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Brief Report

Improvements in Antibiotic Appropriateness for Cystitis in Older Nursing Home Residents: A Quality Improvement Study With Randomized Assignment

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A B S T R A C T

Objective: To determine the impact of an educational quality improvement initiative on the appropriateness of antibiotic prescribing restricted to uncomplicated cystitis in older noncatheterized nursing home residents.
Design: Quality improvement study with randomized assignment.
Settings and Participants: Twenty-five nursing homes in United States were randomized to the intervention or usual care group by strata that included state, urban/rural status, bed size, and geographic separation.
Methods: A 12-month trial of a low-intensity multifaceted antimicrobial stewardship intervention focused on uncomplicated cystitis in nursing home residents vs usual care. The outcome was the modified Medication Appropriateness Index as assessed by a blinded geriatric clinical pharmacist and consisted of an assessment of antibiotic effectiveness, dosage, drug-drug interactions, and duration.
Results: There were 75 cases (0.15/1000 resident days) in intervention and 92 (0.22/1000 resident days) in control groups with a probable cystitis per consensus guidelines. Compared with controls, there was a statistically nonsignificant 21% reduction in the risk of inappropriate antibiotic prescribing (nonzero Medication Appropriateness Index score rate 0.13 vs 0.21/1000 person days; adjusted incident rate ratio 0.79; 95% confidence interval 0.45–1.38). There was a favorable comparison in inappropriateness of duration (77% vs 89% for intervention vs control groups, respectively; $P = .0394$). However, the intervention group had more problems with drug-drug interactions than the control group (8% vs 1%, respectively; $P = .0463$). Similarly, the intervention group had a nonsignificant trend toward more problems with dosage (primarily because of the lack of adjustment for decreased renal function) than the control group (32% vs 25%, respectively; $P = .3170$). Both groups had similar rates of problems with

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choice/effectiveness (44% vs 45%; $P = .9417$). The most common class of antibiotics prescribed inappropriately was quinolones (25% vs 23% for intervention versus control groups, respectively; $P = .7057$).
Conclusions and Implications: A low-intensity intervention showed a trend toward improved appropriate antibiotic prescribing in nursing home residents with likely uncomplicated cystitis. Efforts to improve antibiotic prescribing in addition to the low-intensity intervention might include a consultant pharmacist in a nursing home to identify inappropriate prescribing practices.
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Potentially inappropriate antibiotic use for urinary tract infections is common in nursing homes.[1] We recently reported the results from a quality improvement initiative that showed that unnecessary antibiotic use for unlikely cystitis (eg, asymptomatic bacteriuria) is common and can be reduced.[2] However, even in residents with true cystitis, much of the antibiotic use is potentially inappropriate because of problems with effectiveness, dosing, drug interactions, and duration of use.[3,4]

To the best of our knowledge, only 2 other cluster randomized controlled trials have focused on interventions to improve antibiotic use for urinary tract infections in older nursing home residents.[5,6] However, neither focused on uncomplicated lower tract infections in older patients nor did they examine multiple domains of medication appropriateness. A quasi-experimental trial of antibiotic stewardship was recently published, but urinary tract infections were only 1 aspect of the study.[7] Given this background, we sought to assess the impact of an educational quality improvement initiative on the appropriateness of antibiotic prescribing for probable cystitis in older noncatheterized nursing home residents.

Methods

Design, Setting, and Participants

Study methods are published in detail elsewhere.[2] Briefly, this was a 12-month study involving 25 US nursing homes. We randomized nursing homes to the intervention or usual care by strata that included state, urban/rural status, bed size, and geographic separation. Residents were aged ≥65 years with probable cystitis as per consensus guidelines from a previously published diagnostic algorithm.[7] Data were collected by study- trained licensed- staff personnel at the 25 nursing homes and sent to a central site via secure facsimile. The University of Pittsburgh Institutional Review Board reviewed the study protocol and ruled that it was exempt since it was a quality improvement study.

