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The cost of hospitalised patients due to complicated urinary tract infections – A retrospective observational study in countries with high prevalence of multidrug resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study

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Title: The cost of hospitalised patients due to complicated urinary tract infections – A retrospective observational study in countries with high prevalence of multidrug resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study

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Abstract

Objective: Complicated urinary tract infections (cUTI) impose a high burden on healthcare systems and are a frequent cause of hospitalisation. The aims of this paper are to estimate the cost per episode of patients hospitalised due to cUTI and to explore the factors associated with cUTI-related healthcare costs in eight countries with high prevalence of multidrug resistance (MDR).

Design: This is a multinational observational, retrospective study. The mean cost per episode was computed by multiplying the volume of healthcare use for each patient by the unit cost of each item of care, and summing across all components. Costs were measured from the hospital perspective. Patient-level regression analyses were used to identify the factors explaining variation in cUTI-related costs.

Setting: The study was conducted in 20 hospitals in 8 countries with high prevalence of multidrug resistant Gram-negative bacteria (Bulgaria, Greece, Hungary, Israel, Italy, Romania, Spain and Turkey).

Participants: Data were obtained from 644 episodes of patients hospitalised due to cUTI.

Results: The mean cost per case was 5,700€, with considerable variation between countries (largest value 7,740€ in Turkey; lowest value 4,028€ in Israel), mainly due to differences in length of hospital stay. Factors associated with higher costs per patient were: type of admission, infection source, infection severity, the Charlson comorbidity index and presence of MDR.

Conclusions: The mean cost per hospitalised case of cUTI was substantial and varied significantly between countries. A better knowledge of the reasons for variations in length of stays could facilitate a better standardised quality of care for patients with cUTI and allow a more efficient allocation of healthcare resources. Urgent admissions,

infections due to an indwelling urinary catheterisation, resulting in septic shock or severe sepsis, in patients with comorbidities and presenting MDR were related to a higher cost.

Strengths and limitations of the study

- This is the first study to examine costs of hospitalised patients due to cUTI from a multinational point of view.
- It is focused on countries with a high prevalence of MDR bacteria where cUTI impose a significant burden.
- The study estimates the mean cost per case from a bottom-up perspective, which provided a high level of granularity and the basis for the assessment of sources of variation and drivers of healthcare costs.
- The design of the study did not include a control group to assess the extra length of stay and excess costs of patients who are admitted to hospital due to a different condition and develop UTI during their hospitalisation.
- Country-specific unit cost data was not appropriate for most countries and therefore we applied the same set of unit costs, as estimated in one country, Spain, to the rest of the countries.

INTRODUCTION

Urinary tract infections (UTIs) are highly prevalent worldwide. UTIs that occur in a normal genitourinary tract with no prior instrumentation are considered uncomplicated, whereas complicated UTIs (cUTIs) are associated with structural or functional abnormalities of the genitourinary tract or an underlying disease that interferes with host defence [1]. cUTIs are a frequent cause of hospitalisation as well as a common

complication during hospitalisation and have shown a higher prevalence of antimicrobial resistance compared to uncomplicated UTI [2]. Due to the rapid emergence and dissemination of resistance to antimicrobial agents, leading in some cases to multidrug resistance (MDR), some patients with cUTI are left with few therapeutic options and may progress to more serious stages of the disease [3].

Currently, information about the burden of cUTI is scarce. Reports from the USA show that in the year 2000 cUTI accounted for more than 100,000 hospital admissions, often as a result of pyelonephritis [4]. Data from Europe are very limited, although the last point prevalence survey of European acute care hospitals estimated the prevalence of healthcare-associated infections (HAIs) to be 6%; of these, UTI was the third most common infection (19%) [5]. Based on these point prevalence data, the annual health burden of hospitalised UTI patients was estimated to be 81.2 disability-adjusted life years (DALYs) per 100,000 individuals in the general population [6].

Despite this high burden to healthcare systems and the increased pressure for cost containment in healthcare, few studies have examined the costs of cUTIs. Some papers have measured the cost of community-acquired UTIs [7, 8, 9, 10] and nosocomial UTIs [11, 12], or both [13]. Most of these studies were conducted in the USA [7, 8, 11, 12, 13], while studies undertaken in European countries have mainly focused on women visiting primary care settings with suspected UTIs [9, 10]. Some papers have estimated the impact of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) on the cost of UTI episodes requiring hospitalisation [14, 15]. Estimating the magnitude of the financial impact of this prevalent and potentially avoidable condition is particularly useful for measuring the potential cost savings from averting a case, thereby emphasising the importance of prevention and the sizeable economic consequences of MDR. In addition, cost estimates might inform cost-effectiveness analyses that require data on episode costs in order to compare alternative courses of treatment related to this condition. Therefore, there is a need for

data on the economic burden imposed to healthcare systems due to hospitalised cUTI patients, especially in countries with high prevalence of MDR.

In this paper we present an analysis of the economic burden of cUTI in seven European countries plus Israel, all of which have a high prevalence of MDR. The aims of this study are to estimate the cost per case of hospitalised patients due to cUTI and to investigate the factors associated with cUTI-related health care costs.

The analyses reported in this paper are part of a larger project, "REtrospective observational Study to assess the clinical management and outcomes of hospitalised patients with Complicated Urinary tract INfection in countries with high prevalence of multidrug resistant Gram-negative bacteria (RESCUING study)", with an overall aim of providing information about the epidemiology, clinical management, outcomes and healthcare costs of patients hospitalised with cUTI.

MATERIALS AND METHODS

Setting

This is a multinational observational, retrospective study conducted in 20 hospitals in 8 countries (Bulgaria, Greece, Hungary, Israel, Italy, Romania, Spain and Turkey). Data were collected on patients who had a diagnosis of cUTI as the primary cause of hospitalisation and patients hospitalised for another reason but who developed cUTI during their hospitalisation from January 2013 to December 2014, based on ICD-9 and ICD-10 codes (ICD-9 CM Codes: 590.1, 590.10, 590.11, 590.2, 590.8, 590.80, 590.9, 595.0, 595.89, 595.9, 599.0; ICD-10 CM Codes: N10, N12, N13.6, N15.1, N15.9, N30.0, N30.8, N30.9, N39.0). The study protocol has been published elsewhere [16].

In order to avoid selection bias, all consecutive patients who had ICD-9 or ICD-10 CM codes were reviewed at each site. All patients who met the inclusion criteria as described in [16] were selected for data collection. The analysis presented in this paper

focuses on patients admitted to hospital because of cUTI only; we do not include patients admitted for other reasons who developed cUTI during hospitalisation. The reason is that in the case of latter it is not possible to isolate the incremental cost of cUTI without a matched control group, i.e., comparing similar patients with and without cUTI during their hospital stay (see e.g. [17]).

Study data collection

Data were collected retrospectively for all cUTI episodes at participating hospitals during the study period. Local ethical approval was obtained from each site. For all patients, a standardised set of information was recorded. This included demographics, comorbidities including those required to calculate a modified Charlson score [18], place of acquisition of infection, infection source and severity, microbiological data, imaging test data, infection management, antibiotic therapy, outcomes, details of discharge and readmissions. The follow-up period was 2 months after discharge from the admitting hospital

The perspective of the cost analysis was the hospital provider, as we focus on hospitalised cUTI patients and this is where the majority of the cost burden falls [19, 20].

Study size was defined based on the primary outcome measure of the main study, i.e. treatment failure rate between MDR bacteria and other pathogens [16].

Estimating the cost per case of cUTI

We collected information on healthcare resource utilisation attributed to cUTI for each episode in the dataset. The healthcare components collected were: *i)* length of hospital stay (LOS) (general ward, ICU), *ii)* diagnostic and follow up tests, *iii)* urological interventions and haemodialysis, *iv)* antibiotic treatment before, during and after hospitalisation, and *v)* hospital readmissions and outpatient visits within 60 days of

discharge. For each component, a comprehensive list of specific items was compiled and reviewed by a clinical expert so that it included only healthcare resources that could be attributed to cUTI.

Unit cost data for each cost item were collected for each country by means of a questionnaire sent to the principal investigators of all participating sites. The questionnaire was provided as an online and paper version, and included the list of all healthcare services identified for the management of cUTI (see Supplementary material 1). The response rate for the questionnaire was 90% (18 out of 20). We received at least one response from each country. However, despite efforts to facilitate the complete fulfilment and harmonisation of the questionnaires, responses from some of the sites had missing values for key healthcare costs items, such as the cost of a day in hospital and for the most frequent diagnostic tests and treatment procedures. Furthermore, some sites provided the data in terms of user charges instead of the cost incurred by the hospital in the provision of the services. As a result, we observed a large degree of variation in unit costs across sites that was not attributable only to differences in actual costs between regions. Therefore, we generated a single set of unit costs based on the mean values across three sites within the same country, Spain, which provided consistently estimated values reflecting hospital costs for all the items included in the questionnaire. Using a common set of unit costs across all patients means that any observed variation in costs is due to differences in healthcare resource use. We discuss the limitations of this approach in the discussion section.

Unit cost data were attached to each item of healthcare use. For antibiotic therapy we estimated the cost per mg for each drug for which unit cost data was available, and applied the mean cost per mg to the remaining therapies. We estimated the cost per day with antibiotic therapy based on the dosage and frequency recorded for each drug, which was then combined with the duration of the treatment to estimate total antibiotic therapy costs. Patients might receive more than one antibiotic drug at the same time; in

that case they count as separate antibiotic therapy days. Patients with total hospital LOS >200 days were excluded (3 observations) as these were deemed to be due to coding errors.

