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Risk Factors or Predictors of Developing Ciprofloxacin, Trimethoprim/Sulfamethoxazole and Third Generation Cephalosporin Resistance in *Escherichia coli* Infections: A Systematic Review and Meta-Analysis

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ABSTRACT

The Centers for Disease Control and Prevention (CDC) estimates that by 2050, ten million people a year could be dying as a result of Anti-Microbial Resistance (AMR). An increase in resistance has been observed for trimethoprim/sulfamethoxazole followed by ciprofloxacin and third-generation cephalosporins in the management of *Escherichia coli* infections. To identify risk factors for ciprofloxacin (Cip-REC), trimethoprim/sulfamethoxazole (TMP/SMX-REC,) and third-generation cephalosporin (TGC-REC) resistance in *Escherichia coli* infection relative to controls patients. A systematic search of MEDLINE/PubMed and Embase databases identified case-control, cohort, and cross-sectional studies on risk factors for Cip-REC, TMP/SMX-REC, and TGC-REC-infected patients. A random-effects model was used to pool odds ratios (ORs) of developing resistant *E. coli* infection. This study was registered with PROSPERO (CRD42022297043). A total of 23 studies were included (9891 participants). Overall, 22, 8, and 11 risk factors were identified for developing Cip-REC, TMP/SMX-REC, and TGC-REC infections respectively. The prior antibiotic use [OR=3.19] reported high pooled ORs for Cip-REC infection. TMP/SMX-REC infection was associated with genitourinary abnormalities [OR=2.91]. Further analysis unveiled potential factors for TGC-REC infection; prior history of admission [OR=3.14] and hemodialysis [OR=2.20]. Prior antibiotic usage, genitourinary disorders, and admission history increase the risk of Cip-REC, TMP/SMX-REC, and TGC-REC infections. Modifiable risk factors may help prevent resistant *E. coli* infection.

Key words: *Escherichia coli*, Ciprofloxacin, Trimethoprim, Sulfamethoxazole, Third Generation Cephalosporin

1. INTRODUCTION

Escherichia coli are Gram-negative bacteria within the family Enterobacteriaceae that can harmlessly colonize the human gut or cause intestinal or extraintestinal infections, including severe invasive diseases such as bacteremia and sepsis.[1,2] The incidence rate of *E. coli* infection bacteremia is 44-48 per 100,000 persons for a year.[3,4] *E. coli* is responsible for many infections. For instance, 33% of community-acquired infections, 18% of hospital-acquired infections, and 27% of bacteremia are owing to *E. coli*.[4] In view of this, it is imperative to address the issues on resistance to *E. coli*, which eventually may increase the severity of these infections.

In 2012, the results of a study from the USA found that increasing resistance to antimicrobials like ciprofloxacin and TMP/SMX among *E. coli* isolates. Further, another report, in 2018, from among 18 countries in Europe confirmed that Trimethoprim/Sulfamethoxazole resistance in 32.7% of *E. coli* isolates from urine samples; and, the prevalence of fluoroquinolone resistance was over 20%.[5]

Besides, the use of third-generation cephalosporins was significantly associated with 30-day case fatality risk.[6] In the case of multidrug-resistant *E. coli* infection, treatment options are limited and difficult to eradicate.[7] Therefore, determining risk factors have a high potential that help to combat Antimicrobial Resistance (AMR).[4] Further, there are a few drugs in pipeline and a high level of resistance to the most effective antibiotics, eradicating multidrug-resistant *E. coli* infections is of utmost importance.[8] So, prevention of infection by determining risk factors may help to reduce the incidence of resistant *E. coli* infection.

This systematic review and meta-analysis aimed to determine the risk factors for ciprofloxacin (Cip-REC), trimethoprim/sulfamethoxazole (TMP/SMX-REC,) and third-generation cephalosporin (TGC-REC) resistance *E. coli* infection relative to susceptible *E. coli* infections or patients with no infection.