Intervention

Prior to the implementation of the intervention, we conducted modified Delphi surveys of expert panels of geriatricians and clinical pharmacists to reach consensus on criteria for diagnosing probable cystitis and its optimal empiric anti-infective treatment.[8,9] We used a multifaceted educational intervention consisting of a (1) 1-hour webinar presented by a physician, pharmacist, and nurse who provided information about the project and the consensus recommendations; (2) pocket-sized educational cards with the consensus diagnosis and treatment recommendations; and (3) physician order set forms for the diagnosis and treatment of probable cystitis (Supplementary Material). The control nursing homes received usual care.

Measures

Information collected included date of urinary tract infection onset and symptoms/signs, resident characteristics (age, sex, weight), drug allergies, serum creatinine, specific concurrent medications that might interact with specific antibiotics (ie, warfarin, theophylline, tizanidine, methotrexate, phenytoin, procainamide), urinalysis, urine culture, and antibiotic therapy (ie, name, strength, amount given, schedule, route, and duration). The current study focuses on cystitis and not residents with complicated urinary tract infections or residents with unlikely cystitis. The present substudy focuses on antimicrobial appropriateness as assessed by a geriatric clinical pharmacist (J.H.) and developer of the 10 criteria, weighted, valid, and reliable Medication Appropriateness Index (MAI).[10,11] Any inappropriateness is a secondary outcome measure as the primary outcome of the parent study was prescription of antibiotics for asymptomatic bacteriuria.[2] The modified MAI rated the appropriateness of an antibiotic using only 4 of the 10 criteria: effectiveness, dosage, drug-drug interactions, and duration. For each domain, the index has specific definitions, instructions, and examples (copy available upon request). The geriatric clinical pharmacist (J.H.) reviewed the case report and culture results and applied the 4 items from the MAI to the last antibiotic prescribed for each resident, and rated each item as appropriate (A), marginal (B), or inappropriate (C). For example, if a quinolone was prescribed but the patient had adequate renal function and the urine culture found nitrofurantoin to be sensitive, the rating would be "C" because the recommended empiric narrower spectrum agent was not prescribed. Moderate inter-rater reliability was seen between MAI ratings by a geriatrician (D.N.) and the geriatric clinical pharmacist evaluator (J.H.) (intraclass correlation 0.68). For descriptive purposes, the MAI domains and the antibiotic classes with inappropriateness were calculated. For example, cephalexin could be inappropriate if (1) the urine culture results showed that the organism was sensitive to either nitrofurantoin or trimethoprim/sulfamethoxazole and the patient had adequate renal function and no allergy to either of these 2 agents; (2) too high or low daily dosage was given for the residents renal function; (3) a clinically significant drug interaction occurred; or (4) prescribed antibiotic for more than 3 days for women or more than 7 days for men.

Statistical Analyses

Descriptive statistics were used to summarize continuous (mean, standard deviation) and categorical (frequencies, percentages) variables stratified by study group. We used Wilcoxon rank-sum, χ^2, and Fisher exact tests to compare nursing homes by group status. Poisson regression was used to analyze counts (ie, rate of antibiotic inappropriateness per 1000 resident days), and to calculate incident rate ratio, its significance and 95% confidence interval.[12] We used χ^2 and Fisher exact tests to compare proportions of MAI criteria and antimicrobial classes between the 2 groups. All analyses were conducted using SAS software v 9.3 (SAS Institute, Inc, Cary, NC).

Results

Table 1 shows the characteristics of the intervention and control nursing homes. The homes had an average bed size of more than 100, the majority had electronic medication administration, and health records and were located in the Northeast region. Approximately one-half of nursing homes were for profit and in rural locations. There were no statistically significant differences between the 2 randomized groups.