We computed means and standard deviations as well as medians and interquartile ranges for the cost per case, and we quantified the contribution of each cost item and overall healthcare component to the total cost per case. We also present variations in the overall cost per case by country and for different cost components. All costs were reported in 2016 euros.

Costs were calculated for each case of cUTI requiring a hospital admission. If a patient required a second hospital admission, then if this occurred within 60 days of discharge of the first admission it was counted as a readmission and included in the cost of the first admission. If another admission occurred after 60 days post discharge (either of the index admission or a readmission) then this was counted as a separate case (observation) in the data.

Factors associated with cUTI-related healthcare costs

The analysis of the factors associated with cUTI-related healthcare costs was undertaken using multivariate regression analysis using patient level cost data. The dependent variable was total cost per patient estimated as described above.

To account for skewness of the cost data, generalised linear models with gamma family and log link were used [21]. We also considered using log Normal, Gaussian, inverse Gaussian and negative binomial distributions, but the gamma model gave the best fit in terms of the Akaike Information Criterion. The explanatory variables were demographic factors (age and gender), comorbidities measured by the Charlson morbidity index [18], admission characteristics (urgent versus elective; and admitted from home versus from another facility), infection severity (defined as septic shock or severe sepsis), source of infection (indwelling urinary catheterisation, pyelonephritis,

and other sources), antibiotic resistance profile (defined as non-susceptibility to at least one agent in three or more antimicrobial categories [22]), episode number and 30-day mortality. We did not include as explanatory variables any of the variables used to construct the total cost per patient. We also exclude variables with a high collinearity (r>0.6). We ran three sets of models: i) univariate regression models for each variable separately, ii) a multivariate model including all the covariates, and iii) a reduced multivariate model including only significant variables (where in the case of categorical variables, at least one indicator was non-significant). The variable selection in the reduced model was undertaken using forward and backward inclusion methods. P-values below the 5% level are regarded as statistically significant. Values between 5 and 10% are regarded as weakly significant.

For the quantitative interpretation of the effect of each variable, we computed marginal effects at the mean values of the included covariates. The impact of unobserved heterogeneity due to the hierarchical structure of the data is explored and accounted for by considering country fixed effects models. We also adjust for clustering at the site level and control for the patient episode number. Analyses were undertaken using Stata version 12.

RESULTS

Study population characteristics

Data was collected on 653 cUTI episodes in 637 patients (mean number of episodes per patient, 1.04). There were missing data on LOS for nine episodes, so mean costs per case were computed for 644 cases.

Fifty seven percent of the cohort were females and the mean age was 65.7 years (Table 1). Mean Charlson comorbidity score was 2.4. Ninety one percent of admissions were urgent (as opposed to elective) and 85% of the patients were admitted from home (as opposed from another facility). The infection source was indwelling urinary

catheterisation in 20% of cases, pyelonephritis in 27% of cases, and other sources (including anatomical urinary tract modification and obstructive uropathy) in the remaining 53%. Twenty six percent of the episodes were caused by MDR bacteria. The severity of the infection was categorised as severe sepsis or septic shock in 16% of cases. Five percent of the sample died within 30 days of discharge. The proportion of cases collected by each country ranged from 5% in Bulgaria to 26% in Israel.

Table 1. Summary statistics of cohort characteristics and regression analysis results of total cost per cUTI episode

	N (%) Mean (SD)[a]	Univariate analysis[b]	Multivariate analysis - Full model[c]	Multivariate analysis - Reduced model[d]
Demographics				
Age	65.7 (18.66)[a]	19.77	11.76	
Female	371 (58%)	-796.06	17.59	
Type of admission				
Urgent (vs. Elective)	585 (91%)	458.91	937.87**	991.32**
From home (vs. Other facility)	549 (85%)	-677.89	-577.62	
Infection source (vs. catheterisation)				
Pyelonephritis	171 (27%)	-1,673.18***	-1,802.63***	-1,891.57***
Other source	344 (53%)	-821.88	-709.83	-760.95*
Infection severity (vs. other)				
Septic shock/severe sepsis	100 (16%)	2,415.49***	1,671.77***	1,587.57**
Charlson Comorbidity Index	2.4 (2.39)[a]	324.34***	230.85**	263.48***
Episode number	1.04 (0.24)[a]	1,394.33***	355.91	
Mortality 30 days (yes vs. no)	29 (5%)	571.66	-934.75	
Multidrug resistant (yes vs. no)	166 (26%)	626.99	475.92	581.41*
Country (vs. Turkey)				
Greece	65 (10%)	-597.99	-1,503.81	-1,263.11
Hungary	49 (8%)	-1,734.5**	-2,757.06***	-2,768.68***
Israel	170 (26%)	-3,612.37***	-4,242.55***	-4,007.09***
Italy	36 (6%)	-319.91	-1,065.03*	-930.92
Romania	107 (17%)	-2,389.75***	-2,024.15***	-1,931.49***
Spain	126 (20%)	-819.22	-1,629.41***	-1,422.96**
Bulgaria	31 (5%)	-2,520.07***	-2,853.38***	-2,841.09***
Pseudo-R^2	N/A	N/A	0.111	0.105
Sample sizeb	644		636e	

Note:

*p<0.1.**p<0.05.***p<0.01.

aSummary statistics for continuous variables are shown as mean and standard deviations; for categorical variables we present total number of observation and percentage.

bMarginal effects of univariate regression models for each variable separately.

cMarginal effects of a multivariate model including all the covariates.

dMarginal effect of a reduced multivariate model including only significant variables.

eThere are 8 cases with missing data on mortality at 30 days. Therefore, the sample used in the regression analyses includes 636 cases out of the 644 cases for whom data on cost per case was available.

Estimating the cost per case of cUTI

Table 2 presents unit costs, resource use and total costs separately for each healthcare item as well as for each set of overall cost components. The mean (median) length of stay in hospital was 9 (7) days, and a small proportion of the total stay was in the ICU. Most patients had urine cultures, urinary sediment analyses and blood cultures undertaken, while imaging tests were rarely performed. The urological intervention most often performed was the insertion of an indwelling bladder-catheter. The mean number of antibiotic therapy days before, during and after hospitalisation were 2, 12 and 6 days, respectively. Nearly 10% of patients were readmitted to hospital due to a cUTI recurrence, with a mean readmission stay across the full sample of 1 day (11 days among the subsample of readmitted patients). The mean number of outpatient visits per patient within 60 days of hospital discharge was 0.8.

Table 2. Cost per case by cost component – all countries combined

	Unit cost (€)	Resource use (units)		Total cost (€)		
		Mean (SD)	Median [Q1-Q3]	Mean (SD)	Median [Q1-Q3]	%
Lenght of stay						
General ward (days)	477.4	9.25 (8.49)	7 [5-11]	4,418.5 (4052.4)	3,342 [2,387-5,252]	77.4%
ICU (days)	1,589.6	0.05 (1.19)	0 [0-0]	83.9 (1895.4)	0 [0-0]	1.5%
		9.30 (8.51)	7 [5-11]	4,502.4 (4389.9)	3,342 [2,387-5,252]	78.9%
Diagnostic tests						
Urine culture test	15.1	1.51 (0.82)	1 [1-2]	22.8 (12.5)	15 [15-30]	0.4%
Dipstick analysis	2.8	0.49 (0.85)	0 [0-1]	1.3 (2.3)	0 [0-3]	0.0%
Urinary sediment analysis	2.6	1.02 (0.89)	1 [0-1]	2.6 (2.3)	3 [0-3]	0.0%
Gram stain test	6.3	0.37 (0.68)	0 [0-1]	2.3 (4.2)	0 [0-6]	0.0%
Blood culture	36.7	1.43 (1.56)	1 [0-2]	52.5 (57.1)	37 [0-73]	0.9%
Abdominal Ultrasonography	48.9	0.71 (0.64)	1 [0-1]	34.5 (31.3)	49 [0-49]	0.6%
CT Scan	156.0	0.2 (0.46)	0 [0-0]	32 (72.5)	0 [0-0]	0.6%
Pyelography	105.1	0.02 (0.14)	0 [0-0]	2 (14.2)	0 [0-0]	0.0%
MRI scan	191.6	0 (0.07)	0 [0-0]	0.9 (13.1)	0 [0-0]	0.0%
				151 (109)	115 [75-201]	2.6%
Treatment procedures						
Insertion of catheter	50.0	0.36 (0.48)	0 [0-1]	17.8 (24)	0 [0-50]	0.3%

