E.coli in Urinary Tract Infections from 2000–2016

PEER REVIEWED

Urinary tract infection (UTI) is one of the most common infectious diseases and the most common nosocomial infection in the developed world. Complicated urinary tract infection occurs in individuals with functional or structural abnormalities of the genitourinary tract. A wide variety of organisms is isolated from patients with complicated urinary infection. *E. coli* is the most common organism isolated, but is isolated more frequently in women than in men[1]. UTIs have proven to be a serious challenge for medical professionals due to high incidence, recurrence, complications, diverse etiologic agents, and growing antibiotic resistance. They account for 10–20% of all infections treated in primary care and 30–40% of infections treated in hospitals[2]. Whether community or hospital- acquired, urinary tract infections are commonly caused by *E. coli*[3]. This article evaluates the prevalence of *E. coli* in different countries.

Material and Methods

Literature Review

Literature searches were performed on PubMed using urinary tract infection and *E. coli* as primary search terms. After this initial search, the list included articles published in the last 10 years. After the first cut, the search was limited to articles that presented data per country. In the analysis, we included at least one representing country from North America, South America, Europe and the APAC region (Table 1, Chart 1).

Sample sizes of patients/specimens per country ranged from 22 to 23537. The highest % of *E. coli* causing cUTIs are seen in South Korea and Thailand.

For South Korea, we found two articles. The first presented data from a clinical trial that enrolled Korean patients aged ≥ 18 years with cUTI or acute pyelonephritis (APN) who required

Country	Leading pathogen	%	Second leading pathogen	%	Sample size (n)	Primary condition	Year of the study
REPUBLIC OF KOREA (4,5)	Escherichia coli	85.3	Klebsiella Pneumoniae	10.4	271	cUTI including pyelonephritis	2008-2009
	Escherichia coli	84.3	Klebsiella pneumoniae	NA	1,026	Pyelonephritis	2000-2004
CANADA (6)	Escherichia coli	82.3	Staphylococcus saprophyticus	5.2	327	Cystitis, Pyelonephritis including complicated cases	2008
TURKEY (7)	Escherichia coli	73.9	NA	NA	363	CA UTI[1]	2011-2012
THAILAND (8)	Escherichia coli	73	Klebsiella Pneumoniae	4.6	22	cUTI including pyelonephritis	2013-2014
BRAZIL (9)	Escherichia coli	71.6	NA	NA	31716	UTI	2000-2003
POLAND (10)	Escherichia coli	71.4	Klebsiella Pneumoniae	10.8	396	cUTI	2013
ROMANIA (11)	Escherichia coli	70.4	Klebsiella Pneumoniae	12.5	297	UTI	2011-2012
GREECE, CRETE (12)	Escherichia coli	68.9	Proteus Mirabilis	6.8	4011	CAUTI[1]	2005-2010
ARGENTINA (13)	Escherichia coli	67.7	Klebsiella pneumoniae	11.97	191	CA UTI[1]	2013
CROATIA (14)	Escherichia coli	67.3	Enterococcus spp.	12.6	815	CA UTI[1]	2003
SINGAPORE (15)	Escherichia coli	67	NA	NA	61	cUTI	2010-2014
SPAIN (16)	Escherichia coli	64.17	NA	NA	992	UTI	2007
INDIA (17)	Escherichia coli	59	Klebsiella Pneumoniae	11	4956	UTI	2008-2009
USA (18,19)	Escherichia coli	58	NA	NA	238	cUTI	2015
	Escherichia coli	49.1	Enterococcus spp.	38.6	57	MDR[2] UTI, cUTI	2009-2015
CHINA (20)	Escherichia coli	50	Staphylococcus epidermidis	9	198	Acute uncomplicated cystitis, recurrent UTI or cUTI	2011
PAKISTAN (21)	Escherichia coli	50	NA	NA	50	CA UTI[1]	~2010-2015
THE NEATHERLANDS (22)	Escherichia coli	47	Enterococcus Spp.	14	23,357	cUTI	2012

[1] CA UTI –Community acquired urinary tract infection [2] MDR – Multidrug resistant

Table 1. Table represents % of UTIs caused by E. Coli as main leading pathogen and % of UTIs caused by second leadingpathogen in prospective and retrospective studies. Table also represents primary condition patients had and the timeframe when data were collected.

