The IOU Consensus Recommendations for Empirical Therapy of Cystitis in Nursing Home Residents

Joseph T. Hanlon, PharmD, MS, AGSF,*†‡§ Subashan Perera, PhD,*¶ Paul J. Drinka, MD, AGSF,|| Christopher J. Crnich, MD, MS,**†† Steven J. Schween, RN, MPH, MSN,‡‡ Michele Klein-Fedyshin, RN, MLS,§§ Charles B. Wessel, MLS,§§ Stacey Saracco, RN,* Gulsum Anderson, PhD,* Mary Mulligan, RN,§§ and David A. Nace, MD, MPH* ¶¶

OBJECTIVE: To establish consensus recommendations for empirical treatment of uncomplicated cystitis with antimicrobials in noncatheterized older nursing home residents to be implemented in the Improving Outcomes of UTI Management in Long-Term Care Project (IOU) funded by the Agency for Healthcare Research and Quality.

DESIGN: Two-round modified Delphi survey.

PARTICIPANTS: Expert panel of 19 clinical pharmacists.

MEASUREMENTS: Comprehensive literature search and development/review/edit of draft survey by the investigative group (one geriatric clinical pharmacist, two geriatric medicine physicians, and one infectious disease physician). The expert panel members rated their agreement with each of 31 recommendations for drugs of choice, dosing medications at various levels of renal function, drug-drug interactions to avoid, and duration of therapy by sex on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). Consensus agreement was defined as a lower 95% confidence limit of 4.0 or higher for the recommendation-specific mean score.

RESULTS: The response rate was 95% for the first round, and three recommendations achieved consensus (dosing for nitrofurantoin and trimethoprim/sulfamethoxazole in those without chronic kidney disease, and drug-drug interaction between trimethoprim/sulfamethoxazole and warfarin). In the second round, 90% responded and reached consensus on an additional eight recommendations (two for nitrofurantoin or trimethoprim/sulfamethoxazole as initial drugs of choice, three for dosing ciprofloxacin, nitrofurantoin, and trimethoprim/sulfamethoxazole at various levels of chronic kidney disease, and three drug-drug interactions to avoid: trimethoprim/sulfamethoxazole with phenytoin and ciprofloxacin with theophylline or with tizanidine).

CONCLUSION: An expert panel of clinical pharmacists was able to reach consensus on a set of recommendations for the empirical treatment of cystitis with oral antimicrobials in older nursing home residents. The recommendations were incorporated into a treatment algorithm for uncomplicated cystitis in noncatheterized nursing home residents and used in educational materials for health professionals in an ongoing controlled intervention study. J Am Geriatr Soc 00:1–7, 2018.

Key words: aged; nursing homes; cystitis; urinary tract infection; antibacterial agents

S uspected uncomplicated urinary tract infection (UTI) is the most common reason that antibiotics are prescribed to older nursing home residents.1–3 Most cases of suspected uncomplicated UTIs are in fact asymptomatic bacteriuria for which antibiotics are unnecessary.1,4 Some cases of suspected uncomplicated UTIs are due to cystitis in which
residents are typically not severely ill and present with lower urinary symptoms such as dysuria, urinary urgency/ frequency, or suprapubic pain.4–8 Warning signs or symptoms such as rigors, flank pain, hypotension, or prostatic pain, particularly when associated with significant fever, suggest more complicated upper tract disease or prostatitis8 (Supplementary Appendix S1).

The appropriateness of antibiotics is important because they can have considerable unintended consequences such as adverse drug events and promoting the development of antibiotic-resistant organisms.19 Antibiotic resistance may directly harm an individual through treatment failures, increased need for postacute and long-term care services, prolonged stays, and increased mortality.16 Moreover, antibiotic-resistant urinary tract organisms are associated with increased transfers to acute care facilities and with mortality.1,10 In addition, suboptimal antibiotic use is the leading cause of Clostridium difficile infections that can result in serious and life-threatening complications.1,11

