Evidence Gaps in the Burden of Complicated Urinary Tract Infection

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BACKGROUND

- Complicated urinary tract infections (cUTIs) serve as a model for assessing the efficacy and safety of novel antimicrobial therapies targeting multi-drug-resistant organisms (MDROs). Few studies have evaluated the burden of cUTI and acute pyelonephritis (AP), including those caused by MDROs.

OBJECTIVE

- To identify evidence gaps regarding cUTI and/or AP burden in key countries.

METHODS

- In July 2023, a systematic literature review was conducted using PubMed, Embase, Cochrane, and EconLit databases. The database searches were limited to studies published since 2013 and had no language limitations.
- Our searches identified observational studies evaluating cUTI/AP epidemiology, microbiological causes, economic and humanistic burden, and treatment patterns/outcomes within the last decade from China, Europe, France, Italy, Germany, Japan, Spain, United Kingdom (UK), and United States (US) (PROSPERO-CRD42023454794).

RESULTS

- Of 1,041 studies identified, 154 were selected for full-text review; 118 studies met the inclusion criteria.
- In general, the definition of cUTI varied widely across both clinical practice and scientific research, complicating the applicability of study results.[1]

Global cUTI or AP

Study: Multinational (70 countries)[2]

Incidence/prevalence:
Global prevalence of healthcare-associated UTI, 7.7%

Epidemiology of cUTI and AP

- 30 studies provided prevalence or incidence of cUTI and/or AP, with most conducted in the US (n = 22).
- Only one study estimated the global prevalence of healthcare-associated UTI.[2]

US (n = 22); Key Findings

	Study	Incidence/prevalence
cUTI or AP	3 large database studies	• Estimate of 1.14% in 2017 among adults. cUTI incidence rate of 4.9 cases per 1,000 person-years[3] • 22% of UTI visits in the ED during 2016-2018 were for cUTIs[4] • 17.6% of all UTI discharge codes, excluding CAUTI in 2018, were cUTIs[5]
	Multicenter study (N = 546,092 women)[6]	The prevalence of prenatal AP among all pregnant women was 0.5%, with an incidence rate of 5.3 cases of AP per 1,000 births
	Single-center outpatient study (N = 269)[7]	5.6% of UTI cases and 10.9% of cUTI cases had pyelonephritis
CAUTI	Incidence of CAUTI across 14 studies[5,8-20]	8 studies reported the same CAUTI rate type[13-20]: range of 0.51 per 1,000 catheter-days in an ambulatory setting[17] to 3.19 CAUTIs per 1,000 catheter-days in a VHA nursing home[14]
	NIS database (N = 2,837,385)[5]	4.4% had CAUTI
	Multicenter retrospective study (N = 61,047)[15]	1.41% (95% CI, 1.32%-1.51%) of patients with indwelling catheters had CAUTI

Spain (n = 2)

	Study	Incidence/prevalence
CAUTI	Single-center prospective study (N = 2,283 catheterized patients)[21]	8.2% developed CAUTI
	Retrospective study of CAUTI before (N = 471) and after (N = 209) COVID-19[22]	Similar CAUTI rates found in both periods; 1.53 per 10,000 patient-days

Italy (n = 2)

	Study	Incidence/prevalence
CAUTI	Prospective surveillance (N = 483 adults aged ≥ 65 years)[23]	14.7 (95% CI, 11.7-18.3) per 1,000 catheter-days
	Single-center prospective study (N = 641 adults catheterized for ≥ 48 hours)[24]	• 6.2% developed CAUTI • Incidence: 15.1 (95% CI, 11.9-22.6) per 1,000 catheter-days

Japan (n = 1)

	Study	Incidence/prevalence
CAUTI	Single-center study (N = 1,296 pediatric ICU patients)[25]	1.2% or 2.35 CAUTIs per 1,000 catheter-days

France (n = 1)

