Appropriateness of trimethoprim as empiric treatment for cystitis in 15–55 year-old women: an audit

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ABSTRACT

AIM: To assess whether trimethoprim remains an appropriate empiric treatment for uncomplicated cystitis in women 15–55 years old.

METHODS: General practitioners in Auckland, Nelson-Marlborough, Otago and Southland were invited to participate in this audit of current practice. Participating general practitioners were asked to submit urine to the laboratory for microscopy and culture from any woman aged 15–55 years presenting with uncomplicated cystitis. Urine samples submitted as part of the audit were identified by a “copy to” code. Data on laboratory results were extracted from the laboratory information system.

RESULTS: Data were collected from June 2016 to August 2018. Four hundred and eighty-one samples were submitted, of which 340 (70.7%) met the inclusion criteria of the audit. A urinary pathogen was identified in 181 (53.2%) specimens, of which 148 (81.8%) were *E. coli*, 13 (7.2%) other coliforms and 20 (11.0%) *Staphylococcus saprophyticus*. Of the *E. coli* isolates, 109 of 148 (73.6%, 95% CI 66.6–80.7) were susceptible to trimethoprim, 144 of 144 (100%, 95% CI 100–100) to nitrofurantoin and 143 of 148 (96.6%, 95% CI 93.7–99.5) to cefalexin. Of the urinary pathogens, 139 of 185 (75.1%, 95% CI 68.9–81.4) were susceptible to trimethoprim, 164 of 177 tested (92.7%, 95% CI 88.8–96.5) to nitrofurantoin and 166 of 178 tested (93.3%, 95% CI 89.6–96.9) to cefalexin. Overall, a uropathogen resistant to trimethoprim was detected in 13.5%, to nitrofurantoin in 3.8%, and to cefalexin in 3.5% of samples tested.

CONCLUSION: Similar rates of resistance to trimethoprim were seen in women 15–55 years old presenting with cystitis compared with unselected samples submitted from the general community. Given the high rates of resistance, trimethoprim is no longer appropriate as an empiric treatment option for cystitis in this group. Nitrofurantoin or cefalexin are appropriate alternative empiric treatment options. Given the current recommendation that a urine sample should not be submitted to the laboratory from women with uncomplicated cystitis, ongoing audits will be required to ensure that empiric treatment recommendations remain appropriate.

Cystitis is a common presentation in primary care. Uncomplicated cystitis is defined as occurring in females with a normal urinary tract. The most common cause of uncomplicated cystitis is *Escherichia coli*, with other Enterobacterales and *Staphylococcus saprophyticus* less common causes. Current bpaest guidelines advise against the submission of a urine sample to the laboratory in uncomplicated cystitis. Empiric treatment with trimethoprim or nitrofurantoin is recommended. Since November 2012, trimethoprim has also been available without a prescription from trained pharmacists.

Increasing resistance to trimethoprim has been seen among *E. coli* isolated from urine samples at diagnostic laboratories. The 2016
antibiogram compiled by ESR from data from hospital and community laboratories found that 25.7% of urinary *E. coli* isolates were resistant to trimethoprim.\(^3\) However, if healthcare practitioners are following bpaC\(^2\) guidelines, this may represent an overestimate of the prevalence of resistance as the majority of urines tested would be from treatment failures or complicated urinary tract infections.

To determine the true prevalence of trimethoprim resistance among *E. coli* causing uncomplicated cystitis, we performed culture and susceptibility testing on urine samples from women with uncomplicated cystitis.

### Methods

The audit was conducted from June 2016 to August 2018. Initially community healthcare practitioners from Auckland and Dunedin were invited to participate in the audit with the aim of testing 300 urine samples. Due to slow recruitment community healthcare practitioners from other parts of Otago, Southland and Nelson-Marlborough were invited to participate in August 2017. In total, 38 healthcare practitioners from Otago and Southland, 60 from Nelson and Marlborough, and 34 from the Auckland region participated. Participating healthcare practitioners requested a urine sample for culture and susceptibility testing from any woman aged 15–55 years presenting with uncomplicated cystitis. Samples were submitted to Southern Community Laboratories (Otago and Southland), MedLab South (Nelson and Marlborough), or Labtests (Auckland) for testing. To allow data extraction at the end of the audit, healthcare practitioners added a code (“TRIME”) to the request form in the “copy to” field. Urine samples were processed following normal laboratory protocols, including selective culture on the basis of microscopy results at some sites (only cultured if \(>40\) leukocytes at Labtests, \(>10\) leukocytes at MedLab South, or \(>10\) leukocytes at Southern Community Laboratories Dunedin) and direct susceptibility testing; these cut-offs are based on local evaluations which take into account the population and differences in automated microscopy platforms. Zone sizes were interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.\(^4\) All samples that underwent susceptibility testing were tested against trimethoprim, nitrofurantoin, amoxicillin, cefalexin, amoxicillin-clavulanic acid and cefpodoxime (to screen for extended spectrum \(\beta\)-lactamase, or ESBL, production). At MedLab South and Labtests, susceptibility to ciprofloxacin was routinely tested, while at Southern Community Laboratories fluoroquinolone susceptibility was only assessed if the isolate was resistant to first-line antimicrobials.

