Advanced Emergency Nursing Journal
Vol. 40, No. 3, pp. 162–170

APPLIED
PHARMACOLOGY

Column Editor: Kyle A. Weant, PharmD, BCPS, FCCP

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Outpatient Treatment of Uncomplicated Urinary Tract Infections in the Emergency Department

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ABSTRACT
One of the most commonly treated infections in the emergency department (ED) is an uncomplicated urinary tract infection. Multiple classes of antibiotics are frequently used to treat this condition, but not all have equivalent efficacy, and many may confer risks to not only the patient but society as a whole if used on a large scale. These antibiotic selections should also be guided by local antimicrobial susceptibility patterns, and general multidisciplinary recommendations for therapy should be developed on a local scale to assist prescribing patterns. The proactive development of a routine approach to reviewing and addressing positive cultures following discharge from the ED should also be developed and implemented in order to ensure that optimal patient care is provided. The objective of this review is to assess the available literature to isolate which antibiotics and approaches to care are the most appropriate options for treating uncomplicated outpatient urinary tract infections in the ED. **Key words:** antibiogram, cephalosporins, emergency medicine, fluoroquinolones, fosfomycin, nitrofurantoin, outpatient, pharmacy, urinary tract infection

HEALTH CARE providers must use antibiotics in an informed and judicious manner, with the understanding that careful use of antibiotics is critical in stemming the emergence of antibiotic-resistant bacteria. The provision of optimal antimicrobial stewardship requires that providers develop evidence-based practice standards that overall provide effective and reproducible therapy on a daily basis (Hudepohl, Cunha, & Mermel, 2016; Trinh & Klinker, 2015). An active area to model ongoing reevaluation and

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Disclosure: *The authors report no conflicts of interest.*

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DOI: 10.1097/TME.0000000000000195

research in managing antimicrobial resistance is in the area of one of the most commonly treated infections in the emergency department (ED), uncomplicated urinary tract infections (UTIs). These infections are often defined as dysuria with acute onset, urgency, or frequency in an otherwise healthy female who is not pregnant and devoid of function or anatomical abnormalities of the urinary tract (Nicolle et al., 2005). This is contrasted with asymptomatic bacteriuria, which is the isolation of bacteria in a urine specimen without symptoms or signs suggesting a urinary infection. And it is separate from nonobstructive pyelonephritis, which can also occur in this population, but is pain and tenderness with associated fever. A complicated UTI is an infection in individuals with functional or structural abnormalities of the genitourinary tract that involves either the bladder or the kidneys. Urinary tract infections in men are typically considered complicated. The high prevalence of uncomplicated UTIs in otherwise healthy females provides either ample opportunity either to provide optimal antimicrobial stewardship or to unintentionally promote extensive levels of bacterial resistance in the community (Gupta et al., 2011). In addition, the varying treatment protocols for uncomplicated UTIs also underscores the complex nature of the *Escherichia coli* bacteria, the most common causative organism in this condition, and its varying resistance profiles (Jorgensen et al., 2017).

The routine and common use of cephalosporins and fluoroquinolones has been linked to the selection of antibiotic-resistant organisms and what is commonly referred to as collateral damage (Paterson, 2004). Ultimately, an aggressive pursuit of the most conservative yet effective treatment protocol, or standard treatment recommendations based on guidelines and local resistance patterns, for uncomplicated UTIs will serve as a model of stewardship for treating other common bacterial infections. The implications of a revised UTI treatment protocol and any corresponding educational initiatives could lay the groundwork for future protocol revisions and move the medical community closer to the goal of managing antimicrobials to retain their maximum effectiveness.

The objective of this review is to evaluate the research and subsequent recommendations surrounding antibiotic prescription practices for outpatient uncomplicated UTIs in the ED. The Infectious Diseases Society of America (IDSA) defines acute uncomplicated UTIs as those infections occurring in women who are not pregnant and have no known urological abnormalities or comorbidities (Gupta et al., 2011). The overwhelmingly frequent cause of UTIs is *E. coli* bacteria (75%–95%), bacteria commonly present in the digestive tract (Gupta et al., 2011). *E. coli* is traditionally susceptible to a wide variety of antibiotics, leading clinicians to believe that they have a choice of multiple categories of antibiotics from which they can treat an uncomplicated UTI. This variation in antibiotic treatment can lead to *E. coli*'s resistance to all antibiotics when the antibiotic with the narrowest spectrum of activity is not utilized. The alarming result is that inappropriate UTI treatment can undermine a broad-spectrum antibiotic's ability to treat the more pernicious *E. coli* infections typically found in inpatient hospital settings, systemic infections, and higher-risk patients (Fleming, White, & Southwood, 2014).