Replacement of catheter	50.0	0.13 (0.38)	0 [0-0]	6.5 (19)	0 [0-0]	0.1%
Percutaneous nephrostomy	717.6	0.05 (0.26)	0 [0-0]	37.9 (183.8)	0 [0-0]	0.7%
Insertion of JJ-stent	907.0	0.05 (0.21)	0 [0-0]	40.8 (188.2)	0 [0-0]	0.7%
Abscess drainage	557.6	0.01 (0.12)	0 [0-0]	6.9 (69.2)	0 [0-0]	0.1%
Nephrectomy	3,174.0	0.01 (0.08)	0 [0-0]	19.7 (249.6)	0 [0-0]	0.3%
Mechanical ventilation (days)	350.0	0.12 (0.99)	0 [0-0]	41.8 (346.4)	0 [0-0]	0.7%
Renal replacement (days)	254.7	0.16 (1.53)	0 [0-0]	41.9 (389.8)	0 [0-0]	0.7%
				213.4 (764.8)	0 [0-50]	3.7%
Antibiotic therapy						
Before hospitalisation (days)	1.9	1.95 (5.84)	0 [0-0]	2.6 (20.6)	0 [0-0]	0.0%
During hospitalisation (days)	12.3	12.25 (61.37)	7 [4-11]	197.8 (474.8)	19 [7-149]	3.5%
At discharge (days)	5.9	6 (13.61)	4.5 [0-8]	24.1 (117.5)	2 [0-10]	0.4%
		1.08 (4.53)	0 [0-0]	224.6 (490.3)	32 [14-199]	3.9%
After discharge						
Readmission (days)	477.4	1.08 (4.53)	0 [0-0]	515.2 (2163.4)	0 [0-0]	9.0%
Outpatients (visits)	122.3	0.81 (1.62)	0 [0-1]	99.2 (197.8)	0 [0-122]	1.7%
				614.4 (2197.5)	0 [0-245]	10.8%
Total (first hospital admission only)				**5,064 (4,847)**	**3,627 [2,531-5,985]**	**88.8%**
Total (first hospital admission + antibiotic treatment before & after discharge)				**5,091 (4,844)**	**3,651 [2,542-6,004]**	**89.2%**
Total (hospital admission + antibiotic treatment before & after discharge + readmissions & outpatients visits)				**5,705 (5,438)**	**3,919 [2,664-6,655]**	**100%**

*Unit costs estimated from the three Spanish sites

The mean (median) costs per case were: *i)* including costs incurred during the first hospital admission: 5,064€ (3,627€); *ii) i)* plus antibiotic therapy before and after discharge: 5,091€ (3,651€); and *iii*) *ii*) plus outpatient visits and hospital readmissions within 60 days of discharge: 5,705€ (3,919€).

The cost per case was largely driven by the cost due to the length of stay in hospital, which accounted for nearly 80% of the total cost. This was followed by the contribution of the cost of readmissions and outpatient visits after discharge (11%), treatment procedures (4%), antibiotic therapy (4%) and diagnostic tests (3%).

There was variation in the mean cost per cUTI case by country, with a largest mean (median) value of 7,740€ (5,962€) in Turkey and a lowest value of 4,028€ (3,159€) in Israel (Table 3). Note that variations in total costs shown in this table are only due to variations in the management of patients with cUTI, including LOS, as unit costs of healthcare services are held constant across all countries. Table 3 also shows variations by cost components between countries. This suggests that differences in

LOS are the main reason of the observed differences in total costs between countries; the mean stay in hospital in a general ward varies from 6 days in Israel to 14 days in Italy.

Table 3. Mean cost per case by cost component – by country

	N		Total cost (€)	LOS (€)	DIAG (€)	TREAT (€)	ATB (€)	DISCH (€)	LOS ward (days)	LOS ICU (days)
Bulgaria	31	**Mean (SD)**	4,907 (4,130)	3,943	111	298	355	200	8.26	0.00
		Median [Q1-Q3]	3,660 [3,187-5,258]	2,865	84	0	25	245	6.00	0.00
Greece	65	**Mean (SD)**	7,039 (5,786)	5,670	221	251	586	311	11.88	0.00
		Median [Q1-Q3]	5,581 [3,176-8,934]	4,774	213	50	70	122	10.00	0.00
Hungary	49	**Mean (SD)**	5,656 (5,591)	4,044	170	519	35	888	8.47	0.00
		Median [Q1-Q3]	3,765 [2,606-5,905]	2,865	137	0	19	122	6.00	0.00
Israel	170	**Mean (SD)**	4,028 (2,843)	3,061	133	60	132	641	6.41	0.00
		Median [Q1-Q3]	3,159 [2,254-4,666]	2,387	110	50	16	0	5.00	0.00
Italy	36	**Mean (SD)**	7,221 (8,271)	6,525	173	38	431	54	13.67	0.00
		Median [Q1-Q3]	5,052 [3,670-7,735]	4,536	145	0	268	0	9.50	0.00
Romania	107	**Mean (SD)**	5,024 (3,636)	4,493	107	10	125	288	9.41	0.00
		Median [Q1-Q3]	4,314 [3,096-5,849]	3,819	97	0	37	0	8.00	0.00
Spain	126	**Mean (SD)**	6,674 (6,200)	4,706	193	342	153	1,281	9.86	0.00
		Median [Q1-Q3]	3,992 [2,705-8,696]	3,103	141	0	45	122	6.50	0.00
Turkey	60	**Mean (SD)**	7,740 (8,006)	6,359	105	512	387	376	11.43	0.57
		Median [Q1-Q3]	5,962 [3,375-9,061]	4,774	106	50	101	0	9.00	0.00

*Holding unit costs constant. LOS = Length of stay; DIAG = Diagnostic test; TREAT = Treatment procedures; ATB = Antibiotic therapy; DISCH = After discharge (readmission and outpatient visits); ICU = Intensive Care Unit

Factors associated with cUTI-related health care costs

The statistically significant drivers of cUTI-related healthcare costs were (Table 1): type of admission (with urgent admissions exhibiting a higher cost than elective admissions); source of infection (with catheterisation associated to higher costs compared with other sources); the infection severity (septic shock and severe sepsis showing a larger cost); the Charlson comorbidity index (with larger values associated to a higher cost); MDR profile (episodes presenting MDR showing a higher cost; only significant at 10% significance level); and country (with most countries exhibiting a significant lower cost than Turkey).

DISCUSSION

In this study we have measured the cost per episode of patients hospitalised due to cUTI in eight countries with high prevalence of MDR, and explored the factors that explained variations in cUTI-related healthcare costs. The mean cost per hospitalised cUTI case in our data was estimated as 5,700€, corresponding to the costs of a hospital stay of 9 days on average and including the costs of specific diagnostic and treatment procedures, as well as antibiotic therapy, readmissions due to cUTI reoccurrence and outpatient visits after discharge. The cost per case varied across countries, mainly due to differences in LOS in hospital among patients with cUTI.

Over and above differences across countries, our analysis also identifies a series of factors associated with higher cUTI-related healthcare costs. Urgent admissions, for infections due to an indwelling urinary catheterisation, resulting in septic shock or severe sepsis, in patients with a higher comorbidity index and presenting MDR were related to a higher cost.

Our findings are in line with previous studies that have focused on similar patient groups. Esteve-Palau et al. 2015 [15] estimated a mean cost per patient hospitalised with symptomatic UTI caused by ESBL-producing *E. coli* of 4,980€ in one hospital in Spain, excluding readmissions. The cost was significantly lower, 2,612€, among patients with UTI due to non ESBL-producing *E. coli*. Cardwell et al. 2016 [13] analysed data on adults patients with a discharged diagnosis code for UTI in one hospital in the USA and found a mean hospitalisation cost of $7,586. The costs of nosocomial UTI infections and UTI infections seen in primary care have been shown to be lower. For instance, Saint, 2000 estimated the incremental cost of nosocomial UTIs of $676 and catheter-related bacteremia of $2,836 per case [12]. Tambyah et al., 2002 reported that the mean incremental hospitalisation cost attributable to nosocomial catheter-associated UTI was $589 [11]. On the other hand, studies that focused on UTI

infections treated in primary care have reported a mean cost between 70€ [9] and 236€ [10] per episode.

This is the first study to examine costs of hospitalised patients due to cUTI from a multinational point of view. Moreover, it is focused on countries with a high prevalence of MDR bacteria where cUTI impose a significant burden. In addition, the study estimated the mean cost per case from a bottom-up perspective, which provided a high level of granularity and the basis for the assessment of sources of variation and drivers of healthcare costs. However, the study also has a number of limitations. The design of the study did not include a control group to assess the extra length of stay and excess costs of patients who are admitted to hospital due to a different condition and develop UTI during their hospitalisation. Therefore, we focused in this paper on the analysis of patients who are admitted because of a cUTI. This is to avoid the overestimation that would result among cases admitted for other reasons for whom we cannot isolate the incremental costs that are due to cUTI only. A second limitation of the analysis is that, as discussed in the Methods section, country-specific unit cost data was not appropriate for most countries and therefore we applied the same set of unit costs, as estimated in one country, Spain, to the rest of the countries. While this approach allowed us to explore variations in healthcare costs that are due to differences in the management of cUTI patients across countries rather than due to differences in the unit costs of services, it limits the validity of the country-specific estimates. Related to this latter point, we also acknowledge that the number of observations included in the study for some countries is low, ranging from 31 to 170, which might restrict the generalisability of country-specific findings. The explanatory power of our models was also found to be low, which might suggest that there are other factors not captured by the observed variables included in our models that explain variation in health-care costs, such as hospital policy on LOS. Finally, the perspective of the analysis was that of the hospital provider, however if a societal perspective was considered wider costs

related to cUTI should had been taken into account such as patients' costs and productivity losses due to illness, as well as cost incurred by primary care settings; including these costs would increase the costs of cUTI.

In conclusion, this study showed the costs of patients hospitalised due to cUTI are substantial, but identified wide differences between countries, especially due to differences in length of stay in the hospital. These findings suggest that a better knowledge of the reasons for longer length of stays in some countries could facilitate a better standardised quality of care for patients with cUTI and to allow a more efficient allocation of healthcare resources. The factors associated with higher cUTI-related healthcare costs identified by this study also shed light onto some implications for policy and planning. Prompting preventive measures to minimise cost of hospitalisation might be aimed at increasing the population's knowledge of symptoms and signs of infection, in order to encourage patients to attend primary care facilities earlier, especially those with comorbidities or indwelling urinary catheters, and thus to avoid the development of severe forms of illness after the onset of symptoms and avoid the need for urgent admissions.