2. METHODOLOGY

The protocol of this review was registered in PROSPERO with registration number, CRD42022297043.[9] This study was reported following Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[10–12]

2.1 Search Strategy

This study used electronic databases such as MEDLINE/PubMed and EMBASE, with each database having its search approach. Subject headings and entry terms both were used. The MeSH (Medical Sub Headings) included in the search strategy are as follows "Risk Factors", "*Escherichia coli*", "Drug Resistance, Microbial", "Drug Resistance, Bacterial", "Drug Resistance, Multiple, Bacterial", "*Escherichia coli* Infections", "Hospitals", "Hospitals, Private", "Hospitals, Public", "Hospitals, Teaching", "Secondary Care Centers", "Tertiary Care Centers", "Intensive Care Units", "Hospital Units". The search was narrowed by using the filters - Journal articles, Observational studies, Humans, and the English language. Besides, a citation search was also performed for relevant full-text papers to avoid the omission of potentially eligible publications. The search strategy was developed as per the Cochrane checklist.[13,14] A brief search strategy of MEDLINE/PubMed has been provided in the Supplementary file (S1).

2.2 Eligibility Criteria

The studies of case-control, cohort, and cross-sectional designs reporting risk factors specifically for resistant ciprofloxacin, TMP/SMX, and third-generation cephalosporins in *E. coli* infection were included. In addition, studies on human subjects irrespective of publication year were also considered under inclusion criteria. Studies that reported non- *E. coli* infection, other than mentioned antibiotics, and other than English language were excluded from this review.

2.3 Study Selection

Out of all the articles obtained through the search, the duplicates were removed by using the EndNote software. Further, three independent reviewers (NS.R., M.A., and R.F.) were involved in the screening, and irrelevant papers were excluded based on eligibility criteria in both primary and secondary screening. In primary screening, title and abstract were reviewed for each of the articles that were identified by the search strategy and for secondary screening, full copies of included articles were collected and reviewed. Any discrepancies in screening were resolved by discussing with a third party (P.R.D. and P.T.).

2.4 Data Extraction

Three independent reviewers (P.R.D, N.R. and R.F.) were involved to extract the required data from included articles after the secondary screening. Pre-specified data collection template in Microsoft Excel was used to extract the following data:

Study characteristics: First author, publication year, study design, location and setting of the study conducted, enrollment period, age (mean/median), the sample size of the cases, controls, males and females.

Cases: Participants exposed to *E. coli* infection and reported resistance to ciprofloxacin, TMP/SMX, and third-generation cephalosporins.

Controls: Participants exposed to *E. coli* infection and reported susceptibility to ciprofloxacin, TMP/SMX, and third-generation cephalosporins or participants with no infection.

Outcome: An odds ratio of risk factors for developing ciprofloxacin, TMP/SMX and TGC-resistant E. coli infection.
Any disagreements between the three reviewers were cleared by discussing with the third reviewer (P.T.).

2.5 Quality Assessment

The quality of included observational studies was assessed based on the New Castle Ottawa Scale (NOS) Method which consists of three domains; selection of patients (4 points), comparability (2 points), and ascertainment of exposure (3 points). Based on the final score; each study was interpreted to be of low quality (0-3), moderate quality (4-6), and high quality (7-9).[15] Only moderate and high-quality studies were included for meta-analysis. The quality assessment was evaluated by two independent

investigators (NS.R. and R.F.) and discrepancies were cleared by discussion with the third reviewer (P.T.) to reach a consensus.

2.6 Statistical Analysis

The significant risk factors that might govern antibiotic-resistant *E. coli* infection were determined by qualitative pooled odds ratio (OR) supported by 95%CI. The Z value was used to establish the significance of the pooled OR (a p-value of 0.05 was considered significant). Before the identification of significant risk factors, publication bias and heterogeneity of studies were evaluated. Heterogeneity was evaluated by the I^2 value. If the I^2 was 50% or more, it was considered significant and thus random effect model was chosen. On the other hand, the fixed-effect model was adopted, if the value of the I^2 value was less than 50%.[13] Publication bias was determined visually as well as statistically by a symmetric funnel plot and egger's test respectively.[16] Sensitivity analysis was done by omitting studies to assess the robustness of the results (pooled ORs). All statistical analyses were conducted using the Comprehensive Meta-Analysis (CMA) software.[17,18] Analysis was performed by two independent investigators to prevent analytical errors and discrepancies were cleared by discussing with a third party (P.T.).