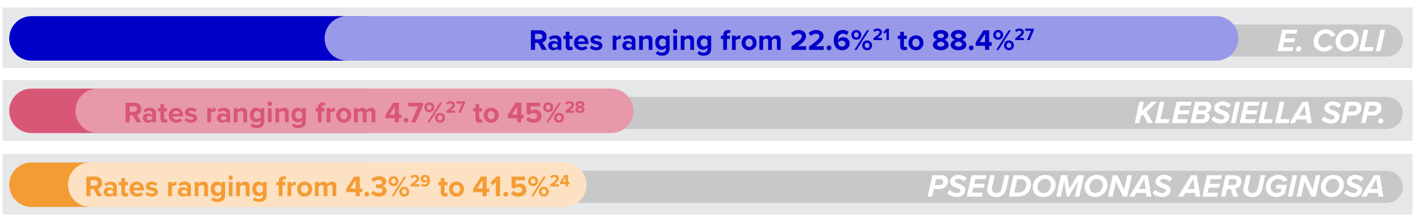
	Study	Incidence/prevalence
cUTI or AP	Nationwide study in women (N = 538)[26]	730 per 100,000 women (95% CI, 550-930)

CAUTI = catheter-associated urinary tract infection; ED = emergency department; ICU = intensive care unit; NIS = National Inpatient Sample; VHA = Veterans Health Administration

Causative Pathogens

Complicated UTI

Most Common Pathogen in Inpatients With cUTI (n = 45 Studies)



- A similar pattern was seen in studies reporting data for outpatient cohorts.
- The proportion of *Klebsiella spp.* was generally higher in inpatient cohorts than in outpatient cohorts.

Acute Pyelonephritis

- Similar to cUTI, the most common pathogens in AP were *E. coli* followed by *Klebsiella spp.*
- 9 of 15 studies reported that gram-positive bacteria, such as *Enterococcus or Staphylococcus*, was 1 of the top 3 causative pathogens.
- Studies reporting data from outpatients and patients in a mixed cohort had similar findings regarding the causative pathogens.

ESBL-Producing Pathogens and Antibiotic Resistance in cUTI and AP

Complicated UTI

- Overall, 46 articles reported the prevalence of extended-spectrum β-lactamase (ESBL)–producing pathogens and or antimicrobial resistance in patients with cUTI (Table 1).

Table 1. Summary: Prevalence of Resistant Pathogens in cUTI

Pathogen/antibiotic resistance	Inpatient setting ranges	Outpatient setting ranges
ESBL producers	2.3% of community-onset UTI to 60% in patients with a history of ESBL isolates[30]	1.01% in patients with ED visits with a primary diagnosis of cUTI[4] to 90.9% of all *E. coli* infections in patients prescribed FFM for symptomatic rUTI[31]
FQ resistance	• UTI caused by *E. coli*: – 34.5% of UTIs[32] to 61.4% of UTIs with concomitant bacteremia[33] • UTI caused by *K. pneumoniae*: – 15.3%[34] to 56.5% of UTIs[35]	0.38%[4] to 27%[36] in outpatients
SMX-TMP resistance	UTI caused by *E. coli*: • 18.1% of UTIs[26] to 45.1% of UTIs with bacteremia[33]	11.5% in patients with recurrent UTI whose previous asymptomatic bacteriuria was not treated[37] to 77% in patients with symptomatic UTI caused by MDR *Enterobacteriaceae*[38]
Carbapenem resistance	The highest carbapenem resistance was found in UTIs caused by *P. aeruginosa* (23.9%)[12]	0.01% with primary or secondary cUTI diagnosis[4]
MDR	Varied from 1.27%[5] to 78.8%[33]	1.05% of UTIs[4] to 78% of all *E. coli* UTIs in a symptomatic rUTI cohort[31]

FFM = fosfomycin; FQ = fluoroquinolone; MDR = multidrug resistant; rUTI = recurrent UTI; SMX-TMP = sulfamethoxazole-trimethoprim.