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Authors' contribution

Conceptualisation: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM; Acquisition of data: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM; Analysis of data: LVT, MP, ES, LL, SM; Writing–original draft preparation: LVT, MP, ES, LL, SM; Writing–review and editing: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM; Agree with manuscript results and conclusions: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM

Data sharing statement

Data are available through the authors upon request (and from the Dryad repository in due course).

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S1. Unit costs questionnaire

RESCUING ECONOMIC FORM

In the questionnaire below we ask for the unit costs of health care resources and services for the diagnosis, treatment and supportive care related to the management of cUTI. This information will allow us to estimate the cost per case as well as the total national burden of cUTI in your country. The questionnaire allows you to save the information already entered and to continue later. By using the same URL/web address, you will be able to continue where you left off.

What is the monetary unit you report in this form?

☐ Euro

☐ Other: _____

Hospital stays and visits

Please provide the unit cost per hospital stay day and outpatient visit in your hospital. Ideally we request the cost specifically among patients with cUTI (for example, the average cost among patients with discharge codes related to cUTI, e.g. ICD-9 CM Codes 590.1, 590.10, 590.11, 590.2, 590.8, 590.80, 590.9, 595.0, 595.89, 595.9, 599.0). If you are unable to provide the unit cost specifically for cUTI patients, please provide the average unit cost for the speciality that cUTI patients are treated in in your hospital (e.g., one of urology, gynaecology, general medicine). If costs are not available by specialty then please provide the average unit costs data across all patients in your hospital. Please specify the details of the data you are providing, such as the patients' ICD codes you used to compute the unit costs or whether the values are related to all types of patients.

Please fill in the table with the costs at your hospital even if you do not have data specifically for cUTI patients; it will be very useful for us, provided you explain in the Details section what these costs refer to.

	Cost per day/visit	Details
Hospital stay per diem in general ward		
Hospital stay per diem in ICU		
Outpatient hospital visit		

Procedures

Please provide the unit costs of the following procedures in your hospital. Next to each procedure we indicate the ICD9-CM procedures codes to make it simpler for you to identify the procedures we are interested in. Please specify the details of the data you are providing, such as the ICD9 codes or the specific name of the procedure you are providing data for.

If you have more than one cost for each procedure please provide the mean, ideally based on the proportion of patients receiving each procedure.

Procedure [ICD9-CM code]	Cost per procedure	Details
Urine culture [9132]		
Dipstick analysis [9139]		
Urinary sediment analysis [9133]		
Gram stain test [9131]		
Blood culture [9052]		

Abdominal Ultrasonography [8876]		
CT Scan [9218, 9219]		
Pyelography [8773, 8774, 8775]		
MRI scan [8895]		
Insertion of an indwelling bladder-catheter [5794]		
Percutaneous nephrostomy [5503, 5504]		
Insertion of JJ-stent [598]		
Abscess drainage [472, 5491]		
Nephrectomy [5501, 5502]		
	Cost per day	Details
Invasive mechanical ventilation [9670, 9671, 9672]		
Dialysis/Renal replacement therapy [3995, 5498]		

Antibiotic therapy

Please provide for the antibiotic therapies listed below the unit cost per dose and specify the relevant dose. Please respond only for the antibiotics used in your hospital, and if there are other antibiotics used frequently in your hospital which are not included in this list, please add them in the space provided.

Antibiotic (intravenous (IV)/oral administration)	Dose	Cost per dose
AMIKACIN (IV)	500 mg	
AMOXICILLIN (oral)	500 mg	
AMOXICILLIN (oral)	750 mg	
AMOXICILLIN (ORAL)	1000 MG	

AMOXICILLIN/CLAVULANIC ACID (IV)	1000/200 mg	
AMOXICILLIN/CLAVULANIC ACID (oral)	500/125 mg	
AMOXICILLIN/CLAVULANIC ACID (oral)	875/125 mg	
AMPICILLIN (IV)	1000 mg	
CEFIXIME (oral)	400 mg	
CEFIXIME (oral)	200 mg	
CEFTAZIDIME (IV)	2000 mg	
CEFTRIAXONE (IV)	1000 mg	
CEFUROXIME (IV)	750 mg	
CEFUROXIME (oral)	500 mg	
CEFUROXIME (oral)	250 mg	
CIPROFLOXACIN (oral)	500 mg	
CIPROFLOXACIN (oral)	750 mg	
CIPROFLOXACIN (IV)	200 mg	
COLISTIN (IV)	1 MUI	
CO-TRIMOXAZOL (oral)	400/80 mg	
CO-TRIMOXAZOLE (IV)	800/160 mg	
CO-TRIMOXAZOLE (IV)	400/80 mg	
CO-TRIMOXAZOLE (oral)	800/160 mg	
DAPTOMYCIN	500 mg	
ERTAPENEM (IV)	1000 mg	
FOSFOMYCIN (IV)	1000 mg	
FOSFOMYCIN (IV)	4000 mg	
FOSFOMYCIN (oral)	500 mg	
FOSFOMYCIN TROMETANOL (oral)	3000 mg	
FOSFOMYCIN TROMETANOL (oral)	2000 mg	
GENTAMICIN	240 mg	
IMIPENEM-CILASTATIN (IV)	500/500 mg	
LEVOFLOXACIN (IV)	500 mg	

LEVOFLOXACIN (oral)	500 mg	
LINEZOLID (IV)	600 mg	
LINEZOLID (oral)	600 mg	
MEROPENEM (IV)	1000 mg	
METRONIDAZOLE (IV)	500 mg	
METRONIDAZOLE (oral)	250 mg	
NITROFURANTOIN (oral)	100	
PIPERACILLIN + TAZOBACTAM (IV)	4000/500 mg	
PIPERACILLIN + TAZOBACTAM (IV)	3000/375 mg	
TEICOPLANIN (IV)	400 mg	
TRIMETHOPRIM	160 mg	
VANCOMYCIN (IV)	500 mg	
Name antibiotic 1		
Name antibiotic 2		
Name antibiotic 3		
Name antibiotic 4		
Name antibiotic 5		

Thank you for filling in this questionnaire.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9; 19
		(b) Give reasons for non-participation at each stage	9; 19
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9; 19
		(b) Indicate number of participants with missing data for each variable of interest	9; 19
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10; 20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11; 20
		(*b*) Report category boundaries when continuous variables were categorized	20-21
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The cost of hospitalised patients due to complicated urinary tract infections – A retrospective observational study in countries with high prevalence of multidrug resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Health economics
Keywords:	Urinary tract infections < UROLOGY, cost of illness, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title: The cost of hospitalised patients due to complicated urinary tract infections – A retrospective observational study in countries with high prevalence of multidrug resistant Gram-negative bacteria: the COMBACTE-MAGNET, RESCUING study

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Abstract

Objective: Complicated urinary tract infections (cUTI) impose a high burden on healthcare systems and are a frequent cause of hospitalisation. The aims of this paper are to estimate the cost per episode of patients hospitalised due to cUTI and to explore the factors associated with cUTI-related healthcare costs in eight countries with high prevalence of multidrug resistance (MDR).

Design: This is a multinational observational, retrospective study. The mean cost per episode was computed by multiplying the volume of healthcare use for each patient by the unit cost of each item of care, and summing across all components. Costs were measured from the hospital perspective. Patient-level regression analyses were used to identify the factors explaining variation in cUTI-related costs.

Setting: The study was conducted in 20 hospitals in 8 countries with high prevalence of multidrug resistant Gram-negative bacteria (Bulgaria, Greece, Hungary, Israel, Italy, Romania, Spain and Turkey).

Participants: Data were obtained from 644 episodes of patients hospitalised due to cUTI.

Results: The mean cost per case was 5,700€, with considerable variation between countries (largest value 7,740€ in Turkey; lowest value 4,028€ in Israel), mainly due to differences in length of hospital stay. Factors associated with higher costs per patient were: type of admission, infection source, infection severity, the Charlson comorbidity index and presence of MDR.

Conclusions: The mean cost per hospitalised case of cUTI was substantial and varied significantly between countries. A better knowledge of the reasons for variations in length of stays could facilitate a better standardised quality of care for patients with cUTI and allow a more efficient allocation of healthcare resources. Urgent admissions,

infections due to an indwelling urinary catheterisation, resulting in septic shock or severe sepsis, in patients with comorbidities and presenting MDR were related to a higher cost.

Strengths and limitations of the study

- This is the first study to examine costs of hospitalised patients due to cUTI from a multinational point of view.
- It is focused on countries with a high prevalence of MDR bacteria where cUTI impose a significant burden.
- The study estimates the mean cost per case from a bottom-up perspective, which provided a high level of granularity and the basis for the assessment of sources of variation and drivers of healthcare costs.
- The design of the study did not include a control group to assess the extra length of stay and excess costs of patients who are admitted to hospital due to a different condition and develop UTI during their hospitalisation.
- Country-specific unit cost data was not appropriate for most countries and therefore we applied the same set of unit costs, as estimated in one country, Spain, to the rest of the countries.

INTRODUCTION

Urinary tract infections (UTIs) are highly prevalent worldwide. UTIs that occur in a normal genitourinary tract with no prior instrumentation are considered uncomplicated, whereas complicated UTIs (cUTIs) are associated with structural or functional abnormalities of the genitourinary tract or an underlying disease that interferes with host defence [1]. cUTIs are a frequent cause of hospitalisation as well as a common

complication during hospitalisation and have shown a higher prevalence of antimicrobial resistance compared to uncomplicated UTI [2]. Due to the rapid emergence and dissemination of resistance to antimicrobial agents, leading in some cases to multidrug resistance (MDR), some patients with cUTI are left with few therapeutic options and may progress to more serious stages of the disease [3].