Much of the antibiotic use for cystitis among nursing home residents is potentially suboptimal. For example, Rotjanapan and colleagues conducted a 6-month study in two Rhode Island nursing homes (total of 270 beds) and found that 72% of residents, all aged 65 and older, with cystitis received unnecessarily broad-spectrum antibiotic therapy.12 In addition, 46% of antibiotics given had a suboptimal dosage, and nearly 70% of residents were given an antibiotic for an excessive duration. Another study by Miller and colleagues reported on the appropriateness of antibiotic prescribing in 18 US nursing homes over a 12-month period.13 Overall, 40% of antibiotics were deemed to be potentially suboptimal. The most common problem was excessive doses of primarily renally cleared antibiotics in 19% of residents. Other problems seen included the use of higher cost antibiotics, therapeutic duplication, impractical directions, prolonged duration, and drug interactions.13

Although there are consensus recommendations for defining, evaluating, and monitoring infections in nursing home residents, they are not specific to the optimal use of antibiotics in treating uncomplicated cystitis.14–18 Given this background, the study objective was to establish consensus recommendations for the optimal prescribing of empirical anti-infectives for uncomplicated cystitis in noncatheterized older nursing home residents via a modified Delphi survey of an expert panel of clinical pharmacists.19,20 The expert recommendations were developed as part of the Improving Outcomes of UTI Management in Long-Term Care Project (IOU), an implementation and dissemination project funded by the Agency for Healthcare Research and Quality aimed at improving antimicrobial stewardship for nursing home acquired cystitis. It should be noted that these expert recommendations provide initial empirical treatment suggestions pending the results of urine culture and sensitivities. The recommendations would not account for any history of prior resistance or recent antimicrobial exposure that a clinician should always consider.

METHODS

To develop the modified Delphi survey, the investigative team worked with two medical librarians at the University of Pittsburgh to conduct a comprehensive literature review restricted to English-language articles in PubMed and Embase using a combination of terms including urinary tract infections, cystitis, antibacterial agents, nursing homes, and aged (ie, persons 65 y and older). Inclusion criteria included those using randomized controlled trial, cohort or case-control, or experimental pharmacokinetic designs. Abstracts of the articles were reviewed. Studies deemed relevant underwent a full article review. In addition, reference lists from review and retrieved articles were scanned for any additional relevant studies.

Using the identified literature and considering four important aspects of medication appropriateness (ie, drugs of choice, dosing medications at various levels of renal function, drug-drug interactions to avoid, and duration of therapy by sex), a clinical pharmacist researcher developed the initial draft of the Delphi survey.19,20 This draft survey was further refined by three internal medicine physician investigators (two from geriatric medicine and one from infectious disease).

The final survey included 31 recommendations and supporting references to be considered by an expert panel (Supplementary Appendix S2). The expert panel consisted of 19 clinical pharmacists (Acknowledgment section lists the details), and they were sent the modified Delphi survey via e-mail and were blinded to the identity of other panel members. They were asked to rate their agreement with each of 31 recommendations on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). After receipt of the completed surveys, means and 95% confidence intervals were estimated for each recommendation. Consensus on agreeing to a recommendation was achieved when the lower 95% confidence limit calculated from participant responses was greater than or equal to 3.0. Consensus on disagreeing to a recommendation was achieved when the upper 95% confidence limit calculated from participant responses was less than or equal to 3.0, and the remainder was treated as failure to reach consensus.

Recommendations that did not achieve consensus in the first round were included in a second round. The same expert panel was asked to further consider the recommendation after providing the group rating mean for each item from the first round and additional targeted or suggested items from the expert panel to better glean consensus. This approach is consistent with previous published work.21,22 For all statistical analyses, SAS v.9.3 (SAS Institute, Cary, NC) was used. The University of Pittsburgh institutional review board approved the study as exempt. The results were summarized into simple treatment recommendations to facilitate clinical use.

RESULTS

The literature search yielded 253 treatment studies in PubMed and 332 in Embase for a total of 462 unique articles, of which 53 were deemed relevant after abstract review. No additional studies were identified from reference lists. There were a few articles from randomized controlled trials. Three-quarters (75%) of the expert panel members were female. Additionally, 68% were board-certified geriatric pharmacists, and an additional 26% were board certified in another specialty. A total of 68% had long-term care experience, and 95% worked with frail older adults.