Acute Pyelonephritis

- 15 studies reported the prevalence of ESBL-producing pathogens and or antimicrobial resistance in patients with AP.
  - In inpatient and outpatient cohorts, the prevalence of ESBL-producing pathogens is higher in patients with complicated AP compared with uncomplicated AP (Table 2).

Table 2. Prevalence of Resistant Pathogens in AP

Country/reference	ESBL producers, % of patients	
	Uncomplicated AP	Complicated AP
Japan[39]	2.3%	16.6%
Spain[40]	1.8% of *E. coli* cases	4% of *E. coli* cases
US[41,42]	2.6%-4.8%	8.1% to 12.2%

Humanistic Burden of cUTI and AP

- No studies evaluating humanistic burden were identified despite the impact of these conditions on patient quality of life.

Economic Burden of cUTI and AP

- Economic studies in cUTI: 53 evaluated direct costs (n = 22) and/or healthcare resource utilization (HCRU) (n = 51).
- Economic studies in AP: Only 1 study (in China) of direct costs.[43]

Direct Costs

- Mean total cost per cUTI case varied across European countries.[44] Hospitalizations contributed the most to direct costs (Table 3).

Table 3. Costs of cUTI

Country	Total cost/hospitalized patient with cUTI
China	Mean, $2,328.28; median, $1,440.61[45]
Italy	Mean, €7,221[44]
Spain	Mean, €6,674[44]
US	Median all-cause 30-day costs in adults[3]: • Outpatient, $1,531 • Inpatient, $13,028
	Weighted (national) average total ED costs of cUTI as primary or secondary diagnosis in 2016-2018: $4,890.41[4]
	Inpatient costs of drug-resistant cUTI: • Mean cost of MDR cUTI, $9,902[46] • Excess cost of triple-resistant vs. non–triple-resistant cUTI, $754 (95% CI, $406-$1,103)[47]

Healthcare Resource Utilization

- Length of stay (LOS) for cUTI hospitalization was similar between studies with a median length of 7 days.[44,48,49]
- Patients with ESBL-producing pathogens and or drug-resistant pathogens had longer LOS than those without.[46,47,50-55]
- ICU admission: In 7 studies, 3% to 43.1% of patients hospitalized for cUTI were admitted to the ICU.[48,51,52,55-58]

Gaps in Epidemiology and Economic Burden of cUTI and AP

- Evidence was limited (1-2 studies) or absent for epidemiology, cost burden, and admissions/readmissions for many of the countries of focus.
- Few studies reported the prevalence and/or incidence rate of cUTI in France (1), Italy (2), Japan (1 study in pediatric patients only), and Spain (2). Except for 1 US study of AP in pregnant women, data on the prevalence and incidence of AP also were lacking. No studies reporting incidence or prevalence rates of cUTI in China, Germany, or the UK were identified.
- 7 studies reported the mortality rate in patients with AP. No studies reporting mortality in patients with AP were identified in France, Germany, Italy, or the UK, and only 1 study each was found for China, Japan, and the US.
- Direct costs of cUTI or AP were reported by only 2 studies each from China and Spain and 1 from Italy. There were no studies of direct costs for cUTI/AP for France, Germany, UK, and the whole region of Europe.
  - No studies were identified reporting indirect costs of patients with cUTI or AP from any the countries or regions of interest. Most HCRU data were on LOS and were available in all countries except Germany.
  - HCRU data on admission to the ICU or readmission to the hospital were reported only from 1 study each from China, France, and Europe.
  - There was no information on ICU admissions or hospital readmissions from Germany, Italy, Japan, or the UK.

CONCLUSIONS

- Substantial knowledge gaps persist in the literature regarding cUTI, including epidemiologic, humanistic, and economic burden studies in key countries. Addressing these gaps is crucial to assessing the added value of novel antibiotics targeting MDROs.

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