Descriptive statistics were calculated in Excel. The Health and Disability Ethics Committee (HDEC) secretariat determined that this was an audit of practice and did not require HDEC review.

### Results

A total of 481 samples were received: 135 samples (28.1%) from Auckland, 121 (25.2%) from the Nelson region, 52 (10.8%) from Marlborough, 163 (33.9%) from Otago and 10 (2.1%) from Southland. Of these, 340 (70.7%) were urine samples from females 15–55 years old. Of the 141 (29.3%) that did not meet the inclusion criteria, seven were from males (5%), nine (6.4%) from females <15 years old, 120 (85.1%) from females >55 years old, and five (3.5%) were mislabeled, were from a urinary catheter or were not a urine sample. The proportion of samples that did not meet the inclusion criteria varied by area: 37 (27.4%) Auckland, 50 (41.3%) Nelson region, 14 (26.9%) Marlborough, 36 (22.1%) Otago, four (40%) Southland.

The culture results of the 340 samples from 15–55 year-old females are shown in Table 1. Overall, a potential pathogen was isolated from 185 (54%) of specimens; of these, *E. coli* was reported from 148 (80%), other Enterobacterales from 13 (7.0%), *S. saprophyticus* from 20 (10.8%), and *Enterococcus* spp. from four (2.2%). Of note, 69 (20.3%) of specimens were not cultured based on microscopic criteria and no significant growth was obtained from 43 (12.6%). The remainder of specimens had evidence of contamination (43; 12.6%).
The antimicrobial susceptibilities of *E. coli* isolates from 15–55 year old females are shown in Table 2. Overall, 109 of 148 isolates (73.6%, 95% CI 66.6–80.7) were susceptible to trimethoprim, 144 of 144 (100%, 95% CI 100–100) were susceptible to nitrofurantoin, and 143 of 148 (96.6%, 95% CI 93.7–99.5) were susceptible to cefalexin; similar susceptibility rates were seen among all *E. coli* isolated from urine from 15–55 year-old females from the community over the same period (Table 3). Only 4 of 147 (2.7%, 95% CI 94.1–100) isolates were resistant to cefpodoxime and were confirmed to produce an extended spectrum β-lactamase. Of 13 other Enterobacterales, 11 of 13 (84.6%) were susceptible to trimethoprim and 11 of 13 (84.6%) to cefalexin; testing was not performed against nitrofurantoin as no interpretative criteria were available. Of *S. saprophyticus*, 19 of 20 (95%) were susceptible to trimethoprim, 18 of 18 (100%) to nitrofurantoin and 12 of 13 (92.3%) to amoxicillin (and hence to cefalexin). Of *Enterococcus* spp. two of two (100%) were susceptible to nitrofurantoin; testing was not performed against trimethoprim as activity is uncertain, nor against cefalexin as *Enterococcus* spp. are intrinsically resistant. Considering all urine samples submitted, and

### Table 1: Urine culture result.

<table>
<thead>
<tr>
<th>Organism</th>
<th>SCL/MedLab South</th>
<th>Labtests</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>107</td>
<td>44.2</td>
<td>41</td>
</tr>
<tr>
<td><em>Coliform</em> (Klebsiella, Enterobacter, Citrobacter, Serratia group)</td>
<td>8</td>
<td>3.3</td>
<td>2</td>
</tr>
<tr>
<td><em>Coliform</em> (Proteus, Morganella, Providencia group)</td>
<td>1</td>
<td>0.4</td>
<td>2</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>16</td>
<td>6.6</td>
<td>4</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>3</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>Other (non-pathogen)</td>
<td>4</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Mixed growth</td>
<td>28</td>
<td>11.6</td>
<td>11</td>
</tr>
<tr>
<td>No growth/no significant growth</td>
<td>35</td>
<td>14.5</td>
<td>8</td>
</tr>
<tr>
<td>Not cultured</td>
<td>40</td>
<td>16.5</td>
<td>29</td>
</tr>
<tr>
<td>TOTAL</td>
<td>242</td>
<td>98</td>
<td>340</td>
</tr>
</tbody>
</table>

