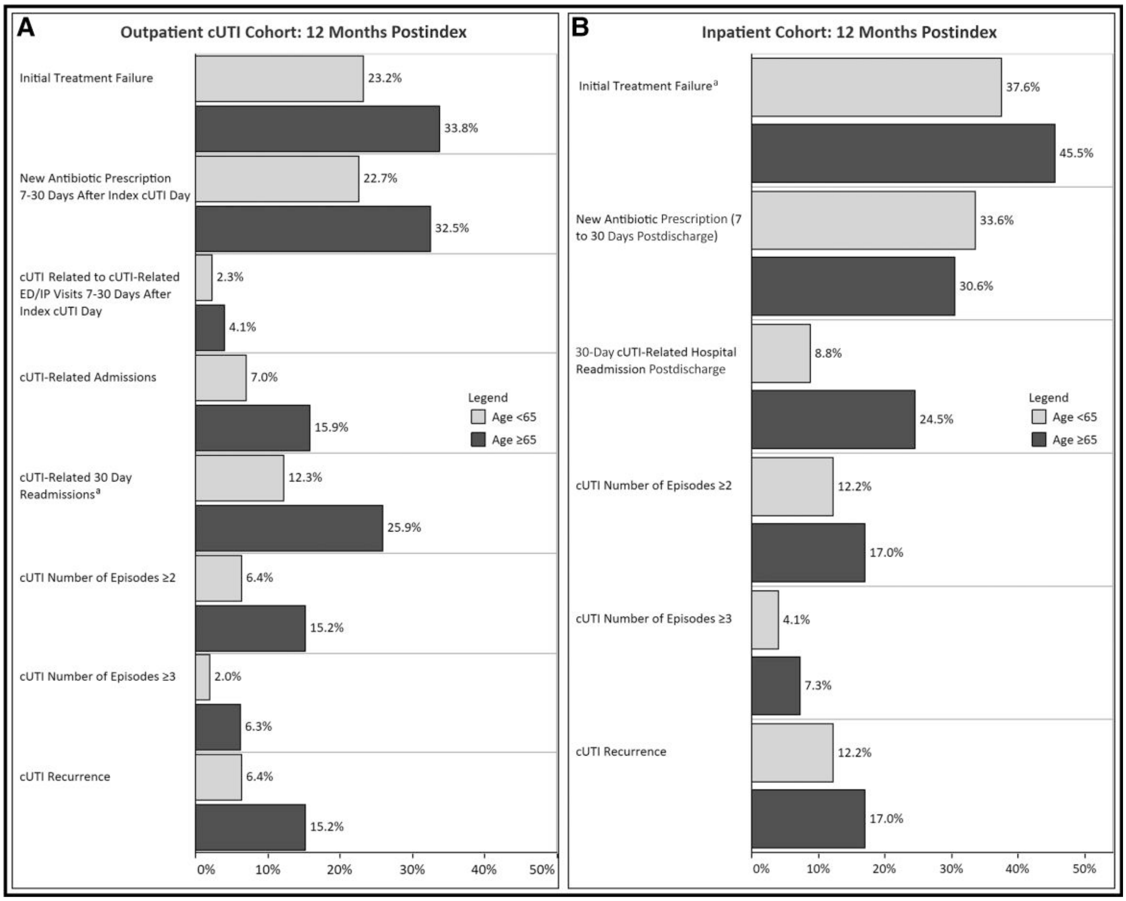

Figure 1. Readmissions, treatment failure, and recurrence by age in the (A) outpatient cohort and (B) inpatient cohort. [a]Among outpatients with a 30-day cUTI-related hospital admission. A patient in the outpatient cohort was considered to have initial treatment failure if 1 of the following occurred within 30 days of the index cUTI date: (1) evidence of a new antibiotic prescription or cUTI-related ED visit/IP admission with a cUTI diagnosis 7–30 days after the index cUTI day or (2) cUTI-related ED or IP admission 7–30 days from the index cUTI day. Abbreviations: cUTI, complicated urinary tract infection; ED, emergency department; IP, inpatient.

(15%). Scant data are currently available on the 12-month incidence of recurrence among adult patients with cUTIs, and the only OP-focused cUTI study that evaluated 12-month cUTI recurrence rates by Anesi and colleagues [25] found that over half of patients had a recurrent UTI [26] in the 12-month follow-up period. While the incidence of recurrence was 5-fold higher than that observed in our study, Anesi et al. performed a 1:1 match of patients with extended-spectrum cephalosporin resistance and susceptible Enterobacterales UTIs and excluded 273 patients (65%) with extended-spectrum cephalosporin susceptible Enterobacterales UTIs. It is likely that the underrepresentation of patients with extended-spectrum cephalosporin-susceptible Enterobacterales UTIs in this study inflated the recurrence rates as extended-spectrum cephalosporin resistance status was a significant predictor of recurrent UTI in adjusted analysis [25]. Our observed cUTI recurrence rates are also lower than the recurrence rates reported for women and men with uncomplicated UTIs [2, 13, 27]. Our study only quantified patients who had subsequent cUTI episodes, and it is likely that many patients in our study had a recurrent UTI that did not rise to the level of a cUTI.