Currently, information about the burden of cUTI is scarce. Reports from the USA show that in the year 2000 cUTI accounted for more than 100,000 hospital admissions, often as a result of pyelonephritis [4]. Data from Europe are very limited, although the last point prevalence survey of European acute care hospitals estimated the prevalence of healthcare-associated infections (HAIs) to be 6%; of these, UTI was the third most common infection (19%) [5]. Based on these point prevalence data, the annual health burden of hospitalised UTI patients was estimated to be 81.2 disability-adjusted life years (DALYs) per 100,000 individuals in the general population [6].

Despite this high burden to healthcare systems and the increased pressure for cost containment in healthcare, few studies have examined the costs of cUTIs. Some papers have measured the cost of community-acquired UTIs [7, 8, 9, 10] and nosocomial UTIs [11, 12], or both [13]. Most of these studies were conducted in the USA [7, 8, 11, 12, 13], while studies undertaken in European countries have mainly focused on women visiting primary care settings with suspected UTIs [9, 10]. Some papers have estimated the impact of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) on the cost of UTI episodes requiring hospitalisation [14, 15]. Estimating the magnitude of the financial impact of this prevalent and potentially avoidable condition is particularly useful for measuring the potential cost savings from averting a case, thereby emphasising the importance of prevention and the sizeable economic consequences of MDR. In addition, cost estimates might inform cost-effectiveness analyses that require data on episode costs in order to compare alternative courses of treatment related to this condition. Therefore, there is a need for

data on the economic burden imposed to healthcare systems due to hospitalised cUTI patients, especially in countries with high prevalence of MDR.

In this paper we present an analysis of the economic burden of cUTI in seven European countries plus Israel, all of which have a high prevalence of MDR. The aims of this study are to estimate the cost per case of hospitalised patients due to cUTI and to investigate the factors associated with cUTI-related health care costs.

The analyses reported in this paper are part of a larger project, "REtrospective observational Study to assess the clinical management and outcomes of hospitalised patients with Complicated Urinary tract INfection in countries with high prevalence of multidrug resistant Gram-negative bacteria (RESCUING study)", with an overall aim of providing information about the epidemiology, clinical management, outcomes and healthcare costs of patients hospitalised with cUTI.

MATERIALS AND METHODS

Setting

This is a multinational observational, retrospective study conducted in 20 hospitals in 8 countries (Bulgaria, Greece, Hungary, Israel, Italy, Romania, Spain and Turkey). Data were collected on patients who had a diagnosis of cUTI as the primary cause of hospitalisation and patients hospitalised for another reason but who developed cUTI during their hospitalisation from January 2013 to December 2014, based on ICD-9 and ICD-10 codes (ICD-9 CM Codes: 590.1, 590.10, 590.11, 590.2, 590.8, 590.80, 590.9, 595.0, 595.89, 595.9, 599.0; ICD-10 CM Codes: N10, N12, N13.6, N15.1, N15.9, N30.0, N30.8, N30.9, N39.0). The study protocol has been published elsewhere [16].

In order to avoid selection bias, all consecutive patients who had ICD-9 or ICD-10 CM codes were reviewed at each site. All patients who met the inclusion criteria were selected for data collection. Inclusion criteria were patients with UTI **and** at least one of

the following: indwelling urinary catheter, urinary retention, neurogenic bladder, obstructive uropathy, renal impairment caused by intrinsic renal disease, renal transplantation, urinary tract modifications, pyelonephritis and normal urinary tract anatomy; **and** at least one of the following signs or symptoms: chills or rigors associated with fever or hypothermia, flank pain (pyelonephritis) or pelvic pain (cUTI), dysuria or urinary frequency, or urinary urgency, costo-vertebral angle tenderness on physical examination and either urine culture with at least 105 CFU/mL or greater of a uropathogen (no more than 2 species) or at least one blood culture growing possible uropathogens (no more than 2 species) with no other evident site of infection. These inclusion criteria are in accordance to the definition of cUTI provided in [17]. The analysis presented in this paper focuses on patients admitted to hospital because of cUTI only; we do not include patients admitted for other reasons who developed cUTI during hospitalisation. The reason is that in the case of latter it is not possible to isolate the incremental cost of cUTI without a matched control group, i.e., comparing similar patients with and without cUTI during their hospital stay (see e.g. [18]). Our data indicates that the proportion of cUTI that are the cause of hospital admission is 65% versus a 35% that develop cUTI during hospitalisation.

Study data collection

Data were collected retrospectively for all cUTI episodes at participating hospitals during the study period. Local ethical approval was obtained from each site. For all patients, a standardised set of information was recorded. This consisted of demographics, comorbidities including those required to calculate a modified Charlson score [19], place of acquisition of infection, infection source and severity, microbiological data, imaging test data, infection management, antibiotic therapy, outcomes, details of discharge and readmissions. The follow-up period was 2 months after discharge from the admitting hospital.

The perspective of the cost analysis was the hospital provider, as we focus on hospitalised cUTI patients and this is where the majority of the cost burden falls [20, 21].

Study size was defined based on the primary outcome measure of the main study, i.e. treatment failure rate between MDR bacteria and other pathogens [16].

Estimating the cost per case of cUTI

We collected information on healthcare resource utilisation attributed to cUTI for each episode in the dataset. The healthcare components collected were: *i)* length of hospital stay (LOS) (general ward, ICU), *ii)* diagnostic and follow up tests, *iii)* urological interventions and haemodialysis, *iv)* antibiotic treatment before, during and after hospitalisation, and *v)* hospital readmissions and outpatient visits within 60 days of discharge. For each component, a comprehensive list of specific items was compiled and reviewed by a clinical expert so that it included only healthcare resources that could be attributed to cUTI.

For unit costs, we planned to use the tool developed by WHO-CHOICE health service delivery costs [22], which provides information on the unit costs of bed-days and outpatient visits across 191 countries. Unfortunately, unit costs from this tool are only available for inpatient and outpatient visits, and for 2007-08, and therefore they could not be used in our study. Instead, unnit cost data for each cost item were collected for each country by means of a questionnaire sent to the principal investigators of all participating sites. The questionnaire was provided as an online and paper version, and included the list of all healthcare services identified for the management of cUTI (see Supplementary material 1). The response rate for the questionnaire was 90% (18 out of 20). We received at least one response from each country. However, despite efforts to facilitate the complete fulfilment and harmonisation of the questionnaires, responses from some of the sites had missing values for key healthcare costs items, such as the

cost of a day in hospital and for the most frequent diagnostic tests and treatment procedures. Furthermore, some sites provided the data in terms of user charges instead of the cost incurred by the hospital in the provision of the services. As a result, we observed a large degree of variation in unit costs across sites that was not attributable only to differences in actual costs between regions. Therefore, we generated a single set of unit costs based on the mean values across three sites within the same country, Spain, which provided consistently estimated values reflecting hospital costs for all the items included in the questionnaire. Using a common set of unit costs across all patients means that any observed variation in costs is due to differences in healthcare resource use. We discuss the limitations of this approach in the discussion section.

For antibiotic therapy we estimated the cost per mg for each drug for which unit cost data was available, and applied the mean cost per mg to the remaining therapies. We estimated the cost per day with antibiotic therapy based on the dosage and frequency recorded for each drug, which was then combined with the duration of the treatment to estimate total antibiotic therapy costs. Patients might receive more than one antibiotic drug at the same time; in that case they count as separate antibiotic therapy days. Patients with total hospital LOS >200 days were excluded (3 observations) as these were deemed to be due to coding errors.

We computed means and standard deviations as well as medians and interquartile ranges for the cost per case, and we quantified the contribution of each cost item and overall healthcare component to the total cost per case. We also present variations in the overall cost per case by country and for different cost components. All costs were reported in 2016 euros.

Costs were calculated for each case of cUTI requiring a hospital admission. If a patient required a second hospital admission, then if this occurred within 60 days of discharge

of the first admission it was counted as a readmission and included in the cost of the first admission. If another admission occurred after 60 days post discharge (either of the index admission or a readmission) then this was counted as a separate case (observation) in the data.

Factors associated with cUTI-related healthcare costs

The analysis of the factors associated with cUTI-related healthcare costs was undertaken using multivariate regression analysis using patient level cost data. The dependent variable was total cost per patient estimated as described above.

The explanatory variables were demographic factors (age and gender), comorbidities measured by the Charlson morbidity index [18], admission characteristics (urgent versus elective; and admitted from home versus from another facility), infection severity (defined as septic shock or severe sepsis), , MDR profile (defined as non-susceptibility to at least one agent in three or more antimicrobial categories [23]), episode number and 30-day mortality. We categorised the source of infection using the following definitions: i) UTI related to indwelling urinary catheterisation including long-term, short-term or intermittent catheterisation; ii) pyelonephritis, consisting of inflammation of the kidney tissue caused by bacterial infection in patients that have no other urinary tract modification; and iii) other sources, which includes UTI related to anatomical urinary tract modification, UTI related to obstructive uropathy and UTI related to other events that do not fulfil any other category. We ran three sets of models: i) univariate regression models for each variable separately, ii) a multivariate model including all the covariates, and iii) a reduced multivariate model including only significant variables (where in the case of categorical variables, at least one indicator was non-significant).