### Table 2: Antimicrobial susceptibility of *E. coli* isolates.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>SCL/MedLab South</th>
<th>Labtests</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible Total tested</td>
<td>% susceptible</td>
<td>Susceptible Total tested</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>79</td>
<td>107</td>
<td>73.8</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>70</td>
<td>107</td>
<td>65.4</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>104</td>
<td>107</td>
<td>97.2</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid&lt;sup&gt;1&lt;/sup&gt;</td>
<td>98</td>
<td>106</td>
<td>92.5</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>103</td>
<td>103</td>
<td>100.0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>47</td>
<td>48</td>
<td>97.9</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>104</td>
<td>107</td>
<td>97.2</td>
</tr>
</tbody>
</table>

<sup>1</sup>Cystitis breakpoint.
assuming that non-\textit{E. coli} Enterobacterales are resistant to nitrofurantoin and \textit{Enterococcus} spp. to trimethoprim and cefalexin, a uropathogen resistant to trimethoprim was detected in 13.5%, nitrofurantoin in 3.8%, and cefalexin in 3.5% of samples.

\section*{Discussion}

In this audit we assessed the ongoing suitability of trimethoprim as empiric treatment for uncomplicated cystitis in women aged 15–55 years old. Overall, a pathogen was isolated from 53.2% of samples, with \textit{E. coli} the most common pathogen (43.5% of all samples). The susceptibility of \textit{E. coli} to trimethoprim was 73.6%. Therefore, trimethoprim is no longer a suitable empiric treatment for uncomplicated cystitis.

A significant number of specimens (69 (20.3%)) were not cultured due to insufficient leukocytes seen on microscopy. Pyuria is a reliable marker of cystitis.\textsuperscript{5,6} The negative predictive value of sieving on the basis of microscopy has previously been established in each laboratory, is high, and is unlikely to lead to microscopy negative/culture positive samples. In the absence of pyuria most samples would be expected to not grow an organism or to grow a skin/faecal contaminant. Those without significant pyuria likely have an alternative diagnosis, such as urethral syndrome or interstitial cystitis.\textsuperscript{7} In addition, there was no significant growth from 43 (12.6%) specimens and evidence of periurethral contamination in 43 (12.6%).

As expected, \textit{E. coli} was the most common uropathogen isolated (81.8% of uropathogens), with \textit{S. saprophyticus} the next most common (11.0%), and non-\textit{E. coli} Enterobacterales less common (7.2%). \textit{Enterococcus} spp. were rarely isolated (1.2%). This is consistent with previous studies, which have found \textit{E. coli} to be the most common cause of uncomplicated cystitis.\textsuperscript{8,9} Other than \textit{S. saprophyticus}, Gram positive bacteria are rarely pathogenic.\textsuperscript{8} Therefore, empiric antimicrobial treatment guidelines for uncomplicated cystitis should primarily consider the local antimicrobial susceptibility of \textit{E. coli} isolates.

The proportion of \textit{E. coli} isolates from women aged 15–55 years old with an uncomplicated cystitis that were susceptible to trimethoprim (73.6%, 95% CI 66.6–80.7) was similar to that of all \textit{E. coli} isolates from the community over the same period (72.0%, 95% CI 71.6–72.4).\textsuperscript{10} This refutes the theory that the organisms isolated from this population differ in their susceptibility to antibiotics compared with the general population. This may be because many healthcare practitioners are following a test and treat approach rather than the \textit{bpac}\textsuperscript{nz} guidelines. The Infectious Diseases Society of America (IDSA) guidelines for treatment of urinary tract infections recommend changing empiric therapy recommendations if the proportion of isolates that are resistant to the empiric antibiotic is greater than 20%.\textsuperscript{11} While many women with uncomplicated cystitis will resolve their symptoms without antibiotic treatment (or with treatment with an ineffective antibiotic), there is a higher symptom burden and rate of pyelonephritis in those managed symptomatically (2% vs 0.4% in a trial of ibuprofen vs fosfomycin).\textsuperscript{12} Susceptibility breakpoints for trimethoprim are set based upon the treatment of uncomplicated cystitis and resistant organisms would be expected to fail therapy.\textsuperscript{13} Furthermore, ongoing empiric usage of trimethoprim will provide a positive selection pressure for trimethoprim-resistant bacteria, especially in the gut, without benefit. This audit confirms that