Another noteworthy finding was the number of antibiotics received by patients during the 12-month follow-up period. Nearly all patients, irrespective of initial setting of care and age strata, received ≥2 OP antibiotics, and ~40% received ≥4 unique OP antibiotics. In most cases, patients received an oral antibiotic, and the most frequently received oral OP antibiotics were fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and cephalosporins across first and subsequent cUTI episodes. While these treatment patterns are consistent with expert guideline recommendations [28], nearly 20% of patients received the same antibiotic twice in the 12-month follow-up period, and 40%–50% of patients with ≥2 cUTI episodes received the same recurrent antibiotic (ie, same OP antibiotic administered in current and previous episode). Although microbiologic data were not available in the database, it is highly plausible that antimicrobial resistance [29, 30] may have contributed to observed treatment patterns as most US regions

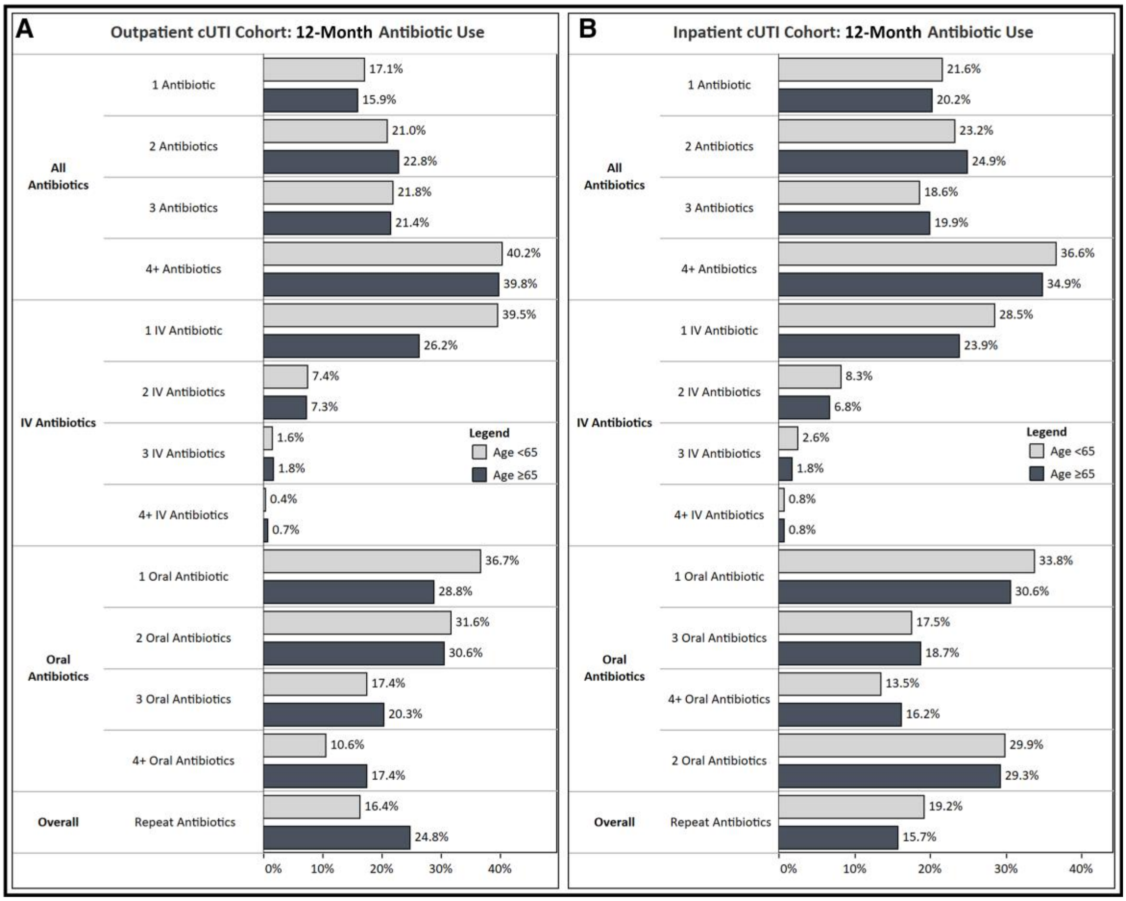

Figure 2. Outpatient antibiotic use in the 12-month follow-up period by age in the (A) outpatient cohort and (B) inpatient cohort. Repeat antibiotic use was defined as the same antibiotic being prescribed in a prior episode. Abbreviations: cUTI, complicated urinary tract infection; IV, intravenous.

have high rates of resistance among common cUTI pathogens to first-line OP cUTI antibiotics [4, 31, 32]. Most likely, many patients received inappropriate initial therapy due to the high resistance rates among uropathogens to first-line cUTI treatment options, and studies demonstrate that patients who fail to receive an early active agent are at increased risk for protracted treatment courses and recurrence [25, 30, 33–38]. Additionally, the average duration of treatment was 13–16 days, depending on the episode. Data suggest that many cUTI patients may be effectively treated with a shorter duration of therapy [39], and the treatment duration findings highlight the importance of implementing standardized outpatient treatment pathways for adult cUTI patients to minimize excessive or inappropriate antibiotic durations [20–23].