3. RESULTS

The search in the databases yielded 1000 results. After deleting the duplicates (50) using EndNote software, 950 articles were reviewed for the title and abstract screening, yielding a total of 601. After secondary screening & full-text review, 266 articles were eligible. A total of 22 papers were found to be suitable for meta-analysis.[19–40] The flow chart of the study selection process is depicted in the PRISMA flow chart in (Figure 1).

A total of 9891 participants were included in this review of which 1893 were cases and 7998 were controls. Among, 2132 were males (case; 406, control; 1726) and females were 4186 (case; 793, control; 3393). Eight studies did not report the proportion of males and females. Most of the included studies were case-control studies (6) followed by cross-sectional (5), retrospective (4), prospective (4) and only 2 studies of nested case-control design. Analysis of the geographical distribution of included studies revealed that particularly, a high number of studies (seven) were conducted in the East Asian region, others were conducted in Korea (5), Taiwan (2) and Europe (4). The remaining individual studies were conducted in the United States of America (USA), Netherland, Italy, France, Canada, Philippines, France, Pennsylvania, Switzerland, and Pakistan. Geographical distribution of included studies is shown in supplementary files (S2). Predominantly,19 studies were performed in single setting whereas only three studies were reported from multiple settings. Patients, intervention, and outcome characteristics are presented in Table 1.

The NOS method revealed that the 12 studies were of 'high quality'. Another 10 studies had 'moderate quality', which could be a result of improper selection of controls. Most of the included studies scored 7 followed by 6 and two of them scored 8 and 9, respectively. Hence, this review included only 'moderate' to 'high-quality' studies. NOS scores for each of the included studies were represented in the Table 1.

3.1 Risk Factors for Ciprofloxacin Resistant *E. Coli* Infection (CREI)

A total of 22 risk factors were identified for CREI including 12 studies with 23447 participants (case; 7898, control; 15549). Eleven risk factors were analyzed using the random-effect model whereas another 11 risk factors pooling was done using the fixed-effect model. The most evident risk factors which hold a large number of studies were the prior antibiotic use (10 studies), diabetes mellitus (9 studies), and exposure to the urinary catheter (9 studies).

Of the 22 risk factors, only eight were statistically significant and seven were positively associated with high pooled odds ratios; prior use of quinolone [OR 33.71, 95%CI 16.05-70.79, p<0.001], prior antibiotic use [OR 3.19, 95%CI 1.70-5.98, p<0.001], recurrent urinary tract infection (UTI) [OR 2.98, 95%CI 1.59-5.59, p<0.001], exposure to urinary catheter [OR 2.15, 95%CI 1.65-2.80, p<0.001], nosocomial infection [OR 1.94, 95%CI 1.31-2.87, p<0.001], diabetes mellitus [OR 1.90, 95%CI 1.45-2.48, p<0.001] and male gender [OR 1.61, 95%CI 1.28-2.03, p<0.001]. Only one of the variables, female gender [OR 0.68, 95%CI 0.50-0.92, p=0.01] was negatively associated with CREI.

Further, statistically insignificant relation was also noticed for a few risk factors; age>65 years [OR1.82, 95%CI 0.97-3.41], corticosteroids or other immunosuppressants [OR 1.30, 95%CI 0.51-3.31], fluoroquinolone use in last 12 months [1.59, 95%CI 0.18-13.98], foreign material in upper urinary tract in last 12 months [1.34, 95%CI 0.17-10.27], hospitalization in department of urology in last 12 months [OR 1.42, 95%CI 0.11-18.59], kidney transplant recipient [OR 1.22, 95%CI 0.17-8.71], no prior treatment [OR 1.00, 95%CI 0.04-25.27], malignancy status [OR 0.70, 95%CI 0.33-1.49], absence of urological malignoma [OR 1.31, 95%CI 0.30-5.74], previous surgery [OR 2.13, 95%CI 0.55-8.26], renal insufficiency [OR 0.98, 95% CI 0.35-2.53], urinary tract abnormality [OR 1.36, 95%CI 0.44-4.25]

vesicoureteral reflux [OR 1.07, 95%CI 0.33-3.50], immunosuppressive therapy [OR 1.90, 95%CI 0.27-13.58]. Identified risk factors for CREI are represented in Table 2.