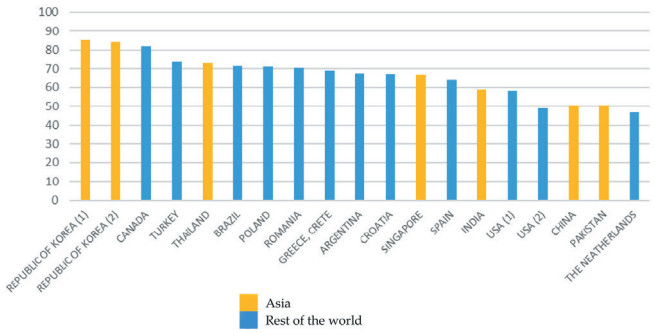


Chart 1. Chart represents per country differences in % of E.Coli caused UTIs in prospective and retrospective studies. Here we distinguished Asian countries from the rest of the world as UTIs caused by E. Coli are the most prevalent in this region.

parenteral antibiotic therapy. Baseline uropathogen needed to be present at ≥ 10^5 CFU/mL. A total of 271 patients were randomised, and in 185 (68%) *E. coli* was cultured[4]. The second article included a retrospective data analysis of patients diagnosed with APN. Bacteria were isolated by urine culture in 504 out of 1026 (49%) patients. *E. coli* was the leading pathogen causing infection in 425 patients [5].

Data used for Thailand included one single-centre study that targeted patients with cUTI including acute pyelonephritis. Samples were sent for microbiology evaluation before the first dose of the drug and mandatory inclusion criteria were as follows: levels of >10^5 CFU/mL uropathogens in midstream urine in women, >10^4 CFU/mL in midstream urine in men, or in straight catheter urine in women, were considered to be significant uropathogens in complicated urinary tract infections. A level of >10^4 CFU/mL uropathogens in midstream urine was considered to be significant in acute uncomplicated pyelonephritis in women. Of 22 isolated uropathogens, 16 were *E. coli*[8].

Regardless of design of the study – single-centred or multicentre trials, the data supporting *E. coli* as a main cause of cUTI and APN were similar.

Klebsiella pneumoniae was the second leading pathogen in both countries.

Rates of isolated *E. coli* in India, China and Pakistan were in a range from 50 to 59% [17, 20, 21]. In addition to presented data for the APAC region, a recently published 30-year study in Japan shows that *E. coli* was the most isolated bacterium for the period 2005–2014. Whereas, in uncomplicated UTI examined over 20 years, *E. coli* was the most frequently isolated species accounting for 47–94% of isolates[23].

All studies presenting data for Europe observed at least 250 patients and the percentage of *E. coli* causing urinary tract infections varied from 47 to 74%.

Countries with the most prevalent urinary infections caused by *E. coli* were: Turkey, Poland and Romania[6, 10, 11].

A study in Poland analysed 381 samples recovered from ambulatory adult patients with clinical symptoms of community-acquired UTI and significant bacteriuria, from 41 hospitals representing all regions of Poland[10]. Analysis showed that in 272 patients, the main pathogen causing infection was *E. coli* which was cultured in 80.6% of uncomplicated cases of UTI, compared to 65.8% in cUTI.

The Romanian study analysed 297 diabetic patients with UTI. This was a retrospective, non-interventional study and showed that the gram-negative bacilli from the Enterobacteriaceae family were predominant, with *E. coli* being the most frequent (70.4%)[11].

One objective of the article from Turkey was to describe the epidemiology and susceptibility of pathogens (including ESBL producers) from hospital-acquired (HA) versus community-acquired (CA) urinary tract infections[7]. Results showed that *E. coli* continues to be the principal pathogen of community UTIs in Turkey.

The reviewed data prompts that the APAC region had higher levels of *E. coli* prevalence compared to Europe. However, the data presented for Europe had larger and similar sample sizes for all countries, which reflects better pathogen surveillance in UTI in the region. Nevertheless, the most prevalent pathogen was *E. coli* in all countries. Additionally available data demonstrate that the percentage of UTIs caused by the second leading pathogen was not higher than 14%.