An unanticipated finding was the high frequency of OP IV antibiotic use. The results indicated that nearly half of patients received an IV antibiotic in the OP setting. In most cases, IV antibiotics were administered for the index cUTI episode, and patients were administered IV antibiotic therapy in a physician's office or infusion suite. While OPAT is increasingly being used as a cost-efficient measure to facilitate early hospital discharge and minimize hospitalizations in otherwise healthy patients [40–42], the average 14-day OPAT costs exceeded $2500 across all cUTI study population subgroups. In addition to 14-day cUTI-related cost considerations with OPAT, data indicate that OPAT-related adverse events and subsequent hospital admissions/readmissions occur frequently [43–51]. There are several oral antibiotics in development with favorable susceptibility, efficacy, and safety profiles [52], and it will be important to determine if these newer oral agents can improve the quality and efficiency of health care for adult cUTI patients relative to existing OP IV cUTI treatments.

The limitations of this study include those inherent in administrative claims database analyses. Clinical laboratory values, physical exam findings, and physician notes were not available, and diagnosis of cUTIs was based on diagnostic and procedure codes. Lack of electronic medical record information prevented us from detailing the exact factors that contributed to the complicated nature of each UTI and the varying burdens and outcomes associated with each cUTI type. As there are no specific codes for complicated UTI, a composite case definition was utilized [3, 53]. Thus, there was potential

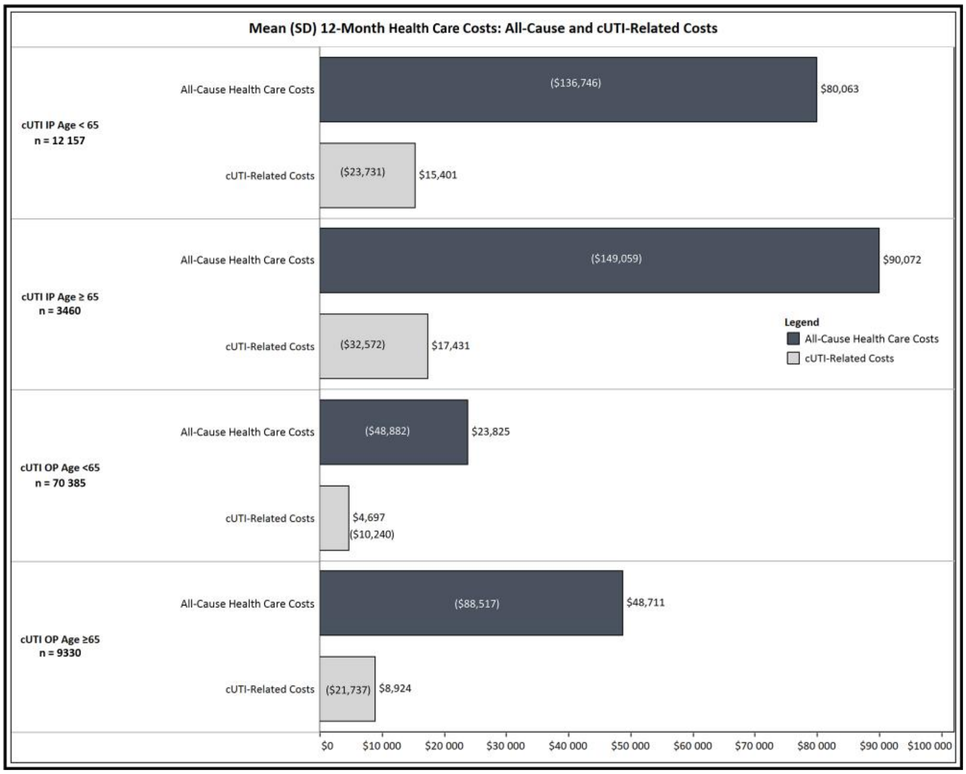

Figure 3. Mean (SD) 12-month all-cause and cUTI-related health care costs by index cUTI setting and age category. Abbreviations: cUTI, complicated urinary tract infection; IP, inpatient; OP, outpatient.

for misclassification of cUTI, covariates, and study outcomes. However, the codes used to identify cUTIs and disease severity (ie, Deyo-CCI) have been previously validated to have high positive predictive values [54–58]. However, it is possible that some of the patients identified as having a cUTI by the algorithms employed may have had asymptomatic bacteriuria. Microbiologic and urinalysis data were also not available, further limiting our ability to assess the presence of an acute cUTI vs asymptomatic bacteriuria. Despite the potential for misclassification of cUTIs, the results reflect a conservative estimate of the costs and associated outcomes of patients with cUTIs in the outpatient setting. Miscoding of asymptomatic bacteriuria as a cUTI would likely underestimate the true burden of cUTIs as patients with acute cUTI require more intensive care and are at greater risk for treatment failure relative to those with asymptomatic bacteriuria [1, 2]. The potential that patients with asymptomatic bacteriuria were managed as having an acute cUTI highlights the well-documented need to develop policies and pathways to reduce the overtreatment of patients with asymptomatic bacteriuria [59, 60].