There were 167 cases with a probable cystitis per consensus guidelines [75 in intervention (0.15/1000 resident days) and 92 (0.22/1000 resident days) in the control homes]. Included in the analysis were 3 intervention and 2 control cases that had a negative urine culture (<100,000 bacteria per milliliter) but received an antibiotic. Seven cases were excluded (3 intervention and 4 control cases) that had a positive urine culture (≥100,000 bacteria per milliliter) as no antibiotic was prescribed. There were no cases in which multiple antibiotics were prescribed simultaneously. There was a statistically nonsignificant reduction in the potentially inappropriate antibiotic rate in the intervention compared with the control group (0.13 vs 0.21 per 1000 resident days; adjusted incident rate ratio 0.79; 95% confidence interval 0.45–1.38). Table 2 describes the types of potentially inappropriate antibiotic prescribing by group status. Favorable comparison between the intervention and control groups were seen in inappropriateness of duration (in most cases too long; $P = .0394$). On the other hand, the intervention group had more problems with drug-drug interactions than the control group (8% vs 1%, respectively; $P = .0463$). Similarly, the intervention group had a nonsignificant trend toward more problems with dosage (primarily because of the lack of adjustment for decreased renal function) than the control group (32% vs 25%, respectively; $P = .3170$). Both groups had similar rates of problems with choice/effectiveness (44% vs 45%; $P = .9417$).

Table 3 shows the most common antibiotics inappropriately prescribed for residents and their average duration in the intervention and control groups. As shown, quinolones was the antimicrobial class with the most problems. Favorable comparison between the intervention and control groups was seen in in lower use of penicillins ($P = .0226$).

Table 1
Characteristics of Nursing Homes

Characteristics	Intervention Group (n = 12) Mean ± SD or Number (Percent)	Control Group (n = 13) Mean ± SD or Number (Percent)	*P* Value
Facility size (beds)	139.7 ± 110.1	127.6 ± 80.3	.8065
Number of admitting physicians	4.9 ± 6.2	8.8 ± 13.4	.2183
Number of nurses	42.3 ± 35.3	40.2 ± 28.7	.7441
For-profit ownership	8 (66.7)	4 (30.8)	.0727
Facility network			.1585
Single	4 (33.3)	8 (61.5)	
Chain	8 (66.7)	5 (38.5)	
Region			1.0000
Midwest/Northwest	3 (25.0)	4 (30.8)	
Northeast	6 (50.0)	6 (46.2)	
Potomac/Southeast	2 (16.7)	2 (15.4)	
South Central/Southwest	1 (8.3)	1 (7.7)	
Facility location			1.0000
Midway	1 (8.3)	1 (7.6)	
Rural	6 (50.0)	6 (46.2)	
Urban	5 (41.7)	6 (46.2)	

SD, standard deviation.

Table 2
Likely Cystitis Cases With Inappropriate Prescribing According to MAI Criteria by Group Status

MAI Criteria	Intervention Cases (n = 75) n (%)	Control Cases (n = 92) n (%)	*P* Value
Choice/effectiveness	33 (44.0)	41 (44.6)	.9417
Dosage	24 (32.0)	23 (25.0)	.3170
Drug-drug interactions	6 (8.0)	1 (1.1)	.0463
Duration	58 (77.3)	82 (89.1)	.0394

SD, standard deviation.

Discussion

To the best of our knowledge, this is the first randomized study that has used a comprehensive multiple criterion antibiotic appropriateness outcome measure. We found a modest difference between groups in antibiotic appropriateness although not statistically significant. Nonetheless, the quality of antibiotic use was problematic despite probable cystitis being appropriately identified. The previous published randomized controlled trial by Loeb et al only focused on the number of antibiotics for all types of urinary tract infections (ie, lower and upper tract).[6] The study by Pettersson et al examined only the proportion of quinolones prescribed in women with lower tract infections.[5] Although the rate of inappropriate antibiotic use was less in the intervention than the control group and the incident rate ratio from our study was less than one, it was not statistically significant. However, the sample size was small and this finding could reflect lack of statistical power for a secondary outcome. This is supported by the positive findings of a reduction in the rate of antibiotics prescribed for asymptomatic bacteriuria reported by the main study manuscript.[2] That said, a more impactful reduction in inappropriate antibiotic use may require greater prescribing provider engagement and the future involvement of consultant pharmacists.[13] Although physicians, nurse practitioners, and physician assistants were invited to participate in the webinars, nearly all participants were nurses. In particular, pharmacists can play an important role in outpatient antibiotic stewardship programs as they play in the inpatient setting.[14]