CRO Data

As the next step, we compared the baseline data of patients enrolled in our prospective international trials from 2014–2016.

The main inclusion criteria for patients to be screened and potentially randomised were presence of complicated urinary tract infection, including acute pyelonephritis. Both studies were designed to follow FDA Guidance for Complicated Urinary Tract Infections[24]. One study enrolled both indications equally and another one allowed enrolment of only 30% of patients with acute pyelonephritis.

Uropathogen at screening needed to be ≥10^5 CFU/mL, similar to requirements from larger studies presented in the literature review.

In all countries involved in clinical trials, *E. coli* was the most prevalent pathogen of cUTI or acute pyelonephritis (Table 2, Chart 2).

In all countries, a second leading pathogen caused 4–29% of infections.

Country	Leading pathogen	%	Second leading pathogen	%	Sample size (n)
MEXICO	Escherichia coli	87.5	Corynebacterium spp.	12.5	8
GEORGIA	Escherichia coli	76.4	Enterococcus faecalis	3.9	127
SOUTH AFRICA	Escherichia coli	73.3	Streptococcus agalactiae	20	15
COLUMBIA	Escherichia coli	72.7	Candida albicans	9.1	11
CZECH REPUBLIC	Escherichia coli	71.4	Candida albicans	9.1	14
HUNGARY	Escherichia coli	69.5	Klebsiella pneumoniae ssp. pneumoniae	13.1	82
US	Escherichia coli	68.8	Klebsiella pneumoniae	9.2	16
POLAND	Escherichia coli	62.6	Klebsiella pneumoniae	4.9	99
ROMANIA	Escherichia coli	58	Candida glabrata	6.3	174
LATVIA	Escherichia coli	56.6	Enterococcus faecalis	6.6	182
RUSSIA	Escherichia coli	55.2	Enterococcus faecalis	10.8	203
MOLDOVA	Escherichia coli	52.6	Enterococcus faecalis	15.8	19
SERBIA	Escherichia coli	48.5	Klebsiella pneumoniae ssp. Pneumoniae	12.1	33
UKRAINE	Escherichia coli	45.5	Enterococcus faecalis	12.7	292
BULGARIA	Escherichia coli	31.6	Enterococcus faecalis	16.3	215
ESTONIA	Escherichia coli	31	Enterococcus faecalis	15.2	158
ITALY	Escherichia coli	28.6	Staphylococcus epidermidis	28.6	7

Table 2. Table represents % of UTIs caused by E. Coli as main leading pathogen and % of UTIs cause by second leading pathogen in industry sponsored prospective studies. Second leading pathogen varies country by country.

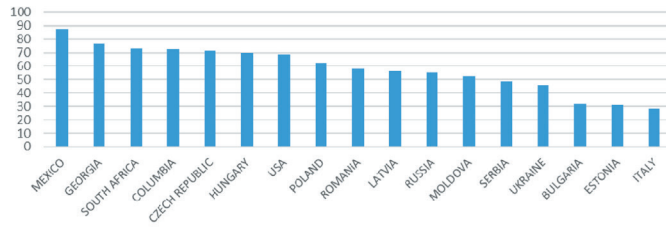


Chart 2. Chart represents per country differences in % of E. Coli caused UTIs in 2 industry sponsored trials managed by us..

Prevalence is amongst the highest in South Africa and South America (Mexico, Columbia). The same can be said for the US, although the sample size is not completely representative and more data would be needed for further conclusions. However, in these countries, *E. coli* is seen as the main pathogen at a rate higher than 70%.

Among European countries, there are no patterns that could show higher-lower prevalence within the region. Georgia, Czech Republic and Hungary are the countries with the highest prevalence of *E. coli* according to the data presented. In 28–71% of cases in Europe, *E. coli* is the main cause of complicated urinary tract infections, including acute pyelonephritis.

