Isolation rates and antibiotic susceptibilities of different Enterobacteriaceae species as urinary tract infection agents in Turkey: a systematic review

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Background/aim: In Turkey, few systematic reviews have analyzed the results of studies on the isolation rates of urinary tract infection agents and their antibiotic susceptibilities. This review was done to fill this gap and enable the correct application of guideline-based medical therapy by determining the isolation rates and antibiotic susceptibilities of different Enterobacteriaceae species in Turkey.

Materials and methods: Relevant studies found from various databases with the help of previously specified search strategies were examined and eliminated according to eligibility criteria. The remaining 22 studies were included in this systematic review.

Results: Escherichia coli was the most frequently isolated species among all agents in both in- and outpatient settings. Only the antibiotic susceptibility data of E. coli could be analyzed because among the 22 studies only E. coli had adequate antibiotic susceptibility data to be analyzed. The calculated resistance rates of the most frequently preferred antibiotics (trimethoprim/sulfamethoxazole, ciprofloxacin, and ceftriaxone) were 46%, 32%, and 19% for outpatients and 54%, 48%, and 28% for inpatients, respectively.

Conclusion: The resistance profiles of commonly used antimicrobial agents are much higher than the thresholds set by international guidelines. Hence, treatment algorithms for urinary tract infections should be designed according to Turkey’s antimicrobial resistance patterns.

Key words: Systematic review, Enterobacteriaceae, Turkey, urinary tract infections

1. Introduction
Urinary tract infections are one of the most commonly seen infections in both in- and outpatient settings (1,2). In Turkey, although studies have been conducted on urinary tract infection agents and their antibiotic susceptibilities, they have generally been regional studies covering limited time periods. There are a limited number of reviews to pool the results of different studies and reveal the isolation rates of different species and their antibiotic susceptibilities in Turkey.

The objective of this review is to contribute to the advancement of empirical treatment, particularly in primary healthcare settings, and to reveal the isolation rates of Enterobacteriaceae species, the most common agents of urinary tract infections, and their antibiotic susceptibilities.

2. Materials and methods
The method used in this review was established by considering the items provided in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols-2015 (PRISMA-P) statement. Based on this guide, information resources were identified and searching strategies were established by a team consisting of three microbiologists, one medical pharmacologist, and one biostatistician who then reviewed the studies and evaluated the data collected according to the specified acceptance/rejection criteria.

2.1. Information resources to review and searching strategies
infection, Turkey” were used as the keyword groups, and searching was performed in both Turkish and English.

2.2. Acceptance/rejection criteria
The following acceptance and rejection criteria were established to use in identifying the articles to assess in the review:

- The study must have been conducted in Turkey.
- The study must have been published between 2009 and 2015.
- The language of publication must be Turkish or English.
- The study must a research paper published in peer-reviewed journals.
- The study must have been performed on individuals above 18 years of age.
- The article must involve at least one result of agent frequency or antibiotic susceptibility.
- At least 30 strains must have been reviewed in the article.
- The results of antibiotic susceptibility tests must have been evaluated with disk diffusion or minimum inhibitory concentration (MIC) results according to Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.

Data on both lower and upper urinary systems were included. Studies that provided the results of the frequency of urinary tract infection agents and their antibiotic susceptibilities mixed with the results of the agents isolated in other system infections and their susceptibilities without specifically indicating the former were not included in the review. Data regarding hospital- and community-acquired infections were separated; however, both were included. Studies involving specific patient groups (e.g., patients who developed neurogenic bladder due to spinal cord injury) were not included.

2.3. Analysis of studies and evaluation of data
Articles found in the database search were collected on a digital platform. Two microbiologists from the team evaluated the articles in accordance with the acceptance/rejection criteria and allocated the ones that complied with the criteria. Data from the selected articles were collected through Microsoft Excel Office and charts and tables were generated. A medical microbiologist and a biostatistician were assigned for this stage.