We were unable to determine the reason(s) why patients received a new prescription (eg, lack or response, occurrence of treatment-related adverse event, use for a different infection). Therefore, the reported percentage of patients with an initial treatment failure should be interpreted with caution as it may have overestimated the true proportion of patients with an actual initial treatment failure due to receipt of a new prescription 7–30 days after the index cUTI date (OP cohort) or 7–30 days postdischarge (IP cohort) and likely represents the upper range of treatment failure. Although the antibiotics administered during the "7–30-day postindex cUTI day/discharge day treatment failure window" were consistent with those used to treat cUTIs (Supplementary Table 2), it is quite possible that antibiotics may have been administered for a non-cUTI indication (eg, sexually transmitted infection, different infection type). Of note, the occurrence of a subsequent 30-day cUTI-related ED/IP visit was the other component of initial treatment failure in both cohorts, and a fair proportion of patients met both parts of the initial treatment failure definition. We believe this finding lends credence to the initial treatment failure end point employed in this study, but further real-world evidence clinical studies are needed to ascertain the true incidence of initial treatment failure in adult patients with cUTIs. Regardless of the actual indication for antibiotic therapy, the most notable antibiotic treatment observation from this study was that nearly all patients, irrespective of initial setting of care and age strata, received ≥2 OP antibiotics, and ~40% received ≥4 unique OP antibiotics. The database did not include information on

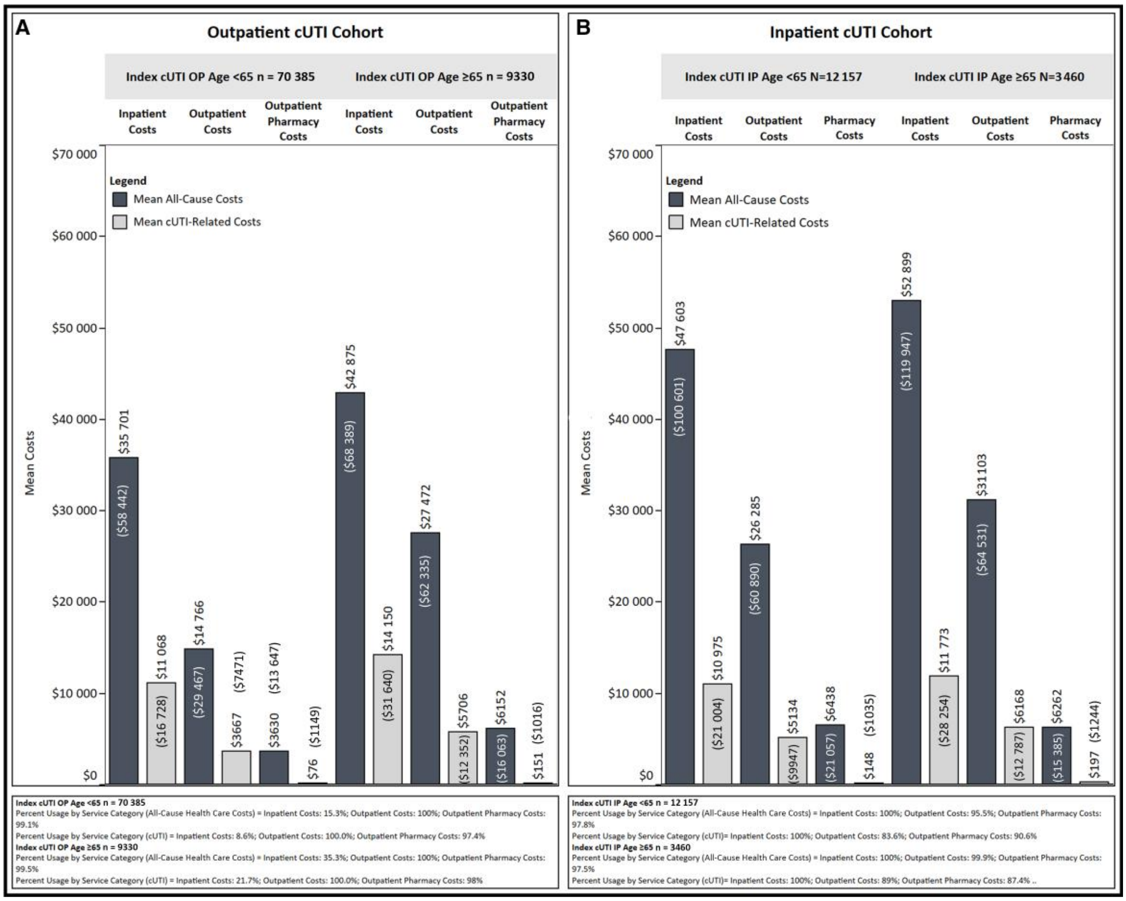

Figure 4. Mean (SD) 12-month all-cause and cUTI-related health care costs by inpatient, outpatient, and outpatient pharmacy among patients with encounters in the (A) outpatient cohort and (B) inpatient cohort. Abbreviations: cUTI, complicated urinary tract infection; IP, inpatient; OP, outpatient.

antibiotics administered in the IP setting, and it is highly likely that patients with IP admissions received more antibiotics than those administered in the OP setting. The collective antibiotics usage findings have important implications for clinical practice as they highlight the critical need to develop targeted OP cUTI stewardship initiatives as overuse of antibiotics is a major driver of antibiotic drug resistance in cUTI patients [61].

The study was limited to individuals with commercial or Medicare Supplemental health coverage (~13.6% of the study population), and the results of this analysis are not generalizable to cUTI patients with other health insurance or without health insurance coverage. Given that 86.4% were from the MarketScan Commercial Database and the average age and CCI score were 48.4 years and 0.77 for the overall study population, the observed findings are likely conservative estimates of the 12-month burden associated with cUTIs in adult patients as many cUTIs occur in older patients with multiple comorbidities [1, 2]. Finally, 12-month cost estimates are likely conservative estimates of cost as they represented payments received vs true health care costs.

