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# Risk Factors of Extended-Spectrum Beta-Lactamases-Producing *Escherichia coli* Community Acquired Urinary Tract Infections: A Systematic Review

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*Infection and Drug Resistance*

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**Purpose:** The prevalence of extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL-EC) has been increasing worldwide since the early 2000s. *E. coli* is found in 70–90% of community-acquired urinary tract infections (CA-UTIs). We performed a systematic literature review to determine the risk factors for CA-UTI caused by ESBL-EC.

**Methods:** We searched the MEDLINE, Cochrane Library, Embase and Web of Science databases without language or date restriction up to March 2019. Two independent reviewers selected studies with quantified risk factors for CA-UTI due to ESBL-EC, and assessed their quality using the Newcastle-Ottawa Scale.

**Results:** Among the 5,597 studies identified, 16 observational studies (n=12,138 patients) met the eligibility criteria. The included studies were performed in various countries, and 14/16 were published after 2012. The most relevant risk factors for CA-UTI due to ESBL-EC identified were prior use of antibiotics (odds ratio (OR) from 2.2 to 21.4), previous hospitalization (OR: 1.7 to 3.9), and UTI history (OR: 1.3 to 3.8). Two risk factors were related to environmental contamination: travelling abroad, and swimming in freshwater.

**Conclusion:** Our findings could allow adapting empiric antibiotic treatments according to the patient profile. Further studies are needed to quantify the relationships between CA-UTI due to ESBL-EC and the environment.

**Keywords:** multi-drug resistant bacteria, enterobacteria infection, community-acquired infection, risk factor, beta-lactam resistance, systematic review

## Introduction

Extended-spectrum beta-lactamases (ESBL) provide resistance to most beta-lactam antibiotics. Their prevalence has been increasing since the early 2000s.<sup>1,2</sup> This is a worldwide phenomenon, but higher resistance rates have been reported in developing countries. The prevalence is currently lower than 10% in Europe,<sup>3–5</sup> but can reach 46% in some South Asian countries.<sup>6–8</sup> In 2017, the World Health Organization (WHO) defined a list of priority antibiotic-resistant pathogens for research purposes in which ESBL-producing enterobacteria are the most critical group.<sup>9</sup> Indeed, these bacteria are resistant to penicillin and third-generation cephalosporins, two antibiotics that are among the most used worldwide due to their broad spectrum of action and low toxicity. In addition, ESBL presence is frequently associated with resistance to fluoroquinolones.<sup>1,10,11</sup>

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Urinary tract infections (UTIs) are among the most common bacterial infections in the community. The enterobacterium *Escherichia coli* (*E. coli*) is found in 70–90% of UTIs. The antibiotic treatment for these infections is most often empiric.<sup>12–14</sup> Therefore, the identification of factors that increase the risk of UTIs caused by ESBL-producing *E. coli* is a major but crucial challenge<sup>15–17</sup> in order to optimize empiric antibiotic treatments and to limit the spread of antibiotic resistance.

In 2018, Tenney et al<sup>18</sup> published a systematic literature review on the risk factors of UTI caused by multi-drug-resistant bacteria but without restriction on specific pathogens (ie, *E. coli*), mechanisms of resistance (ie, ESBL), or settings (ie, community). The most robust risk factors identified were previous use of antibiotics, urinary catheterization, previous hospitalization, and living in a nursing home. However, data extraction for this review was completed in February 2016 before the publication of the WHO list of priority pathogens. Therefore, we thought appropriate to perform an updated systematic review of the literature by focusing on multidrug-resistant enterobacteria because the WHO identified them as a priority for research purposes (ie, ESBL-producing enterobacteria), and as the most frequently found in UTIs (ie, *E. coli*). The spread of these multidrug-resistant bacteria in community settings is becoming a matter of concern because it is harder to control than in hospital settings. Therefore, we decided to focus our review on factors that have been found to be associated with the emergence of community-acquired UTI (CA-UTI) caused by ESBL-producing *E. coli*.