The first-round response rate was 95%. After the first round of the survey, consensus was reached for three
recommendations (using nitrofurantoin 100 mg twice a day and trimethoprim/sulfamethoxazole 160/800 mg twice a day in those without chronic kidney disease, and avoiding a drug-drug interaction between trimethoprim/sulfamethoxazole and warfarin) (Table 1). The panel also reached consensus against considering fosfomycin as a drug of choice, avoiding nitrofurantoin in those with a creatinine clearance (CrCl) lower than 60 mL/min, avoiding trimethoprim/sulfamethoxazole in those with a CrCl lower than 30 mL/min, avoiding ciprofloxacin in patients concurrently receiving glipizide/glyburide, 5 days as the minimum treatment duration for men, and fosfomycin as the cheapest alternative (Table 1).

The second-round response rate was 90%. Four new recommendations were added. The panel reached consensus agreement on nitrofurantoin as the drug of choice for empirical treatment of cystitis for individuals with adequate renal function and a sulfonamide allergy; trimethoprim/sulfamethoxazole as the drug of choice in those with adequate renal function and without a sulfonamide allergy; avoiding nitrofurantoin in those with a CrCl lower than 30 mL/min; avoiding trimethoprim/sulfamethoxazole in those with a CrCl lower than 15 mL/min; for those with adequate renal function, 250 mg twice a day as the appropriate dose of ciprofloxacin; significance of the drug-drug interaction between ciprofloxacin and theophylline, between ciprofloxacin and tizanidine, and between trimethoprim/sulfamethoxazole and phenytoin (Table 2). The panel disagreed that ciprofloxacin and sulfonylureas constitute a significant drug-drug interaction and that men should be treated for a minimum of 10 days (Table 2). Consensus was not reached for the remaining items (Table 2). Figure 1 operationally summarizes the survey results as treatment recommendations.

**DISCUSSION**

We found that an expert panel of clinical pharmacists could achieve consensus agreement on the optimal prescribing of empirical oral anti-infectives in uncomplicated cystitis in older nursing home residents. Regarding drugs of choice,
the panel reached agreement that the preferred drugs were nitrofurantoin and trimethoprim/sulfamethoxazole. This is consistent with recent guidelines and reviews and also is clinically sensible because both drugs are capable of successfully treating Escherichia coli (E. coli) and Klebsiella spp, that together account for up to 83% of cases of UTI in nursing home populations.17,23 Trimethoprim/sulfamethoxazole is more active against Proteus spp, although nitrofurantoin would be preferred when treating Enterococcus. It should also be noted that overall resistance to nitrofurantoin is minimal, and it is a good choice in those with a sulfa allergy.23 Where resistance to E. coli is less than 20%, trimethoprim/sulfamethoxazole may be a reasonable alternative because its average wholesale price is less than nitrofurantoin and avoids the small risk of pulmonary reactions that can be seen with nitrofurantoin.23,24,29,31,32

The expert panel agreement also provides guidance regarding the renal dosing recommendations for several anti-infectives consistent with a previous Delphi survey.22 Although controversial, nitrofurantoin should not be used in residents with an estimated CrCl lower than 30 mL/min because urinary concentrations may be insufficient for it to be effective.33 In those whose CrCl is higher than 15 mL/min, trimethoprim/sulfamethoxazole is an acceptable alternative. Below this level of renal function, the risk of hyperkalemia with trimethoprim/sulfamethoxazole is greater, and alternatives such as ciprofloxacin or fosfomycin should be considered.24,31,34

The panel also identified four clinically important drug-drug interactions, three of which involved narrow therapeutic range drugs (warfarin, phenytoin, and theophylline). A case-control study from Canada found that trimethoprim/sulfamethoxazole in combination with warfarin increased the risk of upper gastrointestinal hemorrhage by nearly 4-fold (adjusted odds ratio [aOR] = 3.84).35 A nearly 2-fold increased risk was also found with ciprofloxacin (aOR = 1.94).35 The finding with trimethoprim/sulfamethoxazole was confirmed by another case-control study from the United States where the risk of bleeding with warfarin was increased by nearly 3-fold (aOR = 2.70).36 This same anti-infective was found in another case-control study to be the culprit interacting with phenytoin in which the risk of toxicity requiring hospitalization was increased more than 2-fold (aOR = 2.11).37 Ciprofloxacin increases the risk of theophylline toxicity by nearly 2-fold (aOR = 1.86).38 Finally, when possible the use of tizanidine should be avoided in those taking ciprofloxacin to avoid toxicity. (Anon. Approved product labeling for ZANAFLEX