Analyses were undertaken using Stata version 12. More details about the statistical methods used in the analyses are reported in the Supplementary material 2.

RESULTS

Study population characteristics

Data was collected on 653 cUTI episodes in 637 patients (mean number of episodes per patient, 1.04). There were missing data on LOS for nine episodes, so mean costs per case were computed for 644 cases. Most common causative pathogens in this sample were *Escherichia coli* (58%), *Klebsiella sp* (14%), *Proteus mirabilis* (7%), *Pseudomonas aeruginosa* (6%) and *Enterococcus sp* (5%). This is consistent with previous studies that have found *E. coli* to be the most commonly isolated organism, especially in cUTI acquired at the community [24] which were the majority in our sample (69% versus 31% associated to health care facilities).

Fifty seven percent of the cohort were females and the mean age was 65.7 years (Table 1). Mean Charlson comorbidity score was 2.4. Ninety one percent of admissions were urgent (as opposed to elective) and 85% of the patients were admitted from home (as opposed from another facility). The infection source was indwelling urinary catheterisation in 20% of cases, pyelonephritis in 27% of cases, and other sources (including anatomical urinary tract modification and obstructive uropathy) in the remaining 53%. Twenty six percent of the episodes were caused by MDR bacteria. The severity of the infection was categorised as severe sepsis or septic shock in 16% of cases. Five percent of the sample died within 30 days of discharge. The proportion of cases collected by each country ranged from 5% in Bulgaria to 26% in Israel.

Table 1. Summary statistics of cohort characteristics and regression analysis results of total cost per cUTI episode

	N (%) Mean (SD)[a]	Univariate analysis[b] [95% CI]	Multivariate analysis - Full model[c] [95% CI]	Multivariate analysis - Reduced model[d] [95% CI]
Demographics				
Age	65.7 (18.66)[a]	19.77 [-7.5; 47]	11.76 [-3.5; 27]	
Female	371 (58%)	-796.06 [-1872.5; 280.4]	17.59 [-582.8; 618]	
Type of admission				
Urgent (vs. Elective)	585	458.91	937.87**	991.32**

	(91%)	[-775.4; 1693.2]	[44.8; 1830.9]	[84.6; 1898]
From home (vs. Other facility)	549	-677.89	-577.62	
	(85%)	[-2429.6; 1073.8]	[-1672.4; 517.1]	
Infection source (vs. catheterisation)				
Pyelonephritis	171	-1,673.18***	-1,802.63***	-1,891.57***
	(27%)	[-2819.3; -527]	[-2812.8; -792.4]	[-2864.4; -918.7]
Other source	344	-821.88	-709.83	-760.95*
	(53%)	[-1946.1; 302.3]	[-1672.3; 252.6]	[-1690.3; 168.4]
Infection severity (vs. other)				
Septic shock/severe sepsis	100	2,415.49***	1,671.77***	1,587.57**
	(16%)	[1050.8; 3780.2]	[437.9; 2905.6]	[280.7; 2894.5]
Charlson Comorbidity Index	2.4	324.34***	230.85**	263.48***
	(2.39)[a]	[116.8; 531.9]	[28.1; 433.6]	[53.9; 473.1]
Episode number	1.04	1,394.33***	355.91	
	(0.24)[a]	[363.8; 2424.8]	[-522; 1233.9]	
Mortality 30 days (yes vs. no)	29	571.66	-934.75	
	(5%)	[-2511.2; 3654.5]	[-3510.7; 1641.2]	
Multidrug resistant (yes vs. no)	166	626.99	475.92	581.41*
	(26%)	[-421.5; 1675.5]	[-221.6; 1173.4]	[-98; 1260.8]
Country (vs. Turkey)				
Greece	65	-597.99	-1,503.81	-1,263.11
	(10%)	[-2692.5; 1496.5]	[-3933.1; 925.5]	[-3782.8; 1256.6]
Hungary	49	-1,734.5**	-2,757.06***	-2,768.68***
	(8%)	[-3216.4; -252.6]	[-4101.8; -1412.3]	[-4278.8; -1258.5]
Israel	170	-3,612.37***	-4,242.55***	-4,007.09***
	(26%)	[-4659.1; -2565.7]	[-5395.7; -3089.4]	[-5426.5; -2587.7]
Italy	36	-319.91	-1,065.03*	-930.92
	(6%)	[-1648.8; 1008.9]	[-2358.1; 228]	[-2501; 639.2]
Romania	107	-2,389.75***	-2,024.15***	-1,931.49***
	(17%)	[-3438.9; -1340.6]	[-3149.8; -898.5]	[-3301.5; -561.5]
Spain	126	-819.22	-1,629.41***	-1,422.96**
	(20%)	[-1942.5; 304.1]	[-2756.9; -501.9]	[-2812.8; -33.1]
Bulgaria	31	-2,520.07***	-2,853.38***	-2,841.09***
	(5%)	[-4454.5; -585.6]	[-4068.1; -1638.7]	[-4354.9; -1327.2]
Pseudo-R^2	N/A	N/A	0.111	0.105
Sample size[b]	644	636[e]		

Note: SD = Standard deviation; CI = Confidence Interval; N/A = Not Applicable

*p<0.1.**p<0.05.***p<0.01.

aSummary statistics for continuous variables are shown as mean and standard deviations; for categorical variables we present total number of observations and percentage.

bMarginal effects of univariate regression models for each variable separately.

cMarginal effects of a multivariate model including all the covariates.

dMarginal effect of a reduced multivariate model including only significant variables.

eThere are 8 cases with missing data on mortality at 30 days. Therefore, the sample used in the regression analyses includes 636 cases out of the 644 cases for whom data on cost per case was available.

Estimating the cost per case of cUTI

Table 2 presents unit costs, resource use and total costs separately for each healthcare item as well as for each set of overall cost components. The mean (median) length of stay in hospital was 9 (7) days, and a small proportion of the total stay was in the ICU. Most patients had urine cultures, urinary sediment analyses and blood cultures undertaken, while imaging tests were rarely performed. The urological intervention most often performed was the insertion of an indwelling bladder-catheter. The mean number of antibiotic therapy days before, during and after hospitalisation were 2, 12 and 6 days, respectively. Nearly 10% of patients were readmitted to hospital due to a cUTI recurrence, with a mean readmission stay across the full sample of 1 day (11 days among the subsample of readmitted patients). The mean number of outpatient visits per patient within 60 days of hospital discharge was 0.8.

Table 2. Cost per case by cost component – all countries combined

	Unit cost (€)	Resource use (units)		Total cost (€)		
		Mean (SD)	Median [Q1-Q3]	Mean (SD)	Median [Q1-Q3]	%
Length of stay						
General ward (days)	477.4	9.25 (8.49)	7 [5-11]	4,418.5 (4052.4)	3,342 [2,387-5,252]	77.4%
ICU (days)	1,589.6	0.05 (1.19)	0 [0-0]	83.9 (1895.4)	0 [0-0]	1.5%
		9.30 (8.51)	7 [5-11]	4,502.4 (4389.9)	3,342 [2,387-5,252]	78.9%
Diagnostic tests						
Urine culture test	15.1	1.51 (0.82)	1 [1-2]	22.8 (12.5)	15 [15-30]	0.4%
Dipstick analysis	2.8	0.49 (0.85)	0 [0-1]	1.3 (2.3)	0 [0-3]	0.0%
Urinary sediment analysis	2.6	1.02 (0.89)	1 [0-1]	2.6 (2.3)	3 [0-3]	0.0%
Gram stain test	6.3	0.37 (0.68)	0 [0-1]	2.3 (4.2)	0 [0-6]	0.0%
Blood culture	36.7	1.43 (1.56)	1 [0-2]	52.5 (57.1)	37 [0-73]	0.9%
Abdominal Ultrasonography	48.9	0.71 (0.64)	1 [0-1]	34.5 (31.3)	49 [0-49]	0.6%
CT Scan	156.0	0.2 (0.46)	0 [0-0]	32 (72.5)	0 [0-0]	0.6%
Pyelography	105.1	0.02 (0.14)	0 [0-0]	2 (14.2)	0 [0-0]	0.0%
MRI scan	191.6	0 (0.07)	0 [0-0]	0.9 (13.1)	0 [0-0]	0.0%
				151 (109)	115 [75-201]	2.6%
Treatment procedures						
Insertion of catheter	50.0	0.36 (0.48)	0 [0-1]	17.8 (24)	0 [0-50]	0.3%
Replacement of catheter	50.0	0.13 (0.38)	0 [0-0]	6.5 (19)	0 [0-0]	0.1%
Percutaneous nephrostomy	717.6	0.05 (0.26)	0 [0-0]	37.9 (183.8)	0 [0-0]	0.7%
Insertion of JJ-stent	907.0	0.05 (0.21)	0 [0-0]	40.8 (188.2)	0 [0-0]	0.7%
Abscess drainage	557.6	0.01 (0.12)	0 [0-0]	6.9 (69.2)	0 [0-0]	0.1%
Nephrectomy	3,174.0	0.01 (0.08)	0 [0-0]	19.7 (249.6)	0 [0-0]	0.3%
Mechanical ventilation (days)	350.0	0.12 (0.99)	0 [0-0]	41.8 (346.4)	0 [0-0]	0.7%
Renal replacement (days)	254.7	0.16 (1.53)	0 [0-0]	41.9 (389.8)	0 [0-0]	0.7%