The aim of this systematic review was to identify risk factors of carrying ESBL-producing *E. coli* among patients with UTI in order to optimize their management in the community.

## Methods

### Study Protocol and Registration

The protocol of this systematic review was registered in the international prospective register of systematic reviews (PROSPERO) database (no. CRD 42018089205) in March 2018. Results were reported according to the PRISMA group recommendations.

### Eligibility Criteria

Studies were eligible for inclusion if they reported factors associated with UTI that was caused by ESBL-producing *E. coli* (identified by a laboratory test) and that occurred in

the community (ie, outside hospitals or medium- and long-stay centers). Hospital-based studies were included only if UTI was diagnosed no later than 48 hours after hospital admission and thus could not be considered a nosocomial infection.<sup>19</sup>

Studies could include adult or pediatric populations without age restriction. Studies on populations who required specialized antibiotic treatment (eg, immunosuppressed patients, patients with kidney graft, with malformation of the urinary tract) were excluded. Only studies on humans were included.

### Sources of Information and Search Strategy

The following databases were searched with no date restriction until the end of March 2019: MEDLINE, Embase, Cochrane Library, and Web Of Science. No filter on date, location, or publication language was used in the search strategy. The initial search equation in MEDLINE was then adapted for each database ([supplemental Table S1](#)). A manual search was also performed in the conference archives of the American Society of Microbiology (ASM), the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), and the International Congress on Infectious Diseases (ICID). No standardized search strategy was used for the grey literature.

When publications were deemed relevant but the published data were insufficient, the authors were contacted by email to provide complementary data. In the absence of a reply, a reminder was sent.

The reference list of all selected publications was analyzed to identify (and include) new relevant articles.

### Study Selection

Only studies published in English, German, French, and Spanish were included. Duplicates were identified and removed. Two researchers (VD, PD) independently screened each title and abstract. Then, the full text of all studies considered to be relevant was obtained. The same two researchers independently assessed these studies for inclusion; any disagreement was resolved by consensus. In the absence of consensus, a third researcher (SL) was consulted.

### Data Collection and Collected Data

The two researchers (VD, PD) independently collected the following data from the selected studies using a standardized

form: (i) study characteristics (title, authors, journal, year of publication, country, objective); (ii) methods (study type, duration, number and location of participating centers, diagnostic and microbiological criteria for community-acquired UTI due to ESBL-producing *E. coli*); (iii) population characteristics (number, sex, age, inclusion and exclusion criteria); (iv) endpoints (variables that could be potential risk factors); (v) results: odd ratios (OR) and 95% confidence interval (95% CI); (vi) funding sources, conflicts of interest.

## Additional Analyses

When the association indicators were not provided by the authors, they were calculated with their 95% CI using the MedCalc<sup>®</sup> software<sup>20</sup> based on the Altman method.<sup>21</sup>

## Study Quality Assessment

Two researchers (VD, PD) independently assessed the methodological quality of the included studies.

Case-control studies were assessed using the Newcastle-Ottawa Scale (NOS)<sup>22</sup>. This scale allows assigning a numerical score to each study. It includes eight items that are classified according to three assessment criteria: selection, comparison, and exposure. For each item, several response options are possible. A star system is used to assess the study quality. A maximum of one star can be assigned to each item, with the exception of the comparability criterion where up to two stars can be assigned. The total score ranges between 0 and 9 stars. A high-quality study will have a high final score.

Cross-sectional studies were assessed using an adapted version of the NOS<sup>22,23</sup> that includes only seven items classified according to three assessment criteria: selection, comparison, and results. Depending on the item, one or two stars can be assigned; the maximum score is 10 stars.

## Results

### Study Selection

A total of 5,984 articles were found (Figure 1): 1,994 via MEDLINE, 64 via Cochrane Library, 3,005 via Embase, and 916 via World Of Science. Five articles were found by manual search of the ASM, ECCMID and ICID conference archives. After duplicate removal, 4,126 articles were eligible for inclusion. Based on the titles and abstracts, 134 articles were selected for full reading. Among the 15 authors contacted to obtain complementary data, four answered. After reading the retained articles, 88 did not meet the inclusion criteria, 19 included some exclusion

criteria, 7 were not found in a language understandable by the authors of the review, and 4 were excluded for insufficient data. In total, 16 studies (n=12,138 patients) were included<sup>24–39</sup>.

