

SUPPLEMENTARY MATERIAL

Treatment Patterns and Adherence to Guidelines for Uncomplicated Urinary Tract Infection in Germany: A Retrospective Cohort Study

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INTRODUCTION

The main manuscript covers the analyses of physician treatment patterns and adherence to uncomplicated urinary tract infection (uUTI) prescribing guidelines in Germany. Please refer to the main paper for details of the study design and patient population. This supplement includes details of secondary/exploratory analyses, which had the following objectives:

1. To assess follow-up uUTI-related healthcare resource utilization (HCRU) and follow-up all-cause HCRU (per index uUTI episode and over 1-year follow-up);
2. To assess follow-up uUTI-related healthcare (HC) costs, and follow-up all-cause HC costs (per index uUTI episode and over 1-year follow-up);
3. To examine uUTI recurrence by additional episodes in the 1-year follow-up period;
4. To examine progression to sepsis, bacteremia, or pyelonephritis in the index episode.

HCRU and HC Costs (per Index uUTI Episode and 1-Year Follow-Up Period)

uUTI-related and all-cause HCRU were examined during the index uUTI episode and the 1-year follow-up period. HCRU endpoints included the number of inpatient visits, number of emergency department (ED) visits, number of outpatient visits, and number of prescriptions. Costs were defined as uUTI-related costs if the primary diagnosis was a urinary tract infection (UTI). Costs included inpatient stay costs, outpatient ED visit costs, outpatient visit costs, pharmacy costs, and total all-cause/uUTI-related costs. Inpatient stay costs were the gross amount per inpatient stay in claims data if the admission date was within the index episode or 1-year follow-up. Outpatient ED visit costs were the gross amount per ED visit in claims data, if date of visit was within the index episode or 1-year follow-up. The index episode uUTI-related billing case (with a primary uUTI diagnosis) was the sum of all services documented in the billing office within the episode. The index episode total was the sum of all services documented during the index episode. The uUTI-related 1-year follow-up costs, if in the billing case the uUTI was documented, was all costs of the billing case, i.e., quarterly. The total HC costs included all costs in all billing cases in the index and four

follow-up quarters. Pharmacy costs were costs for all UTI-related antibiotic prescriptions (by the UTI-diagnosing physician) in the index episode or 1-year follow-up. Total uUTI-related costs were the sum of ED, outpatient, inpatient, and pharmacy costs.

Progression and Risk Factor Analysis

The number and proportion of patients with any diagnosis indicating uUTI disease progression were recorded. These included: acute pyelonephritis, bacteremia, or sepsis, as a primary diagnosis in the ED or inpatient setting. The diagnosis must have been more than 5 days after the index date, but within the index episode.

The impact of baseline patient and treatment factors on sub-optimal outcome, recurrent uUTI in follow-up, and progression in the ED/inpatient setting were analyzed to assess their potential influence as risk factors (based on the evaluated baseline variables).

Statistical Analysis

Comparisons were performed using standardized differences (STDs), with STDs > 10% considered clinically meaningful. All analyses were conducted using R (version 4.0.5). STDs were reported as 100 times their actual value to simplify interpretations and used to compare uUTI cases per key patient baseline characteristics. Multivariate analysis was used to compare appropriate and inappropriate treatment use, as well as sub-groups stratified by outcome (optimal vs sub-optimal), costs, recurrence, and progression. Multi-variate analysis was not applied in the absence of significant STDs.

The following statistical methods were used: negative binomial distribution and logit link for HCRU outcomes; gamma distribution and log link for cost outcomes; and a logistic regression using binomial distribution and logit link for recurrence and progression. Variables with a p -value ≤ 0.25 were selected and added to the multivariate model to account for potential differences between the two groups. The variables were evaluated using a stepwise approach, to demonstrate any difference of $\geq 10\%$ in the multivariate model. The

exponentiated coefficient and its *p*-value were provided to document differences between the two sub-cohorts.