In conclusion, the findings from this study indicate that many cUTIs do not resolve with the initial course of treatment and that a fair proportion of patients have recurrent infections. The results also indicate that many patients receive prolonged durations of OP antibiotics despite data suggesting that shorter courses are as effective as longer durations of treatment [39]. Twelve-month cUTI-related health care costs were substantial and were largely due to IP admissions, ED visits, and OPAT. Regardless of index treatment setting, ~40% of all cUTI patients required therapy with ≥4 antibiotics, and almost half received an IV antibiotic in the OP setting in the 12-month follow-up period. The high frequency of overall, repeat, and IV OP antibiotic use highlights the critical need for new oral cUTI therapies that have activity against highly resistant strains of *E. coli* and other uropathogenic bacteria. As hospital reimbursement and antimicrobial stewardship programs are increasingly tied to quality and efficiency of care, these findings also underscore the need for new treatment approaches that reduce the persistent or recurrent nature of many cUTIs.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. T.P.L. is a consultant for Spero Therapeutics. M.J. is employed by IBM Watson Health and received funding from Spero Therapeutics to conduct this study. E.H.M. is employed by IBM Watson Health and received funding from Spero Therapeutics to conduct this study. M.R. is an employee of Spero Therapeutics. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. The IBM databases only contained de-identified patient records. As this study only used de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval to conduct this study was not necessary or required.

References

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol **2015**; 13:269–84.
2. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am **2014**; 28:1–13.
3. Carreno JJ, Tam IM, Meyers JL, et al. Longitudinal, nationwide, cohort study to assess incidence, outcomes, and costs associated with complicated urinary tract infection. Open Forum Infect Dis **2019**; 6:ofz446. doi: 10.1093/ofid/ofz536.
4. Critchley IA, Cotroneo N, Pucci MJ, Mendes R. The burden of antimicrobial resistance among urinary tract isolates of *Escherichia coli* in the United States in 2017. PLoS One **2019**; 14:e0220265.
5. Zilberberg MD, Nathanson BH, Sulham K, Shorr AF. Antimicrobial susceptibility and cross-resistance patterns among common complicated urinary tract infections in U.S. hospitals, 2013 to 2018. Antimicrob Agents Chemother **2020**; 64: e00346-20.
6. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-resistant bacterial infections in U.S. hospitalized patients, 2012–2017. N Engl J Med **2020**; 382:1309–19.
7. Weiner-Lastinger LM, Abner S, Edwards JR, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015–2017. Infect Control Hosp Epidemiol **2020**; 41:1–18.
8. Lob SH, Nicolle LE, Hoban DJ, Kazmierczak KM, Badal RE, Sahm DF. Susceptibility patterns and ESBL rates of *Escherichia coli* from urinary tract infections in Canada and the United States, SMART 2010–2014. Diagn Microbiol Infect Dis **2016**; 85:459–65.
9. Lodise T, Ye MJ, Zhao Q. Prevalence of invasive infections due to carbapenem-resistant Enterobacteriaceae among adult patients in U.S. hospitals. Antimicrob Agents Chemother **2017**; 61:e00228-17.
10. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol **1992**; 45:613–9.
11. Lodise TP, Izmailyan S, Olesky M, et al. An evaluation of treatment patterns and associated outcomes among adult hospitalized patients with lower-risk community-acquired complicated intra-abdominal infections: how often are expert guidelines followed? Open Forum Infect Dis **2020**; 7:ofaa237. doi: 10.1093/ofid/ofaa237.
12. Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. World J Urol **1999**; 17:415–20.
13. Peck J, Shepherd JP. Recurrent urinary tract infections: diagnosis, treatment, and prevention. Obstet Gynecol Clin North Am **2021**; 48:501–13.
14. Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? BMJ **2000**; 320:1197–1200.
15. Barber AE, Norton JP, Spivak AM, Mulvey MA. Urinary tract infections: current and emerging management strategies. Clin Infect Dis **2013**; 57:719–24.
16. Caldwell N, Srebotnjak T, Wang T, Hsia R. How much will I get charged for this?" Patient charges for top ten diagnoses in the emergency department. PLoS One **2013**; 8:e55491.
17. costhelper health. How much does urinary tract infection treatment cost? Available at: https://health.costhelper.com/uti.html. Accessed 22 February 2022.
18. Lodise TP, Chopra T, Nathanson BH, Sulham K. Hospital admission patterns of adult patients with complicated urinary tract infections who present to the hospital by disease acuity and comorbid conditions: how many admissions are potentially avoidable? Am J Infect Control **2021**; 49:1528–34.
19. Turner RM, Wu B, Lawrence K, Hackett J, Karve S, Tunceli O. Assessment of outpatient and inpatient antibiotic treatment patterns and health care costs of patients with complicated urinary tract infections. Clin Ther **2015**; 37:2037–47.
20. Schrock JW, Reznikova S, Weller S. The effect of an observation unit on the rate of ED admission and discharge for pyelonephritis. Am J Emerg Med **2010**; 28:682–8.
21. Kim K, Lee CC, Rhee JE, et al. The effects of an institutional care map on the admission rates and medical costs in women with acute pyelonephritis. Acad Emerg Med **2008**; 15:319–23.
22. Elkharrat D, Chastang C, Boudiaf M, Le Corre A, Raskine L, Caulin C. Relevance in the emergency department of a decisional algorithm for outpatient care of women with acute pyelonephritis. Eur J Emerg Med **1999**; 6:15–20.
23. Ward G, Jorden RC, Severance HW. Treatment of pyelonephritis in an observation unit. Ann Emerg Med **1991**; 20:258–61.
24. Dumkow LE, Beuschel TS, Brandt KL. Expanding antimicrobial stewardship to urgent care centers through a pharmacist-led culture follow-up program. Infect Dis Ther **2017**; 6:453–9.
25. Anesi JA, Lautenbach E, Nachamkin I, et al. The role of extended-spectrum cephalosporin-resistance in recurrent community-onset Enterobacteriaceae urinary tract infections: a retrospective cohort study. BMC Infect Dis **2019**; 19:163.
26. CDC/NHSN. CDC/NHSN surveillance definitions for specific types of infections 2016. Available at: http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf. Accessed 1 April 2022.
27. Lelie-van der Zande RC, Bouvy ML, Teichert AM. Patterns of recurring dispensing of guideline antibiotics for uncomplicated urinary tract infection in women over a 5-year period: longitudinal patterns of recurring dispensings of Dutch guideline UTI antibiotics. Fam Pract **2021**; 38:286–91.
28. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis **2011**; 52: e103-20.
29. Talan DA, Takhar SS, Krishnadasan A, et al. Emergence of extended-spectrum beta-lactamase urinary tract infections among hospitalized emergency department patients in the United States. Ann Emerg Med **2021**; 77:32–43.
30. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. J Hosp Med **2014**; 9:232–8.
31. Rank EL, Lodise T, Avery L, et al. Antimicrobial susceptibility trends observed in urinary pathogens obtained from New York state. Open Forum Infect Dis **2018**; 5: ofy297. doi: 10.1093/ofid/ofy297.
32. Sanchez GV, Babiker A, Master RN, Luu T, Mathur A, Bordon J. Antibiotic resistance among urinary isolates from female outpatients in the United States in 2003 and 2012. Antimicrob Agents Chemother **2016**; 60:2680–3.
33. Puttagunta S, Aronin S, Gupta V, et al. Impact of initial inappropriate antibiotic therapy on outcome for uncomplicated urinary tract infection due to antibiotic non-susceptible Enterobacteriaceae. Paper presented at: ECCMID; 21–24 April **2018**; Madrid, Spain.
34. Dunne M, Snow K, Mehta R. Failure of empiric treatment of uncomplicated urinary tract infection associated with resistant pathogens. Poster #4561. Poster presented at: ASM Microbe; 20–24 June **2019**; San Francisco, California (USA).
35. Jorgensen S, Zurayk M, Yeung S, et al. Risk factors for early return visits to the emergency department in patients with urinary tract infection. Am J Emerg Med **2018**; 36:12–7.
36. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med **2007**; 167:2207–12.
37. Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract

infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. Clin Infect Dis **2002**; 34:1165–9.
38. Jansaker F, Boel JB, Thonnings S, et al. Pivmecillinam compared to other antimicrobials for community-acquired urinary tract infections with *Escherichia coli*, ESBL-producing or not - a retrospective cohort study. Infect Drug Resist **2019**; 12:1691–1702.
39. Wagenlehner FME, Bjerklund Johansen TE, Cai T, et al. Epidemiology, definition and treatment of complicated urinary tract infections. Nat Rev Urol **2020**; 17: 586–600.
40. Karimaghaei S, Rao A, Chijioke J, Finch N, Nigo M. Characteristics, safety and cost-effectiveness analysis of self-administered outpatient parenteral antibiotic therapy via a disposable elastomeric continuous infusion pump at two county hospitals in Houston, Texas, United States. J Clin Pharm Ther **2021**; 47:211–7.
41. Cox AM, Malani PN, Wiseman SW, Kauffman CA. Home intravenous antimicrobial infusion therapy: a viable option in older adults. J Am Geriatr Soc **2007**; 55: 645–50.
42. Croll NA, Ghadirian E, Sukul NC. Exposure and susceptibility in human helminthiasis. Trop Doct **1982**; 12:136–8.
43. Underwood J, Marks M, Collins S, Logan S, Pollara G. Intravenous catheter-related adverse events exceed drug-related adverse events in outpatient parenteral antimicrobial therapy. J Antimicrob Chemother **2019**; 74:787–90.
44. Means L, Bleasdale S, Sikka M, Gross AE. Predictors of hospital readmission in patients receiving outpatient parenteral antimicrobial therapy. Pharmacotherapy **2016**; 36:934–9.
45. Lane MA, Marschall J, Beekmann SE, et al. Outpatient parenteral antimicrobial therapy practices among adult infectious disease physicians. Infect Control Hosp Epidemiol **2014**; 35:839–44.
46. Krah NM, Bardsley T, Nelson R, et al. Economic burden of home antimicrobial therapy: OPAT versus oral therapy. Hosp Pediatr **2019**; 9:234–40.
47. Keller SC, Wang NY, Salinas A, et al. Which patients discharged to home-based outpatient parenteral antimicrobial therapy are at high risk of adverse outcomes? Open Forum Infect Dis **2020**; 7:ofaa178. doi: 10.1093/ofid/ofaa178.
48. Keller SC, Cosgrove SE, Arbaje AI, et al. It's complicated: Patient and informal caregiver performance of outpatient parenteral antimicrobial therapy-related tasks. Am J Med Qual **2020**; 35:133–46.
49. Hale CM, Steele JM, Seabury RW, Miller CD. Characterization of drug-related problems occurring in patients receiving outpatient antimicrobial therapy. J Pharm Pract **2017**; 30:600–5.
50. Durojaiye OC, Kritsotakis EI, Johnston P, Kenny T, Ntziora F, Cartwright K. Developing a risk prediction model for 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy. Clin Microbiol Infect **2019**; 25:905 e901–7.
51. Allison GM, Muldoon EG, Kent DM, et al. Prediction model for 30-day hospital readmissions among patients discharged receiving outpatient parenteral antibiotic therapy. Clin Infect Dis **2014**; 58:812–9.
52. Veeraraghavan B, Bakthavatchalam YD, Sahni RD. Oral antibiotics in clinical development for community-acquired urinary tract infections. Infect Dis Ther **2021**; 10:1815–35.
53. Lodise T, Ye MJ, Zhao Q. Prevalence of invasive infections due to carbapenem-resistant Enterobacteriaceae among adult patients in US hospitals. Antimicrob Agents Chemother **2017**; 61:6.
54. Huang X, Peterson S, Lavergne R, Ahuja M, McGrail K. Predicting the cost of health care services: a comparison of case-mix systems and comorbidity indices that use administrative data. Med Care **2020**; 58:114–9.
55. Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Med Care **2012**; 50:1109–18.
56. Wiese AD, Griffin MR, Stein CM, et al. Validation of discharge diagnosis codes to identify serious infections among middle age and older adults. BMJ Open **2018**; 8: e020857.
57. Barber C, Lacaille D, Fortin PR. Systematic review of validation studies of the use of administrative data to identify serious infections. Arthritis Care Res **2013**; 65: 1343–57.
58. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol **2007**; 60:397–409.
59. Laan BJ, van Horrik T, Nanayakkara PWB, Geerlings SE. How many urinalysis and urine cultures are necessary? Eur J Intern Med **2021**; 83:58–61.
60. Daniel M, Keller S, Mozafarihashjin M, Pahwa A, Soong C. An implementation guide to reducing overtreatment of asymptomatic bacteriuria. JAMA Intern Med **2018**; 178:271–6.
61. Shah A, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Application of fluoroquinolone resistance score in management of complicated urinary tract infections. Antimicrob Agents Chemother **2017**; 61:e02313–6.