## Characteristics of the Included Studies

All 16 studies were observational; 14 were case-control studies, and 2 were cross-sectional studies. Fourteen studies were published in peer-reviewed journals, and two corresponded to congress posters. Two studies were published between 2006 and 2009, and the others between 2012 and 2017.

These studies were carried out in Asia (n=5), Europe (n=8), South America (n=2) and North Africa (n=1), and concerned adult (n=11) and paediatric populations (n=3). Two studies did not provide any information on the patients' age.

Only two studies concerned patients who were managed in non-hospital settings. The others included also inpatients (n=4), or concerned hospitalized patients in whom UTI was identified within 48 hours after hospital admission in all cases (n=10).

## Study Quality

Nine studies had a score  $\geq 8$ , five had intermediate scores (6 or 7), and two studies had a score  $\leq 6$  (Table 1).

## Risk Factors of ESBL-Producing *E. coli* Urinary Tract Infection

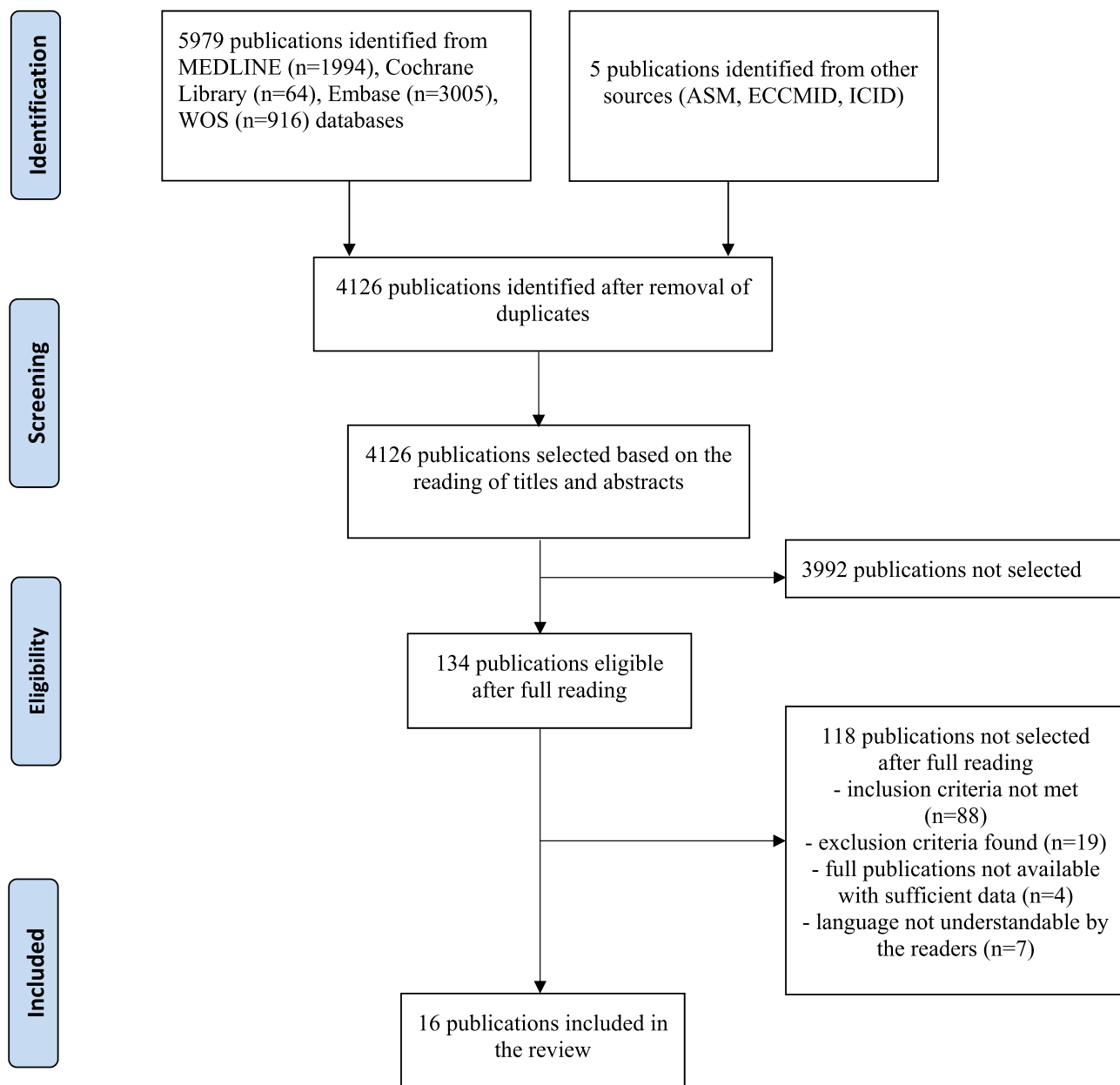
Results are presented in Table 2.