Articles were categorized primarily based on whether they involved in- or outpatient groups to analyze the frequency of isolation of agents. Afterwards, the geographic regions where studies originated were determined considering the Nomenclature of Territorial Units for Statistics (NUTS) of Turkey. Tables showing isolation rates (in %) of agents included in the selected articles were generated. Antibiotic resistance was investigated for ampicillin, cefuroxime, ceftriaxone, ciprofloxacin, gentamicin, cotrimoxazole, carbapenems, piperacillin-tazobactam, and nitrofurantoin. Extended-spectrum beta-lactamase (ESBL) production was noted, if indicated. Resistance rates in percentages were reported separately for in- and outpatient settings. Standardized resistance rates were calculated to minimize the effects of the difference in the number of strains between the articles. Standardized rates are a statistical measure of any rates in a population. These are adjusted rates considering the vital differences between populations. They are calculated by dividing the number of strains of a species that are resistant to an antibiotic by the number of strains of the same species that are expected to be resistant to the same antibiotic considering the average resistance rate in Turkey. For example, the number of ampicillin-resistant Escherichia coli was found to be 59 in 107 strains in an article published from Western Anatolia. If the average of ampicillin-resistant E. coli in Turkey is 61.5%, the number of resistant E. coli expected for that study would be 66. In that case, the standardized resistance rate would be calculated as 59/66 × 100 = 89.9. This method is a tool to observe deviations from average resistance rates. As the standardized rate deviates more from 100, the resistance rates of those analyzed strains become more extreme.

3. Results
The search yielded 94 articles that had been published between 2009 and 2015. After evaluations were performed based on the acceptance/rejection criteria, the review was carried out on 22 articles (3–24). It was observed that 13 of these articles contained data regarding outpatients alone, whereas four of them contained data regarding both in- and outpatient settings. The distribution of studies by NUTS is shown in Figure 1.

The number of articles among those selected as per the suitability criteria that reached the specified number of strains of at least 30 for different species was 22, 6, and 1 for E. coli, Klebsiella and Proteus, and Enterobacter, respectively. None of the articles reviewed reached the number of strains of 30 for the other Enterobacteriaceae genera. The frequencies of isolation of E. coli and Klebsiella spp. among all agents in in- and outpatient settings are shown in Figures 2 and 3. E. coli was more frequently isolated from outpatients (70% of all agents) than inpatients (49% of all agents). Klebsiella spp. was more commonly isolated from inpatients (9.9%) than outpatients (7.3%).

When calculation of antibiotic resistance rates was attempted, it was found that there was a small number of articles reporting antibiotic resistance for other species excluding E. coli (e.g., three articles for Klebsiella). Therefore, antibiotic resistance was investigated for only E. coli. The total number of strains investigated for antibiotic
resistance in 10,090 outpatients and 6065 inpatients is shown in Table 1.

Antibiotic resistance rates for *E. coli* across Turkey were calculated individually for in- and outpatients. Resistance rates are shown in Figures 4 and 5.

Standardized resistance rates were calculated from the expected and observed resistance rates. Standardized resistance rates were found to remain in the range of 70–130 for ampicillin, cephalosporins, ciprofloxacin, and cotrimoxazole, which were included in most of the publications from various geographic regions. This indicated that resistance demonstrated a homogeneous distribution for the relevant antibiotics between different regions. Among the publications, it was seen that there was a limited number of publications studying resistance against other antibiotics and that standardized resistance rates established for these antibiotics were distributed in a wider range. For example, carbapenem resistance was studied in only four of nine articles investigating the resistance rates for inpatients and standardized resistance rates established for carbapenem ranged between 26 and 471. Standardized resistance rates for cotrimoxazole obtained from 14 articles analyzing outpatients are given as an example in Table 2.