RESULTS

uUTI-Related HCRU (per Index uUTI Episode and 1-Year Follow-Up Period)

The mean baseline total healthcare cost was €1039.32; the inappropriate treatment sub-cohort had a higher total cost than the appropriate treatment sub-cohort at baseline (€1056.04 vs €1008.83, respectively; Table S1). The mean index total healthcare cost was €53.79; the appropriate sub-cohort had a significantly higher total cost than the inappropriate treatment sub-cohort at index (€57.38 vs €51.83, respectively; Table S1). The mean total healthcare cost in the follow-up period was €199.57; the inappropriate treatment sub-cohort had a significantly higher total cost than the appropriate treatment sub-cohort at index (€207.41 vs €185.29, respectively; Table S1).

The mean number of uUTI-related inpatient visits in the index episode was 0.0015 in both the appropriate and inappropriate treatment cohorts. In the follow-up period, the mean number of visits was 0.012 for the appropriate treatment cohort and 0.015 for the inappropriate treatment cohort (Table S2).

The mean number of outpatient visits in the index episode was 1.68 for the appropriate treatment cohort and 1.76 for the inappropriate treatment cohort. In the follow-up period, these numbers increased to 4.70 and 5.15 visits, respectively. The mean number of outpatient visits in the index episode was 1.54 for the optimal outcome cohort and 2.85 visits for the sub-optimal outcome cohort. In the follow-up period, these numbers increased to 4.62 and 7.07 visits, respectively (Table S3).

The mean number of uUTI prescriptions in the appropriate treatment cohort was 1.13 for the index episode and 1.57 for the follow-up period. In the inappropriate treatment cohort,

the mean number of uUTI prescriptions was 1.11 for the index episode and 1.57 for the follow-up period.

All-Cause HCRU (per Index uUTI Episode and 1-Year Follow-Up Period)

The mean number of inpatient visits was slightly lower for the appropriate treatment cohort than the inappropriate treatment sub-cohort during the index episode (0.0122 and 0.0137, respectively) and the follow-up period (0.1966 and 0.2197, respectively; Table S4). The mean number of visits was lower for the optimal outcome cohort compared with the sub-optimal outcome cohort in both the index episode (0.010 and 0.031, respectively) and follow-up period (0.203 and 0.262, respectively; Table S5). The mean number of all-cause outpatient visits was lower in the appropriate treatment cohort than the inappropriate treatment cohort for both timespans (Table S4). The mean number of outpatient visits was lower in the optimal outcome group versus the sub-optimal outcome group for both timespans (Table S5).

The mean number of all-cause prescriptions was lower for the appropriate treatment cohort than the inappropriate cohort during both timespans. In the follow-up period, the maximum number of prescriptions received in the appropriate treatment cohort was lower than in the inappropriate treatment cohort (Table S4). Patients in the optimal outcome cohort had a lower mean number of prescriptions versus the sub-optimal outcome cohort in both the index episode and the follow-up period (Table S5).

uUTI-Related HC (per Index uUTI Episode and 1-Year Follow-Up Period)

The mean costs for uUTI-related inpatient visits within the index episode were €4.53 for the appropriate treatment cohort and €4.14 for the inappropriate treatment cohort. In the follow-up period, costs increased to €50.47 and €70.12, respectively (Table S4). By definition, no costs exist for the optimal outcome cohort during the index episode; the mean cost in the

sub-optimal cohort was €28.37. In the follow-up period, mean costs were €51.96 for the optimal outcome cohort and €126.17 for the sub-optimal outcome cohort (Table S5).

Mean costs for outpatient visits in the index episode were €33.08 in the appropriate treatment cohort and €31.75 in the inappropriate treatment cohort during the index episode. These costs increased to €107.83 and €114.22, respectively, in the follow-up period (Table S4). Mean costs in the index episode were €29.25 for the optimal outcome cohort and €48.95 for the sub-optimal outcome cohort group, increasing to €103.93 and €157.10, respectively, in the follow-up period (Table S5).