### Prior Use of Antibiotic

Previous antibiotic intake was the most frequently identified risk factor for UTI due to ESBL-producing *E. coli* (n=12 studies) and was strongly associated with UTI occurrence in most of these studies (OR >4 in 8 of these 12 studies).

Four studies reported antibiotic intake without specifying the classes, with OR values ranging between 3.1 (95% CI: 1.4–6.7) and 5.6 (95% CI: 2.1–14.8) in adults.<sup>27,29,33,37</sup> When looking at the antibiotic classes, beta-lactams (penicillin and cephalosporins) were found to be an independent risk factor in five studies, with ORs ranging between 2.2 (95% CI: 1.1–4.5) and 21.4 (95% CI: 5.4–85.2).<sup>29,33,35–37</sup>

Fluoroquinolones use was associated with higher risk of UTI in three studies.<sup>32,38,40</sup> Søråas et al reported the use of fluoroquinolones as a major risk factor (OR: 19.0), but with very wide confidence intervals (95% CI: 3.3–111.4), but not Ozdogan et al (OR: 2.6, 95% CI: 1.3–5.1).



**Figure 1** Study flowchart according to the PRISMA recommendations.

Nisha et al and Søgaard et al identified nitrofurantoin as a risk factor in children (OR: 11.5, 95% CI: 1.5–89.1) and in the general population (OR: 1.54, 95% CI: 1.05–2.26).

### Prior Hospitalization

Prior hospitalization was identified as a risk factor in three good-quality studies (NOS score: 7 to 9). The OR values ranged between 1.7 (95% CI: 1.3–2.3) and 3.9 (95% CI: 1.2–12.7), depending on the number of prior hospitalizations and time to infection.<sup>27,38,39</sup>

### History of UTIs

UTI history was identified as a risk factor in three (four according to Table 2) studies. The ORs ranged between 1.3 (95% CI: 1.0–1.6) and 3.8 (95% CI: 1.8–8.1), but the definition of “UTI history” was heterogenous: UTI during the previous year,  $\geq 3$  UTI episodes during the previous year, and recurrent acute pyelonephritis.<sup>29,37,38</sup>

### Underlying Condition

Diabetes was a moderated risk factor for UTI due to ESBL-producing *E. Coli* (OR: 3.7 (95% CI: 1.1–12.7)).<sup>34</sup>