3.2 Risk Factors for Trimethoprim/Sulphamethoxazole Resistant *E. Coli* Infection (TREI)

Table 3 summarizes the results of risk factors identified for TREI. Four studies were retrieved to conduct quantitative analysis with total participants of 12493 [case; 3847, control; 8646]. Eight risk factors were identified for TMP/SMX resistance. Among, genitourinary abnormalities [OR 2.91, 95%CI, 1.74-4.85, p<0.001], and male gender [OR 1.89, 95%CI, 1.28-2.97, p<0.001] were significant with high pooled odds ratio. However, one risk factor was associated negatively; inpatient [OR 0.57, 95%CI 0.40-0.82, p<0.01]. Besides, insignificant predictors were UTI [OR 1.19, 95%CI 0.60-2.36], prior UTI [OR 1.63, 95%CI 0.86-3.09], previous antibiotic use [OR 4.35, 95%CI 0.49-38.44], previous quinolone use [OR 1.50, 95%CI 0.08-28.86] and female [OR 0.36, 95%CI 0.00-40.41].

3.3 Risk factors for Third-generation Cephalosporins Resistant *E. Coli* Infection (TGC-REI)

Eleven risk factors were identified for 3GC resistance, reported by four studies with 20392 participants [case; 2831, control; 20345]. Amid, risk factors with statistical significance and positive association were prior history of admission [OR 3.14, 95%CI, 2.23-4.42, p<0.001], hemodialysis [OR 2.18, 95%CI 1.22-3.88, p<0.001], male gender [OR 1.58, 95%CI 1.23-2.04, p<0.001]. Moreover, UTI [OR 0.66, 95%CI 0.47-0.91] is the only negatively associated factor. However, few risk factors were insignificant; cardiovascular disease [OR 1.09 95%CI 0.76-1.58], diabetes mellitus [OR 1.42, 95%CI 0.98-2.07], female [OR 0.74, 95% CI 0.54-1.03], intra-abdominal tract site of infection [OR 1.09, 95%CI 0.77-1.55], recent surgery [OR 1.29, 95%CI 0.44-3.75], prior cephalosporin use [OR 3.84, 95%CI 0.61-24.33], and immunosuppression [OR 1.29, 95%CI 0.68-2.42]. Table 4 illustrates the pooled odds ratios of risk factors for TGC-REI.

3.4 Publication Bias and Sensitivity Analysis

Risk factors, for which data availability was of at least three studies were enrolled to assess publication bias. Preliminary confirmation regarding publication bias was examined through a funnel plot; no obvious asymmetry was found for included studies. Statistical confirmation was evaluated by the eggers test; results revealed insignificant biasness in all studies (Table 2). Hence, it is evident that enrolled studies were free from publication bias. The stability of studies was evaluated through sensitivity analysis. Findings from sensitivity analysis indicated the remaining produced similar results each time removing any one study.

Visual representation of forest plots, sensitivity analysis, funnel plots are presented in supplementary files (S3-S5).