				213.4 (764.8)	0 [0-50]	3.7%
Antibiotic therapy						
Before hospitalisation (days)	1.9	1.95 (5.84)	0 [0-0]	2.6 (20.6)	0 [0-0]	0.0%
During hospitalisation (days)	12.3	12.25 (61.37)	7 [4-11]	197.8 (474.8)	19 [7-149]	3.5%
At discharge (days)	5.9	6 (13.61)	4.5 [0-8]	24.1 (117.5)	2 [0-10]	0.4%
		1.08 (4.53)	0 [0-0]	224.6 (490.3)	32 [14-199]	3.9%
After discharge						
Readmission (days)	477.4	1.08 (4.53)	0 [0-0]	515.2 (2163.4)	0 [0-0]	9.0%
Outpatients (visits)	122.3	0.81 (1.62)	0 [0-1]	99.2 (197.8)	0 [0-122]	1.7%
				614.4 (2197.5)	0 [0-245]	10.8%
Total (first hospital admission only)				**5,064 (4,847)**	**3,627 [2,531-5,985]**	**88.8%**
Total (first hospital admission + antibiotic treatment before & after discharge)				**5,091 (4,844)**	**3,651 [2,542-6,004]**	**89.2%**
Total (hospital admission + antibiotic treatment before & after discharge + readmissions & outpatients visits)				**5,705 (5,438)**	**3,919 [2,664-6,655]**	**100%**

*Unit costs estimated from the three Spanish sites

The mean (median) costs per case were: *i)* including costs incurred during the first hospital admission: 5,064€ (3,627€); *ii) i)* plus antibiotic therapy before and after discharge: 5,091€ (3,651€); and *iii*) *ii*) plus outpatient visits and hospital readmissions within 60 days of discharge: 5,705€ (3,919€).

The cost per case was largely driven by the cost due to the length of stay in hospital, which accounted for nearly 80% of the total cost. This was followed by the contribution of the cost of readmissions and outpatient visits after discharge (11%), treatment procedures (4%), antibiotic therapy (4%) and diagnostic tests (3%).

There was variation in the mean cost per cUTI case by country, with a largest mean (median) value of 7,740€ (5,962€) in Turkey and a lowest value of 4,028€ (3,159€) in Israel (Table 3). Note that variations in total costs shown in this table are only due to variations in the management of patients with cUTI, including LOS, as unit costs of healthcare services are held constant across all countries. Table 3 also shows variations by cost components between countries. This suggests that differences in LOS are the main reason of the observed differences in total costs between countries; the mean stay in hospital in a general ward varies from 6 days in Israel to 14 days in Italy.

Table 3. Mean cost per case by cost component – by country

	N		Total cost (€)	LOS (€)	DIAG (€)	TREAT (€)	ATB (€)	DISCH (€)	LOS ward (days)	LOS ICU (days)
Bulgaria	31	**Mean (SD)**	4,907 (4,130)	3,943	111	298	355	200	8.26	0.00
		Median [Q1-Q3]	3,660 [3,187-5,258]	2,865	84	0	25	245	6.00	0.00
Greece	65	**Mean (SD)**	7,039 (5,786)	5,670	221	251	586	311	11.88	0.00
		Median [Q1-Q3]	5,581 [3,176-8,934]	4,774	213	50	70	122	10.00	0.00
Hungary	49	**Mean (SD)**	5,656 (5,591)	4,044	170	519	35	888	8.47	0.00
		Median [Q1-Q3]	3,765 [2,606-5,905]	2,865	137	0	19	122	6.00	0.00
Israel	170	**Mean (SD)**	4,028 (2,843)	3,061	133	60	132	641	6.41	0.00
		Median [Q1-Q3]	3,159 [2,254-4,666]	2,387	110	50	16	0	5.00	0.00
Italy	36	**Mean (SD)**	7,221 (8,271)	6,525	173	38	431	54	13.67	0.00
		Median [Q1-Q3]	5,052 [3,670-7,735]	4,536	145	0	268	0	9.50	0.00
Romania	107	**Mean (SD)**	5,024 (3,636)	4,493	107	10	125	288	9.41	0.00
		Median [Q1-Q3]	4,314 [3,096-5,849]	3,819	97	0	37	0	8.00	0.00
Spain	126	**Mean (SD)**	6,674 (6,200)	4,706	193	342	153	1,281	9.86	0.00
		Median [Q1-Q3]	3,992 [2,705-8,696]	3,103	141	0	45	122	6.50	0.00
Turkey	60	**Mean (SD)**	7,740 (8,006)	6,359	105	512	387	376	11.43	0.57
		Median [Q1-Q3]	5,962 [3,375-9,061]	4,774	106	50	101	0	9.00	0.00

*Holding unit costs constant. LOS = Length of stay; DIAG = Diagnostic test; TREAT = Treatment procedures; ATB = Antibiotic therapy; DISCH = After discharge (readmission and outpatient visits); ICU = Intensive Care Unit

Factors associated with cUTI-related health care costs

The statistically significant drivers of cUTI-related healthcare costs were (Table 1): type of admission (with urgent admissions exhibiting a higher cost than elective admissions); source of infection (with catheterisation associated to higher costs compared with other sources); the infection severity (septic shock and severe sepsis showing a larger cost); the Charlson comorbidity index (with larger values associated to a higher cost); MDR profile (episodes presenting MDR showing a higher cost; only significant at 10% significance level); and country (with most countries exhibiting a significant lower cost than Turkey).

DISCUSSION

In this study we have measured the cost per episode of patients hospitalised due to cUTI in eight countries with high prevalence of MDR, and explored the factors that explained variations in cUTI-related healthcare costs. The mean cost per hospitalised

cUTI case in our data was estimated as 5,700€, corresponding to the costs of a hospital stay of 9 days on average and including the costs of specific diagnostic and treatment procedures, as well as antibiotic therapy, readmissions due to cUTI reoccurrence and outpatient visits after discharge. As expected, the largest cost component was length of hospital stay, but it is also worth noting that the cost of antibiotic treatment exceeded that incurred to perform diagnostics tests and it was also larger than the costs due to any other treatment received by these patients. The cost per case varied across countries, mainly due to differences in LOS in hospital among patients with cUTI. These differences in LOS do not appear to be related to the models of health care in each participating country – the countries with longest LOS, Turkey, Italy and Greece, have different health care systems, i.e. social insurance system, national health system and mixed system, respectively. Several factors might explain these cross-country variations, including financial incentives inherent in hospital payments methods, availability of beds, and the expansion of early discharge programmes that allow patients to return to their homes to receive follow-up care [25].

Over and above differences across countries, our analysis also identifies a series of factors associated with higher cUTI-related healthcare costs. Urgent admissions, for infections due to an indwelling urinary catheterisation, resulting in septic shock or severe sepsis, in patients with a higher comorbidity index and presenting MDR were related to a higher cost. The presence of catheter on admission and the Charlson comorbidity index have also been found in the literature to increase costs of adult patients hospitalised with UTI, together with time to appropriate therapy [13]. Another study found males, patients with chronic renal failure, ESBL production and outpatient parenteral antibiotic therapy to be associated with higher costs in patients with UTI admitted to hospital [15].

Our cost estimates are in line with previous studies that have focused on similar patient groups. Esteve-Palau et al. 2015 [15] estimated a mean cost per patient hospitalised

with symptomatic UTI caused by ESBL-producing *E. coli* of 4,980€ in one hospital in Spain, excluding readmissions. The cost was significantly lower, 2,612€, among patients with UTI due to non ESBL-producing *E. coli*. Cardwell et al. 2016 [13] analysed data on adults patients with a discharged diagnosis code for UTI in one hospital in the USA and found a mean hospitalisation cost of $7,586. The costs of nosocomial UTI infections and UTI infections seen in primary care have been shown to be lower. For instance, Saint, 2000 estimated the incremental cost of nosocomial UTIs of $676 and catheter-related bacteremia of $2,836 per case [12]. Tambyah et al., 2002 reported that the mean incremental hospitalisation cost attributable to nosocomial catheter-associated UTI was $589 [11]. On the other hand, studies that focused on UTI infections treated in primary care have reported a mean cost between 70€ [9] and 236€ [10] per episode.

This is the first study to examine costs of hospitalised patients due to cUTI from a multinational point of view. Moreover, it is focused on countries with a high prevalence of MDR bacteria where cUTI impose a significant burden. In addition, the study estimated the mean cost per case from a bottom-up perspective, which provided a high level of granularity and the basis for the assessment of sources of variation and drivers of healthcare costs. However, the study also has a number of limitations. The design of the study did not include a control group to assess the extra length of stay and excess costs of patients who are admitted to hospital due to a different condition and develop UTI during their hospitalisation. Therefore, we focused in this paper on the analysis of patients who are admitted because of a cUTI. This is to avoid the overestimation that would result among cases admitted for other reasons for whom we cannot isolate the incremental costs that are due to cUTI only. A second limitation of the analysis is that, as discussed in the Methods section, country-specific unit cost data was not appropriate for most countries and therefore we applied the same set of unit costs, as estimated in one country, Spain, to the rest of the countries. While this approach

allowed us to explore variations in healthcare costs that are due to differences in the management of cUTI patients across countries rather than due to differences in the unit costs of services, it limits the validity of the country-specific estimates. To further explore the heterogeneity of country-specific estimates we planned to use the tool developed by WHO-CHOICE health service delivery costs [22], which provides information on the unit costs of bed-days and outpatient visits across 191 countries. The information from this dataset indicates that variations in cost estimates across countries would be enhanced if country-specific unit costs were used. The countries with the highest unit costs according to this tool, i.e. Spain, Italy and Greece, are among the countries with higher episode costs based on healthcare utilization in our analysis; while the country with the lowest unit cost, Bulgaria, has an estimated episode cost among the lowest in this study. Unfortunately, unit costs values from this tool are only available for inpatient and outpatient visits, and for 2007-08, and therefore they could not be used to construct country-specific estimates. In addition, we acknowledge that the theoretical proper unit cost for a resource is its opportunity cost (the value of the foregone benefits because the resources are not available for their next best alternative use). We take, as most previous studies, a pragmatic approach of using market prices and accounting costs. However, it is worth noting that, especially for inpatient day cost, these values might overestimate their opportunity costs. This is because most hospital costs are fixed and cannot be recouped even if the admission is avoided [26]. We also acknowledge that the number of observations included in the study for some countries is low, ranging from 31 to 170, which might restrict the generalisability of country-specific findings. The explanatory power of our models was also found to be low, which might suggest that there are other factors not captured by the observed variables included in our models that explain variation in health-care costs, such as hospital policy on LOS. Finally, the perspective of the analysis was that of the hospital provider, however if a societal perspective was considered wider costs related to cUTI should had been taken into account such as patients' costs and

productivity losses due to illness, as well as cost incurred by primary care settings; including these costs would increase the costs of cUTI.