**Table 1** Characteristics and Quality of the Included Studies

Authors/Ref Country/Year	Study Type	Patients	Quality (Score)
Søgaard M et al <sup>38</sup> Denmark, 2017	Dual case-control study	Patients from general medicine departments n=7,170 UTI due to ESBL-producing <i>E. coli</i> n=339 Controls: UTI due to non-ESBL-producing <i>E. coli</i> n=3,390	9/9
Hertz FB et al <sup>27</sup> Denmark, 2015	Triple case-control study	Patients from general medicine departments with UTI due to <i>E. coli</i> n=449 ESBL-producing <i>E. coli</i> n=98 Controls: multi-sensitive n=177	9/9
Søraas A et al <sup>35</sup> Norway 2013	Case-control study	All patients with community-acquired UTI due to enterobacteria from 4 hospitals n=290 <i>E. coli</i> subgroup n=272 ESBL-producing <i>E. coli</i> n=95 non-ESBL-producing <i>E. coli</i> n=177	8/9
Artero A et al <sup>31</sup> Spain, 2017	Case-control study	Patients >65 years, hospitalized for community-acquired acute pyelonephritis or urinary sepsis due to <i>E. coli</i> n=310 ESBL-producing <i>E. coli</i> n=85 non-ESBL-producing <i>E. coli</i> n=225	8/9
Calbo E et al <sup>36</sup> Spain, 2006	Case-control study	Outpatients or emergency patients with UTI due to <i>E. coli</i> n=74 ESBL-producing <i>E. coli</i> n=19 Non-ESBL-producing <i>E. coli</i> n=55	8/9
Azap OK et al <sup>37</sup> Turkey, 2009	Case-control study	Outpatients with UTI aged between 18 and 65 years n=510 <i>E. coli</i> subgroup n=464 ESBL-producing <i>E. coli</i> n=51 Non-ESBL-producing <i>E. coli</i> n=413	8/9
Ozdogan FN et al <sup>33</sup> Turkey, 2015	Case-control study	Outpatients with UTI due to <i>E. coli</i> aged >18 years n=200 ESBL-producing <i>E. coli</i> n=100 Non-ESBL-producing <i>E. coli</i> n=100	7/9
Toumi A et al <sup>34</sup> Tunisia, 2015	Case-control study	Patients aged >14 years hospitalized in infectious disease departments for community-acquired acute pyelonephritis due to <i>E. coli</i> n=484 ESBL-producing <i>E. coli</i> n=24 Non-ESBL-producing <i>E. coli</i> n=442	7/9
Castillo-Tokumori F et al <sup>39</sup> Peru, 2017	Case-control study	Outpatients with UTI due to <i>E. coli</i> aged >18 years n=172 ESBL-producing <i>E. coli</i> n=67 Non-ESBL-producing <i>E. coli</i> n=105	7/9
Blanco Victor M et al <sup>24</sup> Colombia, 2015	Case-control study	Emergency patients with UTI due to <i>E. coli</i> with no age restriction n=431 ESBL-producing <i>E. coli</i> n=54 Non-ESBL-producing <i>E. coli</i> n=377	7/9
Savatmorigkongul S et al <sup>29</sup> Thailand, 2016	Cross-sectional study	Emergency patients with UTI due to <i>E. coli</i> aged >15 years n=408 ESBL-producing <i>E. coli</i> n=159 Non-ESBL-producing <i>E. coli</i> n=249	8/10
Park SH et al <sup>30</sup> South Korea, 2015	Case-control study	Patients hospitalized for community-acquired acute pyelonephritis due to <i>E. coli</i> aged >15 years n=300 ESBL-producing <i>E. coli</i> n=75 Non-ESBL-producing <i>E. coli</i> n=225	8/9

(Continued)

Table 1 (Continued).

Authors/Ref Country/Year	Study Type	Patients	Quality (Score)
Kang CI et al <sup>28</sup> South Korea, 2012	Case-control study	Outpatients or emergency patients with infection due to <i>E. coli</i> aged >15 years n=140 Subgroup with UTI alone: ESBL-producing <i>E. coli</i> n=73 Non-ESBL-producing <i>E. coli</i> n=67	6/9
Nisha KV et al <sup>25</sup> India, 2017	Case-control study	Outpatient children with UTI due to <i>E. coli</i> aged 3 months to 18 years n=523 ESBL-producing <i>E. coli</i> n=196 Non-ESBL-producing <i>E. coli</i> n=327	8/9
Pérez Heras I et al. <sup>26</sup> Spain, 2017	Cross- sectional study	Emergency pediatric patients with UTI due to <i>E. coli</i> aged <14 years n=229 ESBL-producing <i>E. coli</i> n=21 Non-ESBL-producing <i>E. coli</i> n=208	4/10
Fan NC et al. <sup>32</sup> Taiwan, 2014	Case-control study	Inpatient children with community-acquired UTI due to <i>E. coli</i> aged <15 years n=312 ESBL-producing <i>E. coli</i> n=104 Non-ESBL-producing <i>E. coli</i> n=208	5/9