<table>
<thead>
<tr>
<th>Appropriate domain</th>
<th>Recommendations</th>
<th>Mean (95% CI)</th>
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<tbody>
<tr>
<td>Drugs of choice for empirical treatment</td>
<td>With adequate renal function or sulfonamide allergy, nitrofurantoin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.41 (4.15-4.67)</td>
</tr>
<tr>
<td>Renal dosing</td>
<td>With adequate renal function but without sulfonamide allergy, TMP/SMZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.35 (4.04-4.66)</td>
</tr>
<tr>
<td>When CrCl &lt;60, avoid nitrofurantoin</td>
<td>3.35 (2.72-3.98)</td>
<td></td>
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<tr>
<td>When CrCl &lt;30, avoid nitrofurantoin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.82 (4.62-5.03)</td>
<td></td>
</tr>
<tr>
<td>When CrCl &lt;15, avoid TMP/SMZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.41 (4.00-4.82)</td>
<td></td>
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<tr>
<td>With reduced renal function but not to the level it should be avoided, TMP/SMZ 160/800 mg per day</td>
<td>4.12 (3.72-4.52)</td>
<td></td>
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<tr>
<td>When CrCl &lt;30, ciprofloxacin 250 mg/d&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.76 (3.34-4.19)</td>
<td></td>
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<tr>
<td>When CrCl &lt;30, ciprofloxacin 500 mg/d&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.06 (2.44-3.67)</td>
<td></td>
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<tr>
<td>With adequate renal function, ciprofloxacin 250 mg twice a day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.47 (4.21-4.74)</td>
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<tr>
<td>With adequate renal function, ciprofloxacin 500 mg twice a day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.53 (1.90-3.16)</td>
<td></td>
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<tr>
<td>Regardless of renal function, fosfomycin 3 g single dose</td>
<td>4.24 (3.74-4.73)</td>
<td></td>
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<tr>
<td>Clinically significant drug-drug interactions</td>
<td>Ciprofloxacin and theophylline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.41 (4.09-4.73)</td>
</tr>
<tr>
<td>Ciprofloxacin and corticosteroids</td>
<td>3.06 (2.72-3.40)</td>
<td></td>
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<tr>
<td>Ciprofloxacin and warfarin</td>
<td>4.06 (3.72-4.40)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin and glipizide/glyburide&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.35 (1.91-2.80)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin and tizanidine&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>4.41 (4.05-4.78)</td>
<td></td>
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<tr>
<td>TMP/SMZ and procanamide</td>
<td>4.06 (3.72-4.40)</td>
<td></td>
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<tr>
<td>TMP/SMZ and phenytoin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.41 (4.15-4.67)</td>
<td></td>
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<tr>
<td>TMP/SMZ and methotrexate</td>
<td>4.06 (3.67-4.44)</td>
<td></td>
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<tr>
<td>TMP/SMZ and angiotensin-converting enzyme inhibitors</td>
<td>3.71 (3.31-4.10)</td>
<td></td>
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<tr>
<td>TMP/SMZ and angiotensin receptor blockers (or potassium supplements)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.71 (3.31-4.10)</td>
<td></td>
</tr>
<tr>
<td>Minimum duration of anti-infective treatment</td>
<td>In women, 3 d</td>
<td>4.00 (3.69-4.31)</td>
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<tr>
<td>In women, 5 d</td>
<td>2.71 (2.27-3.14)</td>
<td></td>
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<tr>
<td>In men, 7 d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.00 (3.64-4.36)</td>
<td></td>
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<tr>
<td>In men, 10 d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.47 (2.06-2.88)</td>
<td></td>
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Abbreviations: CI, confidence interval; CrCl, estimated creatinine clearance in milliliters per minute; TMP/SMZ, trimethoprim/sulfamethoxazole.

<sup>a</sup>Consensus agreement.

<sup>b</sup>New recommendation added in round 2.