### 4. Discussion

Findings obtained from 22 publications selected among 94 based on the suitability criteria specified during the preparation of the review are provided above. During the analysis of both the 94 articles obtained in the first
search and the 22 articles that complied with the criteria, problems were noted in sharing the data obtained from those articles. These problems are listed as follows:

a) Providing data by integrating them in an inappropriate way made the utilization of these data during the review impossible. Examples may include providing the results of isolation rates of gram-negative bacteria isolated at microbiology laboratories without classifying them into sample types or providing the results of common resistance rates belonging to all gram-negative bacteria isolated from urinary cultures.

b) Incomplete demographic information or lack of organization based on information within a study also complicated inferences from the data. Examples may include presenting the results without classifying by age groups.

c) Information about different agents was easily accessible for the researchers regarding urinary tract infections, whereas the fact that the shared information was limited to only one agent was a factor reducing the importance of the studies. Examples may include several studies providing isolation rates of all agents but sharing the result of antibiotic susceptibility for \textit{E. coli} alone.

d) In allocating the data obtained from a study, considering some of the data redundant or insignificant and not sharing them would create problems in future review of the results of the studies. Examples may include not providing isolation rates of rare species, such as \textit{Morganella} spp. or \textit{Serratia} spp.

Along with the articles clearly not complying with the acceptance criteria, we had to eliminate some articles among the 94 articles even if they involved a large number of strains due to the reasons described above (particularly those listed as points a and b). Some of the above-mentioned shortcomings were also noted in the 22 articles that complied with the acceptance criteria and were involved in the review. In assessing the isolation rates, data regarding \textit{E. coli} and \textit{Klebsiella} spp. were accessible, whereas there were limited data about the other genera or species. With respect to antibiotic resistance, only data regarding \textit{E. coli} were taken under review. These shortcomings in the publications are also applicable to this review. Nevertheless, it is worth sharing data regarding \textit{E. coli}, for which the isolation rate was found to be approximately 70% in outpatients and approximately 50% in inpatients, among urinary tract infection agents.

Urinary tract infections are one of the most common infections in both in- and outpatient settings (1,2). They occur with a wide range of diseases from uncomplicated cystitis to urosepsis, which may be fatal. Therefore, urinary tract infections are among the infectious diseases with the most frequent use of therapeutic antibiotics. Intensive

### Table 1. The total number of \textit{E. coli} strains investigated for antibiotic resistance.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Outpatients</th>
<th>Inpatients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>6825</td>
<td>409</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>6927</td>
<td>409</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>8722</td>
<td>751</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>9615</td>
<td>1059</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7613</td>
<td>482</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>9615</td>
<td>1026</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>4103</td>
<td>680</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>7438</td>
<td>678</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1122</td>
<td>306</td>
</tr>
<tr>
<td>ESBL</td>
<td>4744</td>
<td>265</td>
</tr>
<tr>
<td>Total</td>
<td>10,090</td>
<td>6065</td>
</tr>
</tbody>
</table>
use of antibiotics has created the problem of antibiotic resistance in this disease group and made the treatment of uncomplicated cases difficult as well.

In Turkey, the most commonly preferred antibiotics for the treatment of urinary tract infection are cotrimoxazole, ciprofloxacin, and cephalosporins (19,25). However, studies published from Turkey have shown that we have reached the end of the road in the use of these antibiotics. The results obtained from this review show that resistance to cotrimoxazole for *E. coli* has reached 50% and that the empirical use of this antibiotic is only effective half of the time in terms of treatment. Resistance to ciprofloxacin and ceftriaxone in inpatients was found to be approximately 48% and 28%, respectively. The fact that ESBL production is 20% even in outpatients makes the magnitude of the resistance problem clearer. Similar results were also obtained in a systematic review study published in 2013 generated with the results of 101 articles investigating the antibiotic resistance status of *E. coli* strains. According to that study, resistance rates of cotrimoxazole and ciprofloxacin were approximately 50% and 55% in outpatients and inpatients, respectively. Again in that study, the resistance rate of ceftriaxone was found to be 25% in inpatients (26).

Treatment guidelines published in and outside of Turkey recommend the use of cotrimoxazole among the antibiotics specified in the paragraph above, for which there is evidence of resistance problems (27–29). However,
the guidelines published by the American Infectious Diseases Association indicate fosfomycin, nitrofurantoin, and pivmecillinam as the first-choice antibiotics to replace cotrimoxazole and recommend quinolone antibiotics as the second option (28). The treatment guidelines published by the European Urology Association in 2015 listed cotrimoxazole and ciprofloxacin as alternative treatment options and recommended fosfomycin, nitrofurantoin, and pivmecillinam as the first choice (30). In these guidelines, the recommended threshold value for the resistance rate is 20% for treatment with cotrimoxazole in uncomplicated cystitis and 10% for oral ciprofloxacin in acute uncomplicated pyelonephritis for empirical treatment. Considering that the resistance rates for each region detected in our country are much higher than the specified values in the above-mentioned guidelines, adherence to guideline-based medical therapy (GBMT) requires the exclusion of cotrimoxazole from the treatment algorithm for urinary tract infections in Turkey.