This risk factor was also reported in the study by Toumi et al in patients hospitalized for pyelonephritis (OR: 3.0, 95% CI: 1.1–8.0). Similarly, Park et al reported a synergistic effect of diabetes with recurrent acute pyelonephritis (OR: 4.2, 95% CI: 1.3–16.9).

### Patient Care-Related Infections

Catheter-related UTI (OR: 3.3, 95% CI: 1.7–6.6),<sup>29</sup> surgery 3–12 months before infection (OR: 2.7, 95% CI: 1.9–8.0),<sup>37</sup> use of immunosuppressive treatments (OR: 1.5; 95% CI: 1.1–2.1),<sup>38</sup> and chronic corticosteroid treatments (OR: 24.3; 95% CI: 2.4–246.9)<sup>39</sup> were identified as risk factors for UTI due to ESBL-producing *E. coli*.

Two studies investigated a composite “care-related infection” risk factor. Artero et al, who studied patients older than 65 years, defined this risk as the presence of at least one of the following criteria: hospitalization in the previous 3 months, living in a nursing home, and administration of antibiotics in the previous 3 months (OR: 6.8, 95% CI: 3.2–14.3). Kang et al defined this risk factor differently (ie, hospitalization for at least 48 hours in the previous 90 days; having received haemodialysis, intravenous treatment, or wound care at home in the previous 30 days; living in a long-stay facility or in a nursing home) and obtained an OR of 6.8 (95% CI: 2.8–16.2).

Blanco Victor et al described a “complicated urinary tract infection” (pyelonephritis, functional or structural abnormality of the urinary tract, immunosuppression, UTI in men or in pregnant women) as a risk factor of

UTI due to ESBL-producing *E. coli* (OR: 3.9, 95% CI: 1.1–13.9).

### Demographic Factors

Age over 55 years (OR: 2.0, 95% CI: 1.0–3.5)<sup>30</sup> and male sex (OR: 1.6, 95% CI: 1.2–2.1 in the higher quality study by Sogaard et al)<sup>38</sup> also have been reported as risk factors for UTI due to ESBL-producing *E. coli*.

### Other Factors

Søraas et al identified having travelled abroad (Asia, Middle East, Africa) in the previous 6 weeks as a major and independent risk factor (OR: 21; 95% CI: 4.5–97), as well as swimming in freshwater (OR: 2.1; 95% CI: 1.0–4.2).<sup>35</sup>

## Discussion

The purpose of this systematic review was to identify risk factors of UTI caused by ESBL-producing *E. coli*. Our findings confirm the results of previous studies and systematic reviews. Indeed, previous use of antibiotics, hospitalization in the previous months, and history of UTIs were known risk factors.<sup>18</sup> However, travelling to endemic areas seems also an important risk factor (OR: 16.4 [3.4–78.8]), according to the study by Søraas et al who showed that this risk is present for several months after travelling, and it decreases over time. Although this risk factor was identified only in this study, the risk of intestinal carriage of ESBL-producing *E. coli* following a trip in an endemic area, particularly Asia, has been already reported in the