In conclusion, this study showed the costs of patients hospitalised due to cUTI are substantial, but identified wide differences between countries, especially due to differences in length of stay in the hospital. These findings suggest that a better knowledge of the reasons for longer length of stays in some countries could facilitate a better standardised quality of care for patients with cUTI and to allow a more efficient allocation of healthcare resources. The factors associated with higher cUTI-related healthcare costs identified by this study also shed light onto some implications for policy and planning. Prompting preventive measures to minimise cost of hospitalisation might be aimed at increasing the population's knowledge of symptoms and signs of infection, in order to encourage patients to attend primary care facilities earlier, especially those with comorbidities or indwelling urinary catheters, and thus to avoid the development of severe forms of illness after the onset of symptoms and avoid the need for urgent admissions.

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Competing interests statement:

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Authors' contribution

Conceptualisation: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM; Acquisition of data: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM; Analysis of data: LVT, MP, ES, LL, SM; Writing–original draft preparation: LVT, MP, ES, LL, SM; Writing–review and editing: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM; Agree with manuscript results and conclusions: LVT, MP, ES, IW, JMV, MS, SG, JG, CV, NC, LvdH, NER, JC, CV, AM, TB, LL, IA, SM

Data sharing statement

No additional data available

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S1. Unit costs questionnaire

RESCUING ECONOMIC FORM

In the questionnaire below we ask for the unit costs of health care resources and services for the diagnosis, treatment and supportive care related to the management of cUTI. This information will allow us to estimate the cost per case as well as the total national burden of cUTI in your country. The questionnaire allows you to save the information already entered and to continue later. By using the same URL/web address, you will be able to continue where you left off.

What is the monetary unit you report in this form?

☐ Euro

☐ Other: _____

Hospital stays and visits

Please provide the unit cost per hospital stay day and outpatient visit in your hospital. Ideally we request the cost specifically among patients with cUTI (for example, the average cost among patients with discharge codes related to cUTI, e.g. ICD-9 CM Codes 590.1, 590.10, 590.11, 590.2, 590.8, 590.80, 590.9, 595.0, 595.89, 595.9, 599.0). If you are unable to provide the unit cost specifically for cUTI patients, please provide the average unit cost for the speciality that cUTI patients are treated in in your hospital (e.g., one of urology, gynaecology, general medicine). If costs are not available by specialty then please provide the average unit costs data across all patients in your hospital. Please specify the details of the data you are providing, such as the patients' ICD codes you used to compute the unit costs or whether the values are related to all types of patients.

Please fill in the table with the costs at your hospital even if you do not have data specifically for cUTI patients; it will be very useful for us, provided you explain in the Details section what these costs refer to.

	Cost per day/visit	Details
Hospital stay per diem in general ward		
Hospital stay per diem in ICU		
Outpatient hospital visit		

Procedures

Please provide the unit costs of the following procedures in your hospital. Next to each procedure we indicate the ICD9-CM procedures codes to make it simpler for you to identify the procedures we are interested in. Please specify the details of the data you are providing, such as the ICD9 codes or the specific name of the procedure you are providing data for.

If you have more than one cost for each procedure please provide the mean, ideally based on the proportion of patients receiving each procedure.

Procedure [ICD9-CM code]	Cost per procedure	Details
Urine culture [9132]		
Dipstick analysis [9139]		
Urinary sediment analysis [9133]		
Gram stain test [9131]		
Blood culture [9052]		

Abdominal Ultrasonography [8876]		
CT Scan [9218, 9219]		
Pyelography [8773, 8774, 8775]		
MRI scan [8895]		
Insertion of an indwelling bladder-catheter [5794]		
Percutaneous nephrostomy [5503, 5504]		
Insertion of JJ-stent [598]		
Abscess drainage [472, 5491]		
Nephrectomy [5501, 5502]		
	Cost per day	Details
Invasive mechanical ventilation [9670, 9671, 9672]		
Dialysis/Renal replacement therapy [3995, 5498]		

Antibiotic therapy

Please provide for the antibiotic therapies listed below the unit cost per dose and specify the relevant dose. Please respond only for the antibiotics used in your hospital, and if there are other antibiotics used frequently in your hospital which are not included in this list, please add them in the space provided.

Antibiotic (intravenous (IV)/oral administration)	Dose	Cost per dose
AMIKACIN (IV)	500 mg	
AMOXICILLIN (oral)	500 mg	
AMOXICILLIN (oral)	750 mg	
AMOXICILLIN (ORAL)	1000 MG	

AMOXICILLIN/CLAVULANIC ACID (IV)	1000/200 mg	
AMOXICILLIN/CLAVULANIC ACID (oral)	500/125 mg	
AMOXICILLIN/CLAVULANIC ACID (oral)	875/125 mg	
AMPICILLIN (IV)	1000 mg	
CEFIXIME (oral)	400 mg	
CEFIXIME (oral)	200 mg	
CEFTAZIDIME (IV)	2000 mg	
CEFTRIAXONE (IV)	1000 mg	
CEFUROXIME (IV)	750 mg	
CEFUROXIME (oral)	500 mg	
CEFUROXIME (oral)	250 mg	
CIPROFLOXACIN (oral)	500 mg	
CIPROFLOXACIN (oral)	750 mg	
CIPROFLOXACIN (IV)	200 mg	
COLISTIN (IV)	1 MUI	
CO-TRIMOXAZOL (oral)	400/80 mg	
CO-TRIMOXAZOLE (IV)	800/160 mg	
CO-TRIMOXAZOLE (IV)	400/80 mg	
CO-TRIMOXAZOLE (oral)	800/160 mg	
DAPTOMYCIN	500 mg	
ERTAPENEM (IV)	1000 mg	
FOSFOMYCIN (IV)	1000 mg	
FOSFOMYCIN (IV)	4000 mg	
FOSFOMYCIN (oral)	500 mg	
FOSFOMYCIN TROMETANOL (oral)	3000 mg	
FOSFOMYCIN TROMETANOL (oral)	2000 mg	
GENTAMICIN	240 mg	
IMIPENEM-CILASTATIN (IV)	500/500 mg	
LEVOFLOXACIN (IV)	500 mg	

LEVOFLOXACIN (oral)	500 mg	
LINEZOLID (IV)	600 mg	
LINEZOLID (oral)	600 mg	
MEROPENEM (IV)	1000 mg	
METRONIDAZOLE (IV)	500 mg	
METRONIDAZOLE (oral)	250 mg	
NITROFURANTOIN (oral)	100	
PIPERACILLIN + TAZOBACTAM (IV)	4000/500 mg	
PIPERACILLIN + TAZOBACTAM (IV)	3000/375 mg	
TEICOPLANIN (IV)	400 mg	
TRIMETHOPRIM	160 mg	
VANCOMYCIN (IV)	500 mg	
Name antibiotic 1		
Name antibiotic 2		
Name antibiotic 3		
Name antibiotic 4		
Name antibiotic 5		

Thank you for filling in this questionnaire.

Supplementary material 2

Factors associated with cUTI-related healthcare costs – statistical details

The analysis of the factors associated with cUTI-related healthcare costs was undertaken using multivariate regression analysis using patient level cost data. The dependent variable was total cost per patient estimated as described above.

To account for skewness of the cost data, generalised linear models with gamma family and log link were used [1]. We also considered using log Normal, Gaussian, inverse Gaussian and negative binomial distributions, but the gamma model gave the best fit in terms of the Akaike Information Criterion. We did not include as explanatory variables any of the variables used to construct the total cost per patient. We also exclude variables with a high collinearity (r>0.6). The variable selection in the reduced model was undertaken using forward and backward inclusion methods. P-values below the 5% level are regarded as statistically significant. Values between 5 and 10% are regarded as weakly significant.

For the quantitative interpretation of the effect of each variable, we computed marginal effects at the mean values of the included covariates. The impact of unobserved heterogeneity due to the hierarchical structure of the data is explored and accounted for by considering country fixed effects models. We also adjust for clustering at the site level by computing robust standard errors, and control for the patient episode number by including this indicator as an explanatory variable in the models.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9; 19
		(b) Give reasons for non-participation at each stage	9; 19
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9; 19
		(b) Indicate number of participants with missing data for each variable of interest	9; 19
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10; 20
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11; 20
		(*b*) Report category boundaries when continuous variables were categorized	20-21
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.