It is also relevant to discuss the types of antibiotic inappropriateness seen in this study. The intervention had a favorable impact on the most common problem, which was prolonged duration of antibiotic use in both women and men. The educational intervention materials based on the modified Delphi survey study recommended the use of antibiotics for no more than 3 days for women and 7 for men. The high rate of antibiotics with overly long durations may represent uncertainty and the fact that these recommended durations have not been derived from efficacy trials in older nursing home residents. This high rate is consistent with the findings from Miller et al, the only other study that used the MAI to evaluate the appropriateness of antibiotic use in older nursing home residents with urinary tract infections.[4] It is also consistent with the study by Rotjanapan et al where nearly 70% were given an antibiotic for an inappropriate duration in the study.[3] Results from a study by Kistler et al showed that 28% of antibiotics were prescribed for more than 7 days.[15]

It is also notable that quinolones were the most common inappropriately prescribed antibiotic, especially when the empiric drugs of choice nitrofurantoin or trimethoprim would have been equally effective. This too is consistent with the findings from the studies of Miller et al and Rotjanapan et al.[3,4] Of concern is that such practices may lead to residents becoming colonized with resistant organisms, which are associated with increased transfers to acute care facilities, and mortality.[16–18] Moreover, it exposes them to a class of medications

Table 3
Most Common Antibiotics Prescribed Inappropriately by Group Status

Antibiotics/Classes	Intervention (n = 75)		Control (n = 92)		*P* Value for Difference in % Use
	n (%)	Duration (d) Mean ± SD	n (%)	Duration (d) Mean ± SD	
Cephalosporins	16 (21.3)	7.0 ± 2.4	10 (10.9)	6.0 ± 1.8	.0636
Nitrofurantoin	9 (12.0)	5.3 ± 1.7	11 (12.0)	6.6 ± 2.1	.9931
Penicillins	6 (8.0)	8.0 ± 1.5	19 (20.7)	6.8 ± 1.7	.0226
Trimethoprim/Sulfamethoxazole	11 (14.7)	6.0 ± 1.8	11 (12.0)	6.5 ± 1.5	.6065
Quinolones	19 (25.3)	7.1 ± 2.6	21 (22.8)	6.0 ± 2.0	.7057
Others	5 (6.7)	6.8 ± 2.5	13 (14.1)	5.6 ± 3.3	.1218

that may put them at risk for adverse drug reactions such as tendinitis/tendon rupture, hypoglycemia, and delirium.[19] The higher use of penicillins in the control group is potentially problematic due to higher urinary tract infection treatment failure rates with this antibiotic class.[20]

There are a number of potential limitations that warrant discussion. As mentioned above, the small sample size and secondary nature of outcomes may have limited our statistical power. However, we believe the magnitude of the incident rate ratio represents the most likely approximation of the "true estimate" of the intervention's effectiveness. If true, a larger well-designed study could find the reduction to be statistically significant. An additional potential limitation is that a single clinical pharmacist (J.H.) conducted all the MAI evaluations. It is important to note that this individual was the original developer of the MAI and his inter-rater reliability with a geriatrician was acceptable. A typical pharmacist in long-term care may have a lesser degree of agreement with a physician prescriber as there is a learning curve to become competent in the use of the MAI. Typically, this will require a pair of individuals to apply the MAI to the drug therapy of 10 to 20 patients with careful attention to the explicit directions provided. Then, it is helpful to compare ratings and reach consensus on discordances. Moreover, we do not have any information about which of the three main interventions (ie, webinar, pocket cards, order sheets) were thought to be most useful. Although we cannot be absolutely certain that none of the physicians in this study rounded in both intervention and control homes, we limited the chance of cross-contamination by imposing geographic separation between facilities randomized to different groups. In addition, we did not collect information identifying the total number of homes served by physicians, nor was it possible to identify the number. More importantly, the quality of educational exposures received by physicians outside our intervention could not be assessed in a pragmatic remotely conducted study such as ours. Antimicrobial stewardship has received national attention, particularly in nursing homes. Thus, it is likely that physicians in both intervention and control groups received additional educational exposures. However, any such exposure would be most likely to occur evenly across the two groups. Finally, although nursing homes from the current study came from numerous US states, it is possible that the study findings may not generalize to all other regions not represented in the study.