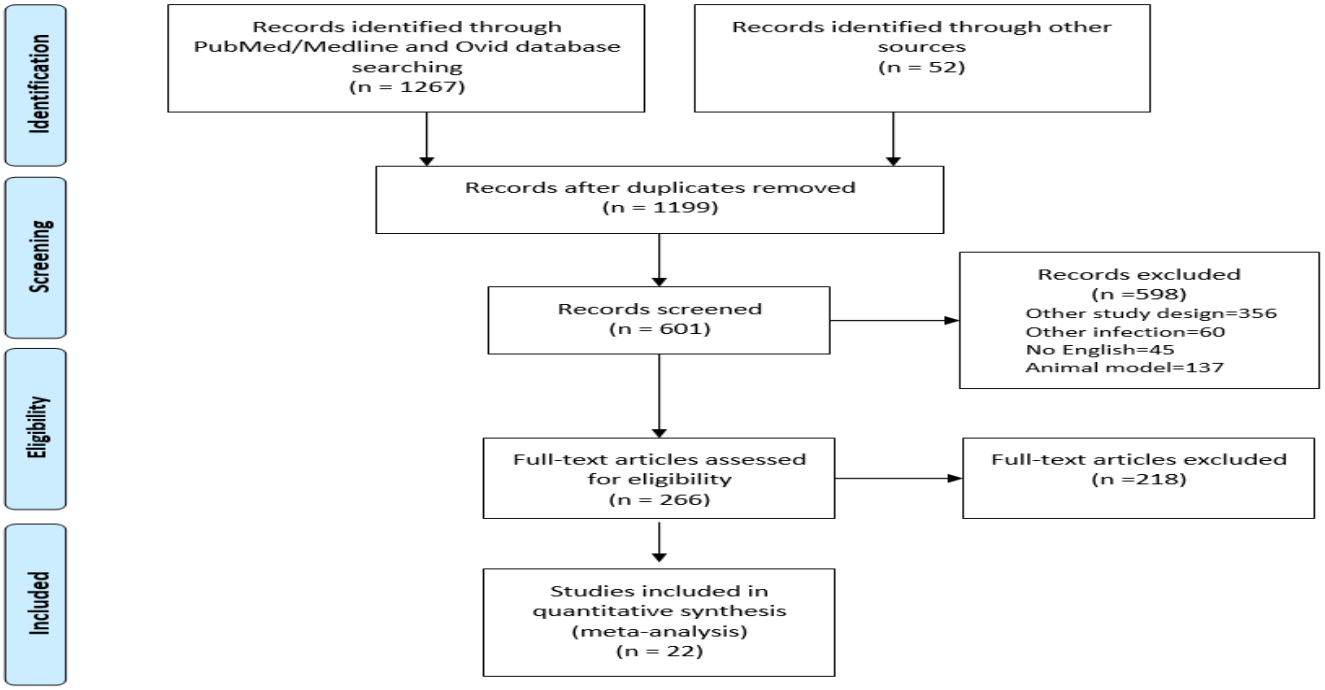

Figure 1: Selection of studies: PRISMA flow chart

Table 1: Characteristics of the included studies

#	Study	Study design	Enrollment Period	Country	Setting	Total sample size	Cases	Controls	NOS score	Quality of study
1	Lee2016	Retrospective	Jan 2006 - Dec 2015	Korea	Single	123	26	97	6	Moderate
2	Ena1995	Case-Control	Jan 1990 - Dec 1992	Spain	Single	105	54	51	7	High
3	Pena1995	Case-Control	1992-1998	Spain	Single	81	27	54	6	Moderate
4	Killgore2004	Retrospective	Jan 2001-Dec 2001	USA	Single	120	40	80	7	High
5	Garau1999	Retrospective	Jan 1992-Dec 1997	Spain	Single	572	70	502	7	High
6	Park2015	Prospective	Apr 2012-Jun 2012	Korea	Multiple	229	67	162	7	High
7	Mulder2016	Nested case-control	1 Jan 2000-31 Jan 2014	Netherland	Single	1080	110	970	7	High
8	Mcdonald2001	Cross-sectional	Aug 1998-Dec 1998	Taiwan	Multiple	66	9	57	7	High
9	Lee2014	Retrospective	Jan 2003 – Dec 2009	Korea	Single	731	45	686	6	Moderate
10	Lin2019	Retrospective	Jan 2015 – Dec 2015	Taiwan	Single	676	133	543	6	Moderate
11	Fulgenzio2021	Case Control	1 Jan2011 - 31 Dec 2016	Italy	Single	1797	244	1553	6	Moderate
12	Sotto2000	Prospective	Nov 1998 – Feb 1999	France	Single	320	65	255	7	High
13	Allen1995	Case-Control	Dec 1992-Dec1994	Canada	Single	548	274	274	7	High
14	Gangcuangco2015	Prospective	Jul 2010-Oct 2011	Philippines	Single	179	74	105	6	Moderate
15	Cheong2001	Case-control	Sep 1993 - Aug 1998	Korea	Single	120	40	80	6	Moderate
16	Eom2002	Case-control	Jan 2000-Dec 2000	Korea	Single	140	60	80	6	Moderate
17	Courpon-Claudinon2010	Prospective	2005	France	Multiple	1051	39	1012	6	Moderate
18	Karotchwil2015	Nested case-control	1 Jul, 2011-30 Jun, 2014	Pennsylvania	Single	200	100	100	6	Moderate
19	Nicoletti2010	Cross-sectional	1 Jan, 2006 - 31 Aug, 2007	Switzerland	Single	275	61	214	8	High
20	Smithson2012	Cross-sectional	Jan 2008 - Jan 2011	Spain	Single	153	52	101	7	High
21	Ahmed2015	Cross-sectional	1 Jan, 2011, to 31 Dec, 2012	USA	Single	1159	237	922	7	High
22	Jadoon2015	Cross-sectional	26 Dec 2011 - 25 Jun 2012	Pakistan	Single	166	66	100	9	High