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|c|}
\hline
\textbf{Antibiotic} & \textbf{SCL/MedLab South} & \textbf{Labtests} & \textbf{Total} & \textbf{SCL/MedLab South} & \textbf{Labtests} & \textbf{Total} & \textbf{SCL/MedLab South} & \textbf{Labtests} & \textbf{Total} \\
\hline
\textbf{Trimethoprim} & 5,862 & 7,665 & 76.5 & 27,898 & 39,210 & 71.2 & 33,760 & 46,875 & 72.0 \\
& & & & & & & & & 71.6–72.4 \\
\textbf{Cefalexin} & 7,493 & 7,669 & 97.7 & 37,215 & 39,224 & 94.9 & 44,708 & 46,893 & 95.3 \\
& & & & & & & & & 95.1–95.5 \\
\textbf{Nitrofurantoin} & 6,854 & 6,913 & 99.1 & 38,998 & 39,223 & 99.4 & 45,852 & 46,136 & 99.4 \\
& & & & & & & & & 99.3–99.4 \\
\hline
\end{tabular}
\caption{Antimicrobial susceptibility of all \textit{E. coli} isolates from urine samples from 15–55 year-old women submitted from the community over the period of the study.}
\end{table}
trimethoprim susceptibility among women aged 15–55 years old with an uncomplicated urinary tract infection is similar to laboratory data for all urines submitted to laboratories. Therefore, it should be reconsidered whether trimethoprim should continue to be recommended as first line empiric option.

Alternative empiric treatment options include nitrofurantoin and cefalexin. The rate of susceptibility to nitrofurantoin and cefalexin in this audit was high (100% [95% CI 100–100] and 96.6% [95% CI 93.7–99.5] of E. coli and 92.7% [95% CI 88.8–96.5] and 97% [95% CI 89.6–96.9] of all uropathogens respectively), consistent with local susceptibility patterns.10 As EUCAST provides no interpretative criteria for nitrofurantoin susceptibility for non-E. coli Enterobacteriales,14 they were considered resistant in this study. However, using CLSI interpretative criteria, the 2017 Australian Group on Antimicrobial Resistance (AGAR) Gram-negative Sepsis Outcome Programme (GNSOP) reported that 89.4% of Enterobacter cloacae complex, 98.2% of Klebsiella oxytoca, and 76.9% of K. pneumoniae were susceptible to nitrofurantoin; Proteus mirabilis is considered intrinsically resistant.15 Therefore, in many instances nitrofurantoin may still be effective in the treatment of uncomplicated cystitis caused by non-E. coli Enterobacteriales. Furthermore, non-E. coli Enterobacteriales are uncommon causes of uncomplicated cystitis in this demographic group (7.0% of uropathogens isolated). While the current preparations of nitrofurantoin require dosing four times per day, twice daily preparations are available overseas but are unavailable currently in New Zealand.

Of note our findings were similar regardless of region despite variability in prevalence of multi-drug resistant organisms within New Zealand. These findings support a national approach to a change in recommended empiric treatment.

A major limitation of this audit (which could be reduced in future audits) is that no clinical information was collected on patients, therefore it is not possible to determine if they met the criteria for an uncomplicated cystitis. Indeed, 29.3% of samples received did not meet the age and gender based inclusion criteria of the study, or were the wrong specimen type; therefore it is possible that a proportion of samples included in analysis were submitted from women who did not have uncomplicated cystitis.

In conclusion, in this multi-region New Zealand audit, we have found high rates of resistance to trimethoprim among E. coli isolated from the urine of women aged 15–55 years old with uncomplicated cystitis. Therefore, trimethoprim can no longer be recommended as first-line empiric treatment for uncomplicated cystitis in this patient group. Nitrofurantoin and cefalexin are better empiric treatment options; empiric treatment guidelines in some regions have already been changed as a result of this audit. A better tolerated twice daily nitrofurantoin preparation should be made available as a matter of priority. Ongoing audits should be conducted to determine the ongoing suitability of new empiric treatment recommendations.
Appendix