Conclusions and Implications

Despite the potential limitations, a low-intensity intervention showed a trend toward improved appropriate antibiotic prescribing in nursing home residents with likely uncomplicated cystitis. The modest improvement may be due to involvement primarily by nurses in the intervention. Efforts to improve antibiotic prescribing in addition to the low-intensity intervention might include a consultant pharmacist in a nursing home to identify inappropriate prescribing practices.

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Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2020.07.040.

References

1. Ashraf MS, Gaur S, Bushen OY, et al. Diagnosis, treatment, and prevention of urinary tract infections in post-acute and long-term care settings: A consensus statement from AMDA's Infection Advisory Subcommittee. J Am Med Dir 2020;21:12–24.e2.
2. Nace DA, Hanlon JT, Crnich CJ, et al. A multifaceted antimicrobial stewardship program for the treatment of uncomplicated cystitis in nursing home residents. JAMA Internal Med 2020;180:944–951.
3. Rotjanapan P, Dosa D, Thomas KS, et al. Potentially inappropriate treatment of urinary tract infections in two Rhode Island nursing homes. Arch Intern 2011;171:438–443.
4. Miller SW, Warnock R, Marshall LL. Appropriateness of antibiotic prescribing for urinary tract infections in long-term care facilities. Consult Pharm 1999;14:157–177.
5. Pettersson E, Vernby A, Mölstad S, et al. Can a multifaceted educational intervention targeting both nurses and physicians change the prescribing of antibiotics to nursing home residents? A cluster randomized controlled trial. J Antimicrobial Chemother 2011;66:2659–2666.
6. Loeb M, Brazil K, Lohfeld L, et al. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: Cluster randomised controlled trial. BMJ 2005;331:669–673.
7. Sloane PD, Zimmerman S, Ward K, et al. A 2-year pragmatic trial of antibiotic stewardship in 27 community nursing homes. J Am Geri Soc 2020;68:46–54.
8. Nace D, Perera SK, Hanlon JT, et al. The Improving Outcomes of UTI Management in Long-Term Care Project (IOU) consensus guidelines for the diagnosis of uncomplicated cystitis in nursing home residents. J Am Med Dir 2018;19:765–769.
9. Hanlon JT, Perera S, Drinka PJ, et al. Consensus guidelines for empiric treatment of uncomplicated cystitis in noncatheterized nursing home residents. J Am Geriatr Soc 2019;67:539–545.
10. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assess drug therapy appropriateness. J Clin Epidemiol 1992;45:1045–1051.
11. Hanlon JT, Schmader KE. The Medication Appropriateness Index at 20: Where it started, where it has been and where it may be going. Drugs Aging 2013;30:893–900.
12. Lawless JE. Negative binomial and mixed Poisson regression. Can J Statistics 1987;15:209–225.
13. Marcum ZA, Handler SM, Wright R, et al. Interventions to improve suboptimal prescribing in nursing homes. Am J Geriatr Pharmacother 2010;8:183–200.
14. Dobson EL, Klepser ME, Pogue JM, et al. Outpatient antibiotic stewardship: Interventions and opportunities. J Am Pharmacists Assoc 2017;57:464–473.
15. Kistler CE, Zimmerman S, Scales K, et al. The antibiotic prescribing pathway for presumed urinary tract infections in nursing home residents. J Am Geriatr Soc 2017;65:1719–1725.
16. Gruneir A, Bell CM, Bronskill SE, et al. Frequency and pattern of emergency department visits by long-term care residents—A population-based study. J Am Geriatr Soc 2010;58:510–517.

17. Mody L. Infection control issues in older adults. Clin Geriatr Med 2007;23:499–515.
18. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: A call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008;46:155–164.
19. Anon. FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm612995.htm. Accessed January 4, 2020.
20. Mody L, Juthani-Mehta M. Urinary tract infections in older women: A clinical review. JAMA 2014;311:844–854.