Table 2: Risk factors for Ciprofloxacin Resistant *E. Coli* Infection (CREI)

#	Risk factors	Studies	Cases	Controls	Heterogeneity			Model	Effect estimate, OR [95% CI]	Ranking of risk factors	Z value	P-value	Egger's test
					$\chi 2$	P-value	I^2						P-value
1	Prior use of quinolone	5	68	10	1.31	0.86	0	Fixed	33.71 [16.05, 70.79]	1	9.29	<0.001	0.57
2	Prior antibiotic use	10	228	211	52.21	<0.001	83	Random	3.19 [1.70, 5.98]	2	3.61	<0.001	0.52
3	Recurrent UTI	7	208	160	25.23	<0.001	76	Random	2.98 [1.59, 5.59]	3	3.4	<0.001	0.07
4	Urinary catheter	9	161	181	52.84	<0.001	85	Random	2.15 [1.65, 2.80]	4	5.64	<0.001	0.59
5	Previous surgery	4	12	15	5.84	0.12	49	Fixed	2.13 [0.55, 8.26]	5	1.09	0.28	0.15
6	Nosocomial Infection	5	59	129	10.63	0.03	62	Random	1.94 [1.31, 2.87]	6	3.31	<0.001	0.39
7	Diabetes Mellitus	9	127	256	3.85	0.87	0	Fixed	1.90 [1.45, 2.48]	7	4.7	<0.001	0.91
8	Immunosuppressive Therapy	2	14	10	3.94	0.05	75	Random	1.90 [0.27, 13.58]	8	0.64	0.52	-
9	Age greater than 65years	5	192	171	16.51	0.002	76	Random	1.82 [0.97, 3.41]	9	1.87	0.06	-
10	Male	8	262	632	6.79	0.45	0	Fixed	1.61 [1.28, 2.03]	10	4.05	<0.001	0.93
11	Fluoroquinolone use in last 12 months	2	85	85	29.96	<0.001	97	Random	1.59 [0.18, 13.98]	11	0.42	0.68	-
12	Hospitalization in department of urology in last 12 months	2	45	45	30.26	<0.001	97	Random	1.42 [0.11, 18.59]	12	0.27	0.79	-
13	Urinary tract abnormality	3	74	369	14.08	<0.001	86	Random	1.36 [0.44, 4.25]	13	0.53	0.6	0.16
14	Foreign material in upper urinary tract in last 12 months	2	25	25	11.94	<0.001	92	Random	1.34 [0.17, 10.27]	14	0.28	0.78	-
15	Absence of urological malignoma	2	5	5	0.23	0.63	0	Fixed	1.31 [0.30, 5.74]	15	0.36	0.72	-
16	Corticosteroids or other immunosuppressants in last 12 months	2	12	12	0.04	0.85	0	Fixed	1.30 [0.51, 3.31]	16	0.55	0.58	-
17	Kidney transplant recipient	2	2	2	1.03	0.31	3	Fixed	1.22 [0.17, 8.71]	17	0.19	0.85	-
18	Vesico-ureteral reflux	5	4	5	4.86	0.18	38	Fixed	1.07 [0.33, 3.50]	18	0.11	0.91	0.74
19	No prior treatment	2	144	144	48.36	<0.001	98	Random	1.00 [0.04, 25.27]	19	0	1	-
20	Renal insufficiency	3	8	19	2.52	0.28	21	Fixed	0.98 [0.35, 2.53]	20	0.05	0.96	0.66
21	Malignancy	2	26	28	1.31	0.25	24	Fixed	0.70 [0.33, 1.49]	21	0.93	0.35	-
22	Female	4	153	1122	0.08	0.99	0	Fixed	0.68 [0.50, 0.92]	22	2.5	0.01	0.79