Discussion

A comparison of the literature data to our own data showed no major difference for *E. coli* in urinary tract infections (Chart 3). The patient population limited to complicated urinary tract infections (cUTI) and acute pyelonephritis (APN) can explain the lower percentages of infections caused by *E. coli* in our studies, compared to the broader patient set in retrospective epidemiology trials. Additionally, no significant discrepancies were observed comparing our own data and retrospective analysis data for Poland and Romania. The sample sizes observed in retrospective studies were larger and the prevalence of *E. coli* higher. This can also be explained with more strict terms for prospective clinical trials compared to retrospective studies and with the fact that *E. coli* is more predominant in uncomplicated urinary tract infections compared to complicated urinary tract infections[10].

Among all countries represented, the APAC region had the highest prevalence of UTIs caused by *E. coli*.

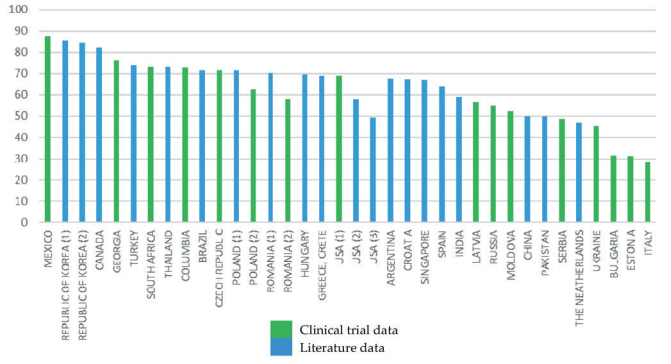
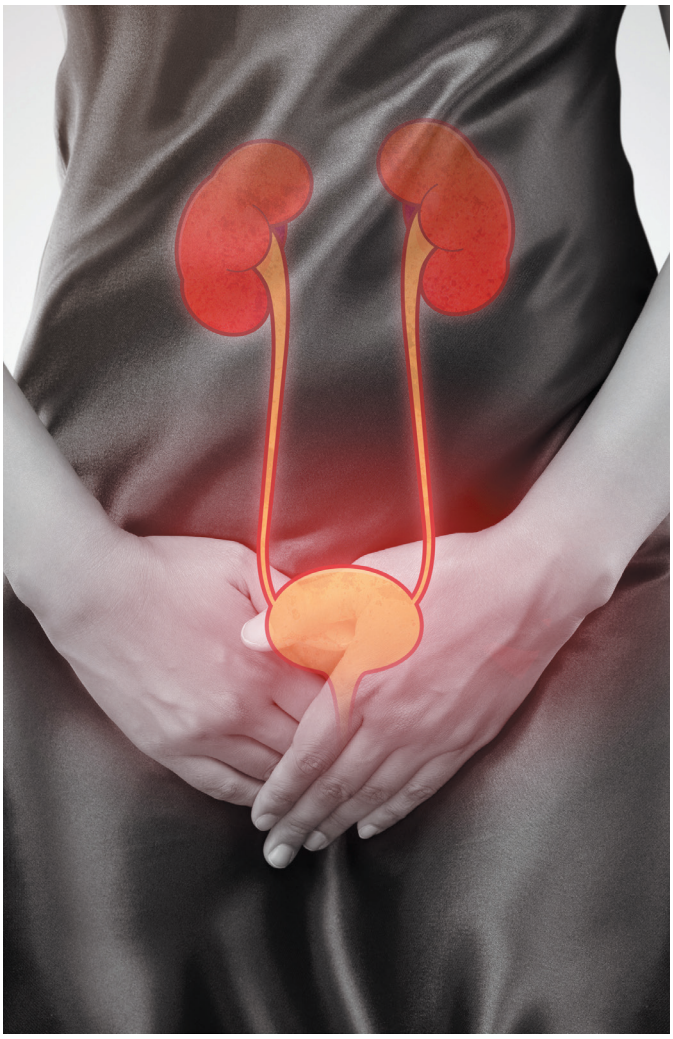


Chart 3. Chart represents per country differences in % of E.Coli caused UTIs in prospective (literature data and our own data) and retrospective studies.

Conclusion

The percentage of UTIs caused by *E. coli* varies from country to country, but it remains the leading pathogen causing UTI. The APAC region has the highest prevalence of UTIs caused by *E. coli*. These findings do not vary significantly among data sets gathered in prospective and retrospective studies.



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