TRIME auditors

Deirdre Ahern (Lister Court Medical Centre), Anwar Alackal Ismail (Shorecare A&M Centre-Smales Farm), Glenn Anderson (Greenwood Health), Bruce Arroll (Greenstone Family Clinic), Glenda Barber (Stoke Medical Centre), Rae Bennets (Stoke Medical Centre), Andre Bonny (Mapua Health Centre), Fiona Brow (Medplus Lake Road Family Medical), Ian Bryce (Scott Street Health), Frances Butler (Queens Park Medical Centre), Scott Cameron (Wairau Community Clinic), Joanne Cannon (Queenstown Medical Centre), Alessandra Caramello (Queenstown Medical Centre), Taisia Cech (Stoke Medical Centre), Jane Chalmers (Vercoe Brown Associates), Jing (Anna) Chen (Medplus Lake Road Family Medical), James Chisnall (Greenwood Health), Deon Claassens (George Street Medical), Jessica Cullen (Lister Court Medical Centre), Niall Curran (Queenstown Medical Centre), Thomas Currie (Stoke Medical Centre), Simon Davies (Queenstown Medical Centre), Kathleen Deacon (Queen Park Medical Centre), Roger Deacon (Queen Park Medical Centre), Layla Derweesh (Picton Medical Centre), David Dixon (Nelson East Family Medical Centre), Sharon Dooley (Independent Midwife), Christopher Drury (Picton Medical Centre), Tim Ewer (Mapua Health Centre), Alice Faulkner (Nelson East Family Medical Centre), Margaret Gardener (Family Planning Dunedin), Guy Gardner (Francis Street Medical), Rosland Gelattly (Scott Street Health), Susan Grindlay (Helensburgh Medical Centre), Martin Hadler (Medplus Lake Road Family Medical), Martin Hadler (Shorecare A&M Centre-Smales Farm), Mathew Hamilton (Albany Street Medical Centre and Otago University Student Health), Simone Hart (Queenstown Medical Centre), Gaylene Hastie (Queenstown Medical Centre), Norman Henley (Ellerslie Medical Centre), Thomas Herd (Medplus Lake Road Family Medical), Rebecca Higgins (Healthzone Institute For Sport & Health), Paul Hogg (Herne Bay Medical Centre), Michele Hollis (Medplus Lake Road Family Medical), David Hopcroft (Medplus Lake Road Family Medical), M Hossain (Stoke Medical Centre), Martin Hudson (Greenwood Health), Rachel Inder (Medplus Lake Road Family Medical), Alison Jenkins (Family Planning Dunedin), Marianne Kim (Medplus Lake Road Family Medical), Dinah Kohner (Nelson City Medical Centre), Julian Lawry (Hobsonville Family Doctors), Anna Lehmann (Greenstone Family Clinic), Jean Lim (Medplus Lake Road Family Medical), Bruce Lintern (Picton Medical Centre), Chen Luo (Medplus Lake Road Family Medical), Sophie-Lee Mace (Greenwood Health), Emma Macfarlane (Family Planning Dunedin), Lindsay Macharg (Queenstown Medical Centre), Richard Macharg (Queenstown Medical Centre), Heidi Macrae (Medplus Lake Road Family Medical), Heidi Mayer (Greenwood Health), Joanne McClelland (George Street Medical), Anne McGregor (Helensburgh Medical Centre), Lisa Mcilwraith (Mapua Health Centre), David Mckay (Helensburgh Medical Centre), Paul McLaughlin (Stoke Medical Centre), Mary Mcwatters (Francis Street Medical), Torrance Richardmerkle (Hobsonville Family Doctors), Kirsty Moore (Greenwood Health), Ruth Moore (Francis Street Medical), Deborah Morris (Greenwood Health), Philip Morris (Lister Court Medical Centre), Fiona Morrison (Amity Health Centre and Otago Polytechnic Student Health), Jennifer Naper (Nelson East Family Medical Centre), Kylie Osborne (Nelson East Family Medical Centre), Mele Paea (Turuki Health Care-Mangere), Sarah Perano (Picton Medical Centre), Tim Phillips (Mapua Health Centre), Simon Phillips (Stoke Medical Centre), Colette Pienaar (Greenwood Health), Geraldine Poynter (St Heliers Health Centre), Anna Riddiford (Nelson East Family Medical Centre), Rachel Robertson (Queenstown Medical Centre), Rachel Rowlands (White Cross Lunn Ave), Victoria Samuels (Scott Street Health), Jocelyn Sangster (Greenwood Health), Jon Scott (Central Medical), Elizabeth Scott (Fiordland Medical Practice and Titoki Medical), Jan Shapcott (Wairau Community Clinic), Joanne Shooter (Hobsonville Family Doctors), Annie Si (Medplus Lake Road Family Medical), Sara Simmons (Picton Medical Centre), Milne Simpson (Queenstown Medical Centre), Jann Singer (Hobsonville Family Doctors), Elinor Slater (Queenstown Medical Centre), Kathryn Smith (Queenstown Medical Centre), Richard Smithers (Picton Medical Centre), Sonja Sparrow (Queenstown Medical Centre), Kirsty Stewart (Stoke Medical Centre), Alannah Stockwell (Nelson Family Medicine),
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**Competing interests:**
Dr Elvy reports personal fees from Pharmaceutical Society of New Zealand outside the submitted work.

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