Table 3: Risk factors for Trimethoprim/Sulphamethoxazole Resistant *E. Coli* Infection (TREI)

#	Risk factors	Studies	Cases	Controls	Heterogeneity			Model	Effect estimate, OR [95% CI]	Ranking of risk factors	Z value	P value
					χ2	P-value	I²					
1	Previous antibiotic use in the past 6 months	2	257	403	53.47	<0.001	98	Random	4.35 [0.49, 38.44]	1	1.32	0.19
2	Genitourinary abnormalities	2	251	204	3.18	0.07	69	Random	2.91 [1.74, 4.85]	2	4.08	<0.001
3	Male gender	2	48	89	1.29	0.26	22	Fixed	1.89 [1.28, 2.79]	3	3.21	0.001
4	Prior urinary tract infection	2	28	42	10.43	0.001	90	Random	1.65 [0.97, 2.81]	4	1.83	0.07
5	Previous quinolone use	2	10	17	3.84	0.05	74	Random	1.50 [0.08, 28.86]	5	0.27	0.79
6	Urinary tract infection	3	46	67	5.34	0.07	63	Random	1.19 [0.60, 2.36]	6	0.5	0.62
7	Inpatient	2	59	114	0.67	0.41	0	Fixed	0.57 [0.40, 0.82]	7	3.02	0.003

Table 4: Risk factors for Third-generation Cephalosporins Resistant *E. Coli* Infection (TGC-REI)

#	Risk factors	Studies	Cases	Controls	Heterogeneity			Model	Effect estimate, OR [95% CI]	Ranking of risk factors	Z value	P value
					χ2	P-value	I²					
1	Prior cephalosporin use	2	52	138	18.39	<0.001	95	Random	3.84 [0.61, 24.33]	1	1.43	0.15
2	Prior history of admission	2	105	313	0.03	0.87	0	Fixed	3.14 [2.23,4.42]	2	6.54	<0.001
3	Hemodialysis	2	17	43	1.24	0.27	19	Fixed	2.18 [1.22, 3.88]	3	2.63	<0.001
4	Male	2	129	954	0.58	0.45	0	Fixed	1.58 [1.23, 2.04]	4	3.56	0.001
5	Diabetes Mellitus	3	124	602	4.23	0.12	53	Random	1.42 [0.98, 2.07]	5	1.86	0.06
6	Recent surgery	2	88	607	4.18	0.04	76	Random	1.29 [0.44, 3.75]	6	0.46	0.64
7	Immunosuppression	2	17	382	0	0.03	0	Fixed	1.29 [0.68, 2.42]	7	0.78	0.44
8	Cardiovascular	2	74	309	0.68	0.41	0	Fixed	1.09 [0.76, 1.58]	8	0.48	0.63
9	Intra-abdominal tract site of infection	2	56	409	0.25	0.62	0	Fixed	1.09 [0.77, 1.55]	9	0.5	0.62
10	Female	2	100	776	1.11	0.29	10	Fixed	0.74 [0.54, 1.03]	10	1.78	0.07
11	Urinary tract infection	2	70	581	0.44	0.51	0	Fixed	0.66 [0.47, 0.91]	11	2.51	0.01

4. DISCUSSION

To the best of the knowledge of authors, this is the only systematic review that evaluated risk factors for ciprofloxacin, TMP/SMX and third-generation cephalosporins resistant *E. coli* infection. The key findings of this review have the potential to provide important epidemiological evidence to inform the development and implementation of effective preventive strategies against such resistant infection. This review is based upon a total of 9891 participants -with 1893 cases and 7998 controls, respectively. In selected studies, predominantly the data were collected from one hospital/healthcare organization; single setting. Only three studies relied upon data from multiple setting. Majority of the included studies were found to be from European setting.

In the electronic databases, several observational studies have reported risk factors for antimicrobial-resistant *E. coli* infection but possess some limitations; like low sample size, being confined to a specific location, only a few risk factors reported and some studies enrolled inappropriate controls that can induce bias (more precisely selection bias). This current study has utilized all available observational studies for qualitative pooling of the data and performed the quality assessment, sensitivity analysis, and publication bias which can overcome cited limitations.