**Table 2** Identified ESBL-E coli Community-Acquired Urinary Tract Infection Risk Factors

Risk Factors (Reference)	Adjusted OR	CI	Sample Size
<b>Care related factors</b>			
Prior use of antibiotics			
In the last 30 days <sup>27</sup>	1.8	[1.0–3.1]	n=449
[39]	3.1	[1.4–6.7]	n=172
In the last 3 months <sup>34</sup>	4.0	[1.6–10.0]	n=484
In the previous year <sup>30</sup>	4.6	[1.9–11.0]	n=300
Time NS <sup>28</sup>	5.6	[2.1–14.8]	n=140
Prior use of broad spectrum antibiotic			
Any, 31–365 days before index date <sup>38</sup>	0.9	[0.5–1.7]	n=7,170
Penicillin, 31–365 days before index date <sup>38</sup>	1.0	[0.7–1.5]	n=7,170
Prior use of beta-lactams			
In the last 90 days <sup>35</sup>	4.5	[1.8–11.0]	n=290
[37]	4.6	[2.0–10.7]	n=510
Prior use of penicillin			
Any, time NS <sup>29</sup>	2.7	[1.2–6.3]	n=408
Prior use of cephalosporine			
Cefuroxime, time NS <sup>36</sup>	21.4	[5.4–85.2]	n=74
2GC, time NS <sup>33</sup>	3.9	[1.8–8.5]	n=200
Cephalosporin, time NS <sup>29</sup>	2.2	[1.1–4.5]	n=408
3GC, time NS <sup>33</sup>	2.2	[1.01–5.0]	n=200
Prior use of Macrolide			
Any, 31–365 days before index date <sup>38</sup>	1.5	[1.1–2.2]	n=7,170
Prior use of nitrofurantoin			
31–365 days before index date <sup>38</sup>	1.54	[1.1–2.3]	n=7,170
Prior use of fluoroquinolones			
Any, in the last 30 days <sup>27</sup>	2.1	[0.6–7.3]	n=449
Any, in the last 90 days <sup>35</sup>	19.0	[3.3–111.4]	n=290
Any, time NS <sup>33</sup>	2.6	[1.3–5.1]	n=200
[28]	9.9	[2.2–44.6]	n=140
Prior hospitalization			
Any, in the last 30 days <sup>27</sup>	3.9	[1.2–12.7]	n=449
Any, in the last 3–12 months <sup>39</sup>	2.9	[1.3–6.6]	n=172
1–2 hospitalizations, in the previous year <sup>38</sup>	1.7	[1.3–2.3]	n=7,170
> 3 hospitalizations, in the previous year <sup>38</sup>	3.9	[2.6–5.8]	n=7,170
Prior surgery, in the last 3–12 months <sup>39</sup>	2.8	[1.9–8.0]	n=172
History of UTIs			
Any, in the previous year <sup>38</sup>	1.3	[1.01–1.6]	n=7,170
≥3 episodes of UTI, in the previous year <sup>37</sup>	3.8	[1.8–8.1]	n=510
History of UTI due to E. coli, time NS <sup>29</sup>	3.4	[1.8–6.7]	n=408
Renal or urological disorder			
History of recurrent acute pyelonephritis <sup>30</sup>	1.7	[0.7–3.9]	n=300
Recurrent acute pyelonephritis + history of diabetes <sup>30</sup>	4.2	[1.3–16.9]	n=300
Renal disease <sup>38</sup>	1.6	[1.0–2.5]	n=7,170
Urological abnormality <sup>34</sup>	3.5	[1.0–11.5]	n=484
Prior urinary catheterization <sup>29</sup>	3.3	[1.7–6.6]	n=408
History of prostatic disease <sup>37</sup>	9.6	[2.1–44.8]	n=510
Diabetes			
[35]	3.7	[1.1–12.7]	n=290
[34]	3.0	[1.1–8.0]	n=484
[30]	1.7	[0.8–3.4]	n=300

(Continued)



Table 2 (Continued).