The mean cost of uUTI prescriptions in the index episode was €19.62 in the appropriate treatment cohort and €15.82 in the inappropriate treatment cohort. In the follow-up period, costs increased to €26.60 and €22.71, respectively (Table S4). Prescription costs in the index episode were €15.37 and €27.27 for the optimal outcome and suboptimal outcome cohorts, respectively. In the follow-up period, these costs increased to €21.95 and €36.11, respectively (Table S5).

All-Cause HC (per Index uUTI Episode and 1-Year Follow-Up Period)

All-cause inpatient visit costs were lower for the appropriate treatment cohort than the inappropriate treatment cohort in both the index episode and the follow-up period (Table S4). All-cause inpatient costs were lower in the optimal outcome cohort than the sub-optimal outcome cohort for both timespans (Table S5). Outpatient visit costs were almost the same for the appropriate treatment and inappropriate treatment cohorts in both the index episode and follow-up period (Table S4). Mean costs were lower in the optimal outcome cohort than the sub-optimal outcome cohort in both the index episode and the follow-up period (Table S5).

All-cause costs for prescriptions for the appropriate and inappropriate cohorts were similar in the index episode but lower for the appropriate than the inappropriate cohort in the

follow-up period (Table S4). Costs for prescriptions were lower in the optimal than in the sub-optimal cohort in both the index episode and follow-up period (Table S5).

Progression and Risk Factor Analysis

The number of patients with progression was lower in the appropriate treatment cohort ($n = 7$; 0.013%) than the inappropriate treatment cohort ($n = 14$; 0.015%). The number of patients with progression was higher in the sub-optimal outcome cohort ($n = 19$; 0.087%) than the optimal outcome cohort ($n = 2$; 0.001%).

Age in the population ranged from 12 to 108 years and represented a significant predictor of a sub-optimal outcome. The region of residence contributed significantly to the risk of sub-optimal outcome: South, West, and East Germany all had a lower risk of sub-optimal outcome than North Germany. Baseline costs in the outpatient setting and the baseline number of prescriptions increased the risk of a sub-optimal outcome.

Factors associated with a reduced risk of recurrence included receipt of treatment in East Germany and the comorbidities abdominal pain, bronchitis, obesity, and respiratory tract infection. A higher number of prescriptions during baseline increased the risk of recurrence.

The biggest risk factor for sub-optimal treatment was age; the remaining factors could be categorized as complications and previous uUTIs. The risk of recurrence was increased by baseline recurrence and sexual activity, which is known to increase the risk of uUTI.

Table S1 Baseline HCRU, HC, and recurrence between appropriate and inappropriate treatment cohorts

Variable	Overall	Appropriate treatment	Inappropriate treatment	STD (x100) ^a
Mean baseline HCRU, <i>n</i> (SD)				
Number of inpatient visits	0.09 (0.37)	0.089 (0.364)	0.098 (0.379)	1.488
LOS inpatient visits	0.47 (3.61)	0.444 (3.592)	0.489 (3.616)	0.800
Number of ED visits	0.09 (0.45)	0.094 (0.475)	0.083 (0.441)	1.632
Number of outpatient visits	13.93 (11.76)	13.802 (11.678)	14.006 (11.804)	1.127
Number of prescriptions	6.80 (9.63)	6.079 (8.664)	7.192 (10.100)	7.853
Mean baseline healthcare costs, € (SD)				
Inpatient visit costs	211.98 (1,266.81)	200.33 (1,251.63)	218.37 (1,275.01)	0.925
ED visit costs	20.89 (184.67)	23.30 (181.15)	19.56 (186.56)	1.322
Outpatient visit costs	588.74 (579.14)	592.30 (599.93)	586.78 (567.42)	0.604
Prescription costs	217.72 (1,285.17)	192.90 (756.99)	231.32 (1,497.51)	2.353
Total costs	1039.32 (2,066.75)	1008.83 (1,767.13)	1056.04 (2,213.71)	1.586
Baseline episodes and recurrence				
Mean number of episodes, <i>n</i> (SD)	0.05 (0.29)	0.048 (0.283)	0.053 (0.298)	1.190
Recurrent, <i>n</i> (proportion)	1718 (0.012)	536 (0.010)	1182 (0.013)	2.046

ED, emergency department; HCRU, healthcare resource utilization; LOS, length of stay; SD, standard deviation; STD, standardized differences.