<sup>c</sup>Consensus disagreement.
Our study had several potential limitations. First, although the panel agreed that anti-infective treatment in men more than 5 days but less than 10 days in duration was acceptable for uncomplicated cystitis, we were unable to reach consensus regarding the optimal duration of treatment. For women, most sources are clear that the duration of use for anti-infectives for cystitis should range between 3 and 7 days. Therefore, we operationalized the duration of use as 7 days for men and 3 days for women in the final recommendations (Figure 1). We included nitrofurantoin in these duration recommendations based on the expert opinion of the Delphi panel. Although not routinely recommended in men because of the concern for prostatitis, our recommendations specifically focus on cystitis for which nitrofurantoin is indicated. We do not suggest use of nitrofurantoin for complicated UTI. Although a 5-day course of nitrofurantoin is often recommended in women, this is due to a dearth of studies looking at 3-day courses. Only a few studies using a 3-day course have been conducted, and these involved younger women. Treatment success was observed in these studies. Pharmacodynamic effects of nitrofurantoin include a short static kill time for E. coli (complete eradication in 8 hours), although a dynamic kill time appears to be influenced more by dosing rather than duration of treatment. Given that clinical trials have not established an optimal duration of therapy for nitrofurantoin, and that our work here is based on expert opinion, it is reasonable that clinicians might consider using a 5-day course of nitrofurantoin. Future studies are clearly needed to define the optimal dose and duration of therapy for nitrofurantoin in cystitis.

Second, we used a convenience sample of clinical pharmacists for this modified Delphi survey. However, they came from 10 states and included clinical pharmacists from academia, community-based care, and managed care. Third, face-to-face meetings of the panelists were not held due to the prohibitive cost and other practical considerations. However, remote participation was believed to be advantageous in maintaining

Figure 1. Empirical treatment of uncomplicated bladder infection (cystitis) in nursing home residents 65 years of age and older without a urinary catheter. eCrCl = estimated creatinine clearance.
blinding and limits confounding arising from dominant personalities. Finally, as new research contributes additional information about emerging resistance patterns, optimal durations of therapy, and safe and effective medication use in older adults, the list of anti-infective drugs and associated prescribing information will likely need to be updated.

As with all treatment recommendations, clinical judgment is paramount. It is important to note that active patient monitoring without empirical antibiotic use may also be acceptable while awaiting culture results. These guidelines are meant for empirical treatment pending culture results. Clinicians should reassess a patient’s clinical progress along with antibiotic appropriateness once culture results and sensitivities return. Referred to as an antibiotic time-out, this reassessment offers the clinician an opportunity to refine antibiotic prescribing by narrowing the antimicrobial spectrum, reducing treatment duration, and potentially discontinuing unnecessary additional treatment. When using this treatment recommendation, clinicians should also be mindful of local resistance patterns in their facility as well as disease severity, recent antibiotic use, and/or prior history of antimicrobial resistance in an individual patient because these factors may influence the choice of the empirical antimicrobial selected.

In conclusion, an expert panel of clinical pharmacists was largely able to reach consensus agreement on a set of recommendations for the empirical treatment of uncomplicated cystitis with oral anti-infective medications in older nursing home residents. These recommendations were incorporated into a consensus-based treatment algorithm for uncomplicated cystitis in noncatheterized older nursing home residents and used in educational materials for health professionals in an ongoing controlled intervention study (AHRQ R18 HS023779). Although these recommendations are a starting point to assist current clinical care, future research is needed to better inform decisions regarding antibiotic selection and optimal durations of therapy, particularly with nitrofurantoin, for nursing home residents with uncomplicated cystitis.

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Author Contributions: Study concept and design: All authors. Acquisition of subjects and/or data: Hanlon and Saracco. Data analysis: Hanlon, Nace, and Perera. Interpretation of data: Hanlon, Perera, Drinka, Crinch, Nace, and Schweon. Preparation of manuscript: All authors.

Sponsor’s Role: The sponsor had no role in the design, methods, data collection, analysis, or preparation of this article.

REFERENCES


SUPPORTING INFORMATION
Additional Supporting Information may be found in the online version of this article.

Appendix S1. The IOU Consensus Recommendations for the diagnosis of uncomplicated cystitis in nursing home residents

Appendix S2. Delphi Treatment Survey.