Appendix A. Description of MarketScan Databases

The MarketScan Commercial Database contained the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents, covered under a variety of fee-for-service and managed care health plans, including exclusive provider organizations, PPOs, POS plans, indemnity plans, and health maintenance organizations. The MarketScan Medicare Supplemental Database contained the health care experience (both medical and pharmacy) of retirees with Medicare Supplemental insurance paid for by employers. Both MarketScan Databases provided detailed cost, use, and outcomes data for health care services performed in the inpatient and outpatient settings. The medical claims were linked to outpatient prescription drug claims and person-level enrollment data using unique enrollee identifiers. Health care costs were based on paid amounts of adjudicated claims, including insurer and health plan payments as well as patient cost-sharing in the form of copayment, deductible, and coinsurance. Cost for services provided under capitated arrangements were estimated using payment proxies based on paid claims at the procedure level using the MarketScan Commercial and Medicare Supplemental databases. The MarketScan databases contain an indicator variable on whether claims are capitated ($0 costs). A payment proxy is built based on the average cost by procedure, region payer, and calendar year for commercial and Medicare databases separately and is applied to assign a market value to capitated claims, thus keeping them for cost analyses. Capitated claims make up a small proportion of the commercial and Medicare databases. Abbreviations: POS, point of service; PPO, preferred provider organization.

Appendix B. Diagnosis and Procedure Codes Used to Identify cUTIs

To identify a cUTI, patients were required to have ≥1 inpatient or outpatient claim with a diagnosis code in any position from Group A or ≥1 inpatient or outpatient claim with a diagnosis code in any position from Group B and ≥1 inpatient or outpatient claim with a diagnosis or procedure code in any position from Group C within 7 days of each other.

ICD-10-CM Diagnosis Code	Description	Group
N10	Acute tubulo-interstitial nephritis	A
N110	Nonobstructive reflux–associated chronic pyelonephritis	A
N118	Other chronic tubulo-interstitial nephritis	A
N12	Tubulo-interstitial nephritis, not specified as acute or chronic	A
N151	Renal and perinephric abscess	A
N159	Renal tubulo-interstitial disease, unspecified	A
N16	Renal tubulo-interstitial disorders in diseases classified elsewhere	A