Results from a study in USA confirmed the enhancement of antimicrobial resistance by the use of fluoroquinolone, especially in the case of enteric bacteria. In addition, it was found that an increase in the use of ciprofloxacin by 40% led to a proportional increase by double in antibiotic resistance.[41] The rising rate of resistance is most noticeable in the management of *E. coli* infections where ciprofloxacin has become increasingly prevalent.

The risk factors revealed by this systematic review for developing CREI are the prior use of quinolone, prior antibiotic use, recurrent UTI, exposure to urinary catheter, nosocomial infection, diabetes mellitus, male gender, exposure to the urinary catheter, nosocomial infection, immunosuppressive therapy, previous surgery, malignancy status, urinary tract abnormality, vesicoureteral reflux, renal insufficiency, prior treatment and fluoroquinolone use in last 12 months.

Recurrent UTI in adults is defined as a repeated UTI with a frequency of two or more UTIs in the last six months or three or more UTIs in the last 12 months.[42] Many studies revealed that ciprofloxacin is preferred in recurrent UTIs as a prophylactic antimicrobial. Further, it has the possibility to stimulate the extended spectrum beta-lactamase (ESBL) production in *E. coli* which is considered as a causative enzyme for resistance development[43]. Based on the findings of this review, patients reporting recurrent UTIs are more likely to have CREI than controls.

According to the CDC estimation, each year around 47 million antibiotics are used inappropriately.[44] Antibiotic use for infections, largely affecting the urinary and respiratory tract, may lead to resistance to that antibiotic probably within a month or may persist up to 12 months.[45] The reason behind this is adaptation of bacteria towards antibiotic's mechanism of action, upon frequent use which can develop resistance.[46] Prior use of antibiotics particularly extensive use of broad-spectrum antibiotics like ciprofloxacin is a vital risk factor for AMR in resistant *E. coli* infection.

Hyperglycemia caused by an insufficiency or absence of the insulin hormone is the defining characteristics of Diabetes Mellitus, a metabolic illness. *E. coli* plays a protective role in the gut although it is the major cause of extraintestinal infections in diabetes patients. *E. coli* is responsible for 70% of UTIs in diabetic patients.[47] The major reason for the common infection is high glucose levels which perhaps suppress the immune system by diminishing neutrophil and antioxidant function.[48] Additionally, glucose helps *E. coli* for fast replication.[47] In accordance with the findings of this review, patients who have diabetes mellitus have a higher risk of developing CREI as well as TGCEI compared to controls.

According to the literature, resistance to TMP/SMX and ciprofloxacin was found to be 33.6% and 18%, respectively in patients diagnosed with UTIs. In addition, this resistance was reported common in males (32.7%) as compared to women (15.9%).[49] Furthermore, resistance to *E. coli* is more frequent since it is a common pathogen to cause UTIs as compared to other species.[49] Hence, UTI in is one of the major predictors of antimicrobial resistant *E. coli* infection as demonstrated by the meta-analysis of relevant data.

The results of this review identified that participants with genitourinary abnormalities and male gender were at more risk for developing TMP/SMX resistant *E. coli* Infection compared to controls. Previously, a few studies also reported male gender as a risk factor for antimicrobial resistance.[7,26] This review has come up with similar results; the male gender is a common risk factor for all pointed antimicrobial resistance. Additionally, the participants with the variables like the prior history of admission, hemodialysis and male gender were found to be at more risk for developing TGC-REI.

The limitations of this study must also be considered prior to applying the results. Only articles in the English language were included; and, therefore, making a generalization could be erroneous. The continuous variables were excluded, only two

databases were explored, studies deficit of sample size was excluded.

5. CONCLUSION

The patients with prior antibiotic use, genitourinary abnormalities, and prior history of admission face a greater risk of developing Cip-REC, TMP/SMX-REC, and TGC-REC infections, respectively. The identification of modifiable risk factors for specific antibiotic-resistant infections could play a significant part in the prevention of the threat posed by resistant *E. coli* infections.

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