^aDifferences are categorized via STDs. STDs were reported as 100 times the absolute value of the actual STD to simplify interpretation. STDs > 10% were considered clinically meaningful and are indicated by bold text.

Table S2 Comparison of HCRU outcomes between appropriate versus inappropriate treatment cohorts

Outcome variable	During	Appropriate treatment		Inappropriate treatment		STD	Ratio means	Effect	p-value
		Mean	SD	Mean	SD				
Number of uUTI-related inpatient visits	Follow-up	0.0115	0.1260	0.0152	0.1422	2.788	1.326	1.134	2.23E-02
	Index episode	0.0015	0.0397	0.0015	0.0407	0.167	1.046	0.903	4.97E-01
LOS of uUTI-related inpatient visits	Follow-up	0.1090	2.1233	0.1542	2.4402	1.977	1.415	1.046	7.75E-01
	Index episode	0.0109	0.5038	0.0121	0.5704	0.216	1.107	0.935	8.23E-01
Number of uUTI-related ED visits	Follow-up	0.0026	0.0586	0.0023	0.0556	0.557	0.877	0.991	9.43E-01
	Index episode	0.0015	0.0400	0.0011	0.0345	0.962	0.758	0.845	2.84E-01
Number of uUTI-related outpatient visits	Follow-up	4.7041	4.3563	5.1456	4.8640	9.561	1.094	1.047	1.58E-31
	Index episode	1.6823	1.1736	1.7640	1.2690	6.689	1.049	1.027	3.41E-10
Number of uUTI-related prescriptions	Follow-up	1.5686	1.0445	1.5695	1.0727	0.081	1.001	0.990	1.92E-02
	Index episode	1.1451	0.4092	1.1281	0.4086	4.161	0.985	0.981	2.53E-04

ED, emergency department; HCRU, healthcare resource utilization; LOS, length of stay; SD, standard deviation; STD, standardized difference; uUTI, uncomplicated urinary tract infection.

Table S3 Comparison of HCRU outcomes between optimal versus sub-optimal cohorts

Outcome variable	During	Optimal outcome		Sub-optimal outcome		STD	Ratio means	Effect	p-value
		Mean	SD	Mean	SD				
Number of uUTI-related inpatient visits	Follow-up	0.0111	0.1188	0.0295	0.2101	10.777	2.654	2.234	2.38E-47
	Index episode	0	0	0.0100	0.1035	13.647			
LOS of uUTI-related inpatient visits	Follow-up	0.1134	2.1229	0.2775	3.2693	5.953	2.447	2.372	2.57E-04
	Index episode	0	0	0.0773	1.4085	7.762			
Number of uUTI-related ED visits	Follow-up	0.0022	0.0542	0.0036	0.0689	2.286	1.657	1.793	1.89E-04
	Index episode	0.0011	0.0336	0.0023	0.0497	2.887	2.149	2.447	3.13E-07
Number of uUTI-related outpatient visits	Follow-up	4.6200	4.3960	7.0675	5.6805	48.190	1.530	1.430	0.00E+00
	Index episode	1.5373	0.9795	2.8484	1.8105	90.078	1.853	1.797	0.00E+00
Number of uUTI-related prescriptions	Follow-up	1.4428	0.9351	2.2806	1.4034	70.259	1.581	1.542	0.00E+00
	Index episode	1.0251	0.1599	1.7481	0.7214	138.370	1.705	1.704	0.00E+00

ED, emergency department; HCRU, healthcare resource utilization; LOS, length of stay; SD, standard deviation; STD, standardized difference; uUTI, uncomplicated urinary tract infection.