Risk Factors (Reference)	Adjusted OR	CI	Sample Size
Prior medication			
Prior immunosuppressive therapy <sup>38</sup>	1.5	[1.1–2.1]	n=7,170
Chronic treatment with corticosteroids <sup>39</sup>	24.3	[2.4–246.9]	n=172
<b>Demographic characteristics</b>			
Male sex [38]	1.6	[1.2–2.1]	n=7,170
Age >55 years [30]	2.0	[1.02–3.5]	n=300
Citizenship Northern Europe vs other countries <sup>38</sup>	0.4	[0.2–0.7]	n=7,170
<b>Environmental factors</b>			
Travelling abroad (Asia, Middle East, Africa) In the previous 6 weeks <sup>35</sup>	16.4	[3.4–78.8]	n=290
Same regions between 6 weeks and 2 years before <sup>35</sup>	2.2	[1.1–4.3]	n=290
Swimming in freshwater [35]	2.1	[1.02–4.2]	n=290
Number of fish meals per week [35]	0.6	[0.5–0.9]	n=290

literature.<sup>40,41</sup> However, additional studies are needed to confirm the importance of this risk factor.

The heterogeneity of the definitions of risk factors among studies is the main limitation of this review. For example, the risk factor “previous use of antibiotics” requires to specify the time between the previous use of antibiotics and UTI occurrence. However, among the 12 studies that investigated this factor, only five gave this information, and among them, three reported use of antibiotics in the three months before UTI. The same is true for “history of UTIs”. Previous UTI frequencies and characteristics varied among studies, thus making difficult the accurate description of this factor.

Most risk factors were related to patient healthcare. Two studies introduced a composite factor referred to as “care-related infection”. While the definition proposed by Kang et al was derived from the literature,<sup>42</sup> the one used by Artero et al is questionable since it encompassed heterogeneous criteria such as hemodialysis and residence in nursing home without any obvious justification. In both cases, the clinical application of these factors appeared difficult because they are composed of risk factors that have very different ORs when studied individually as shown in our review. Moreover, only three studies were carried out exclusively in paediatric populations among whom two were of low quality (NOS

score  $\leq 5$ ). Therefore, it is difficult to draw conclusions for this specific population.

Another limitation is that most studies were performed in hospital settings. This bias is caused by the difficulties of health data collection in the community, with patients and caregivers often scattered over a large territory. Although we included only studies on patients with UTI detected within the first 48h after hospital admission to exclude a nosocomial infection, patients recruited in hospital might not be representative of *E. coli* BLSE-infected subjects in the community (comorbidity, age . . .). More studies conducted in the community would enable to refute or confirm this bias. Nevertheless, this patient population highlights the risk of importing multi-resistant *E. coli* from the community to the hospital,<sup>43</sup> and the importance of the rapid identification of potential carriers.

This systematic review identified two new risk factors: prior treatment with nitrofurantoin and swimming in freshwater. Prior treatment with nitrofurantoin was reported in two studies.<sup>25,38</sup> However, Søgaaard et al stressed the risk of possible confusion concerning this factor. Indeed, nitrofurantoin is used for the prevention of recurrent UTI that is also a risk factor of UTI in studies carried out in hospital settings.<sup>44,45</sup> This might explain its identification as a risk factor of UTI caused

by ESBL-producing *E. coli*. Moreover, the association reported by Nisha et al was among hospitalised children. So, this association should be interpreted with caution. Nevertheless, as nitrofurantoin is recommended as first-line therapy in the treatment of uncomplicated cystitis in most countries, other studies are needed to confirm that this antibiotic is (or not) an independent risk factor.

The other new risk factor identified by one study was swimming in freshwater. Environmental contamination, particularly of aquatic environments, by ESBL-producing *E. coli* has been already described in the literature.<sup>46–48</sup> Our systematic review highlights the impact of this contamination on human health. Its presence in the environment makes more complex the implementation of models to predict infection or colonization by ESBL-producing *E. coli*. Several predictive models were proposed based on previously identified risk factors,<sup>49,50</sup> essentially related to patient care and patient characteristics. The limits of these models are their medium sensitivity and their low external validity. Additional factors of environmental origin could be considered to improve the latter. Therefore, more studies are needed to precisely determine the environmental factors associated with the increased prevalence of UTIs caused by ESBL-producing *E. coli* in order to better manage them and to identify potential carriers. Moreover, local specificities should be taken into account to develop robust predictive models. Finally, studies on community patients should be promoted to allow a generalisation of the conclusions.

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All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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