Based on the results of the present review, nitrofurantoin was noted as an antibiotic included in those guidelines and appropriate for empirical treatment, particularly in outpatient settings, with resistance rates of 5% and 15% for outpatient and inpatient settings, respectively. Piperacillin-tazobactam was noted as an antibiotic with a low resistance rate of 8% in inpatients. There are publications indicating that piperacillin-tazobactam may be used in the presence of ESBL-producing *E. coli*, and there are ongoing randomized controlled studies comparing its efficacy against these strains versus carbapenems (31–34). The European Urology Association guidelines also describe piperacillin-tazobactam as an alternative antibiotic in the treatment of acute uncomplicated severe cases (30). When consideration is given to the frequency of ESBL in our country, piperacillin-tazobactam appears to be a good candidate for empirical treatment in an inpatient setting.

Consequently, data on *E. coli* and *Klebsiella* spp. were compiled for isolation frequency, whereas only data on *E. coli* were compiled for antibiotic resistance rates. Nevertheless, it is considered that the results obtained for *E. coli*, the most important pathogen among urinary tract infection agents, will be effective in assisting with the selection of the right antibiotic to ensure treatment success.

In conclusion, the application of GBMT requires awareness of resistance rates against antimicrobial agents for a successful therapeutic outcome. This systematic review demonstrated that resistance profiles of commonly used antimicrobial agents are much higher than the thresholds set by the international guidelines. Hence, treatment algorithms for urinary tract infections should be designed according to Turkey’s antimicrobial resistance patterns. The high resistance rates against commonly used antimicrobial agents like ampicillin, cefuroxime, ciprofloxacin, and cotrimoxazole must be considered while recommending/selecting these agents for national guidelines.

<table>
<thead>
<tr>
<th>Region</th>
<th>Strain (n)</th>
<th>Cotrimoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Anatolia</td>
<td>107</td>
<td>90</td>
</tr>
<tr>
<td>Middle Eastern Anatolia</td>
<td>285</td>
<td>99</td>
</tr>
<tr>
<td>Aegean</td>
<td>663</td>
<td>89</td>
</tr>
<tr>
<td>Aegean</td>
<td>619</td>
<td>90</td>
</tr>
<tr>
<td>Aegean</td>
<td>164</td>
<td>97</td>
</tr>
<tr>
<td>Eastern Marmara</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>251</td>
<td>95</td>
</tr>
<tr>
<td>İstanbul</td>
<td>1892</td>
<td>115</td>
</tr>
<tr>
<td>Eastern Marmara</td>
<td>341</td>
<td>72</td>
</tr>
<tr>
<td>Middle Eastern Anatolia</td>
<td>98</td>
<td>134</td>
</tr>
<tr>
<td>Aegean</td>
<td>4534</td>
<td>101</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>100</td>
<td>*</td>
</tr>
<tr>
<td>Entire Country</td>
<td>110</td>
<td>96</td>
</tr>
<tr>
<td>Eastern Marmara</td>
<td>255</td>
<td>77</td>
</tr>
<tr>
<td>İstanbul</td>
<td>54</td>
<td>*</td>
</tr>
<tr>
<td>Middle Eastern Anatolia</td>
<td>202</td>
<td>92</td>
</tr>
<tr>
<td>Middle Eastern Anatolia</td>
<td>321</td>
<td>*</td>
</tr>
</tbody>
</table>

*No data are available regarding this antibiotic.

General resistance rate = (total observed resistances/total number of strains).

Expected resistance valuei = (general resistance rate × number of strains in articlei).

Standardized resistance rate i = (observed resistance i/expected resistancei) × 100.
References