^aDifferences are categorized via STDs. STDs were reported as 100 times the absolute value of the actual STD to simplify interpretation.

STDs >10% were considered clinically meaningful and are indicated by bold text.

Table S4 uUTI-related healthcare costs between appropriate versus inappropriate cohorts

Outcome variable	During	Appropriate treatment		Inappropriate treatment		STD	Ratio means	Effect	p-value
		Mean (€)	SD (€)	Mean (€)	SD (€)				
uUTI-related inpatient visits costs	Follow-up	50.47	1,361.61	70.12	1,551.36	1.346	1.389		
	Index episode	4.53	189.45	4.14	163.97	0.219	0.914	0.943	8.30E-01
uUTI-related ED visits costs	Follow-up	0.39	13.49	0.36	15.59	0.188	0.930	1.030	8.91E-01
	Index episode	0.15	4.62	0.11	3.74	0.870	0.753	0.786	2.93E-01
uUTI-related outpatient visits costs	Follow-up	107.83	104.79	114.22	112.90	5.863	1.059	1.000	9.82E-01
	Index episode	33.08	31.47	31.75	30.01	4.316	0.960	0.950	2.38E-23
uUTI-related prescriptions costs	Follow-up	26.60	18.92	22.71	19.03	20.474	0.854	0.841	0.00E+00
	Index episode	19.62	7.14	15.82	8.22	49.320	0.807	0.801	0.00E+00
Total uUTI-related costs	Follow-up	185.29	1,372.22	207.41	1,563.97	1.503	1.119	0.963	3.84E-01
	Index episode	57.38	193.16	51.83	168.06	3.064	0.903	0.879	1.40E-16

ED, emergency department; SD, standard deviation; STD, standardized difference; uUTI, uncomplicated urinary tract infection.

^aDifferences are categorized via STDs. STDs were reported as 100 times the absolute value of the actual STD to simplify interpretation.

STDs > 10% were considered clinically meaningful and are indicated by bold text.

Table S5 uUTI-related healthcare costs between optimal versus sub-optimal cohorts

Outcome variable	During	Optimal outcome		Sub-optimal outcome		STD	Ratio means	Effect	p-value
		Mean (€)	SD (€)	Mean (€)	SD (€)				
uUTI-related inpatient visits costs	Follow-up	51.96	1281.83	126.17	2324.47	3.954	2.428		
	Index episode	0.00	0.00	28.37	445.74	9.002			
uUTI-related ED visits costs	Follow-up	0.36	15.52	0.42	10.58	0.423	1.155	1.559	1.11E-01
	Index episode	0.11	3.83	0.22	5.25	2.460	2.054	2.721	2.16E-03
uUTI-related outpatient visits costs	Follow-up	103.93	102.77	157.10	136.24	44.059	1.512	1.398	0.00E+00
	Index episode	29.25	26.54	48.95	43.45	54.706	1.673	1.654	0.00E+00
uUTI-related prescriptions costs	Follow-up	21.95	16.56	36.11	26.44	64.185	1.645	1.603	0.00E+00
	Index episode	15.37	4.54	27.27	13.93	114.905	1.774	1.771	0.00E+00
Total uUTI-related costs	Follow-up	178.21	1,292.86	319.80	2,338.26	7.494	1.795	1.580	1.35E-14
	Index episode	44.73	27.31	104.81	448.66	18.904	2.343	2.254	0.00E+00

ED, emergency department; LOS, length of stay; SD, standard deviation; STD, standardized difference; uUTI, uncomplicated urinary tract infection.

^aDifferences are categorized via STDs. STDs were reported as 100 times the absolute value of the actual STD to simplify interpretation. STDs > 10% were considered clinically meaningful and are indicated by bold text.