Continued

ICD-10-CM Diagnosis Code	Description	Group
N2884	Pyelitis cystica	A
N2885	Pyeloureteritis cystica	A
N2886	Ureteritis cystica	A
N35111	Postinfective urethral stricture, not elsewhere classified, male, meatal	A
N35112	Postinfective bulbous urethral stricture, not elsewhere classified	A
N35113	Postinfective membranous urethral stricture, not elsewhere classified	A
N35114	Postinfective anterior urethral stricture, not elsewhere classified	A
N35116	Postinfective urethral stricture, not elsewhere classified, male, overlapping sites	A
N35119	Postinfective urethral stricture, not elsewhere classified, male, unspecified	A
N3512	Postinfective urethral stricture, not elsewhere classified, female	A
T83510A	Infection and inflammatory reaction due to cystostomy catheter, initial encounter	A
T83511A	Infection and inflammatory reaction due to indwelling urethral catheter, initial encounter	A
T83512A	Infection and inflammatory reaction due to nephrostomy catheter, initial encounter	A
T83518A	Infection and inflammatory reaction due to other urinary catheter, initial encounter	A
N139	Obstructive and reflux uropathy, unspecified	B
N3000	Acute cystitis without hematuria	B
N3001	Acute cystitis with hematuria	B
N3010	Interstitial cystitis (chronic) without hematuria	B
N3011	Interstitial cystitis (chronic) with hematuria	B
N3020	Other chronic cystitis without hematuria	B
N3021	Other chronic cystitis with hematuria	B
N3030	Trigonitis without hematuria	B
N3031	Trigonitis with hematuria	B
N3040	Irradiation cystitis without hematuria	B
N3041	Irradiation cystitis with hematuria	B
N3080	Other cystitis without hematuria	B
N3081	Other cystitis with hematuria	B
N3090	Cystitis, unspecified without hematuria	B
N3091	Cystitis, unspecified with hematuria	B
N340	Urethral abscess	B
N341	Nonspecific urethritis	B
N342	Other urethritis	B
N343	Urethral syndrome, unspecified	B
N35014	Post-traumatic urethral stricture, male, unspecified	B
N35028	Other post-traumatic urethral stricture, female	B
N358	Other urethral stricture	B
N35811	Other urethral stricture, male, meatal	B
N35812	Other urethral bulbous stricture, male	B
N35813	Other membranous urethral stricture, male	B
N35814	Other anterior urethral stricture, male	B
N35816	Other urethral stricture, male, overlapping sites	B
N35819	Other urethral stricture, male, unspecified site	B
N3582	Other urethral stricture, female	B
N359	Urethral stricture, unspecified	B
N35911	Unspecified urethral stricture, male, meatal	B
N35912	Unspecified bulbous urethral stricture, male	B
N35913	Unspecified membranous urethral stricture, male	B
N35914	Unspecified anterior urethral stricture, male	B
N35916	Unspecified urethral stricture, male, overlapping sites	B
N35919	Unspecified urethral stricture, male, unspecified site	B
N3592	Unspecified urethral stricture, female	B
N360	Urethral fistula	B
N361	Urethral diverticulum	B
N362	Urethral caruncle	B
N365	Urethral false passage	B
N368	Other specified disorders of urethra	B

Continued

ICD-10-CM Diagnosis Code	Description	Group
N99110	Postprocedural urethral stricture, male, meatal	B
N99111	Postprocedural bulbous urethral stricture, male,	B
N99112	Postprocedural membranous urethral stricture, male	B
N99113	Postprocedural anterior bulbous urethral stricture, male	B
N99114	Postprocedural urethral stricture, unspecified	B
N99115	Postprocedural fossa navicularis urethral stricture	B
N99116	Postpore ureal urethral stricture, overlapping sites	B
N9912	Postprocedural urethral stricture, female	B
N37	Urethral disorders in diseases classified elsewhere	B
N390	Urinary tract infection, site not specified	B
N1330	Unspecified hydronephrosis	C
N1339	Other hydronephrosis	C
N139	Obstructive and reflux uropathy, unspecified	C
N200	Calculus of kidney	C
N201	Calculus of ureter	C
N202	Calculus of kidney with calculus of ureter	C
N209	Urinary calculus, unspecified	C
N312	Flaccid neuropathic bladder, not elsewhere classified	C
N319	Neuromuscular dysfunction of bladder, unspecified	C
N320	Bladder–neck obstruction	C
N3289	Other specified disorders of bladder	C
N329	Bladder disorder, unspecified	C
N3644	Muscular disorders of urethra	C
N400	Benign prostatic hyperplasia without lower urinary tract symptoms	C
N401	Benign prostatic hyperplasia with lower urinary tract symptoms	C
N402	Nodular prostate without lower urinary tract symptoms	C
N403	Nodular prostate with lower urinary tract symptoms	C
N4283	Cyst of prostate	C
N99510	Cystostomy hemorrhage	C
N99511	Cystostomy infection	C
N99512	Cystostomy malfunction	C
N99518	Other cystostomy complication	C
Q6210	Congenital occlusion of ureter, unspecified	C
Q6211	Congenital occlusion of ureteropelvic junction	C
Q6212	Congenital occlusion of ureterovesical orifice	C
Q6231	Congenital ureterocele, orthotopic	C
Q6239	Other obstructive defects of renal pelvis and ureter	C
R338	Other retention of urine	C
R339	Retention of urine, unspecified	C
R3914	Feeling of incomplete bladder emptying	C
Z436	Encounter for attention to other artificial openings of urinary tract	C
Z466	Encounter for fitting and adjustment of urinary device	C
ICD-10-PCS code	Description	Group
0T9B70Z	Drainage of bladder with drainage device, via natural or artificial opening	C
0T9B80Z	Drainage of bladder with drainage device, via natural or artificial opening endoscopic	C
0T2BX0Z	Change drainage device in bladder, external approach	C
3C1ZX8Z	Irrigation of indwelling device using irrigating substance, external approach	C
CPT code	Description	Group
51702	Insertion of temporary indwelling bladder catheter; simple (eg, Foley)	C
51703	Insertion of temporary indwelling bladder catheter; complicated (egg, altered anatomy, fractured catheter/balloon)	C

Abbreviations: CPT, current procedural terminology; cUTI, complicated urinary tract infection; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; ICD-10-PCS, International Classification of Diseases, Tenth Revision, Procedure Coding System.