EMERGENCY DEPARTMENT ANTIBIOGRAM DEVELOPMENT

The IDSA guidelines for using antibiotics state that it is an appropriate empiric selection if the efficacy of an antibiotic is greater than 80% (Warren et al., 1999). Therefore, antibiotic prescribing in the ED needs to be guided by local resistance patterns and the percentage of UTI-causative organisms that are susceptible in the ED. The importance of developing unit-specific antibiograms was recently described in an assessment of data from 4,515 hospitals looking at 365,490 health care-associated infections (Weiner et al., 2016). The source of the data came from acute care hospitals, long-term acute care hospitals, and inpatient

rehabilitation facilities. This study found an increase in the magnitude of the resistance percentages from 2011 to 2014, including an increase in *E. coli*'s resistance to fluoroquinolones. Resistant phenotypes were more common among device-associated infections. In some institutions it may be challenging to develop an ED-specific antibiogram, either through technological or clinical-based practice decisions, in which case hospital-wide data should be utilized. However, it is important to note that if a hospital-wide antibiogram is utilized to guide the therapy of the outpatient treatment of uncomplicated UTIs, then resistance to commonly used antibiotics is likely to be overestimated because of the inclusion of such patients. Subsequently, this can lead to the unnecessary and inappropriate prescribing of antimicrobials with a broader spectrum of action, further contributing to the development of antimicrobial resistance in the outpatient arena.

One study sought to further evaluate this concept through the comparison of *E. coli* susceptibilities to antibiotics prescribed in the ED in patients presenting with uncomplicated cystitis to the institution's hospital-wide antibiogram (Smith, Bazzoli, Chung, Johnson, & Martin, 2015). These cases of *E. coli* were evaluated for susceptibility to four antibiotics: cefazolin, ciprofloxacin, trimethoprim/sulfamethoxazole (TMP/SMX), and nitrofurantoin. There was noted to be statistically greater susceptibility of cultures arising from the ED to TMP/SMX (80% vs. 71%), cefazolin (97% vs. 87%), and ciprofloxacin (89% vs. 73%) than those of the general hospital antibiogram between the outpatient and inpatient cultures. A much larger investigation looking at 25,418 outpatient and 5,560 inpatient urinary isolates in pediatric patients also compared antibiotic resistance patterns to ascertain whether there was any difference (Saperston, Shapiro, Hersh, & Copp, 2014). The authors determined the prevalence and resistance patterns of the six most common bacteria, including *E. coli*. The resistance pattern was noted to be significantly lower in the outpatient setting compared with the inpatient setting for TMP/SMX and beta-lactams. The authors of both studies concluded that existing inpatient antibiograms are significantly overestimating antimicrobial resistance rates in the community and that separate antibiograms should be developed to help guide therapy.

ANTIMICROBIAL SELECTION

Multiple antimicrobials exist in the armamentarium for the outpatient treatment of uncomplicated UTIs in the ED. The IDSA guidelines specifically discuss the use of TMP/SMX, nitrofurantoin, fosfomycin, fluoroquinolones, and beta-lactams (Gupta et al., 2011). A recent comprehensive review of the literature also focused on the outpatient treatment of uncomplicated UTIs, specifically in adult women younger than 65 years (Grigoryan, Trautner, & Gupta, 2014). The authors reviewed literature in this population since 2000 with regard to the use of TMP/SMX, nitrofurantoin, fosfomycin, fluoroquinolones, and beta-lactams. The authors of both reviews note that each agent has its own advantages and disadvantages and the choice of which specific agent to use should be made on an individual basis utilizing patient-specific factors and local antibiograms.

Previously, TMP/SMX was recommended as a first-line agent in the IDSA guidelines; however, secondary to growing resistance rates, this is no longer the case (Gupta et al., 2011). This agent must be evaluated periodically within the context of individual institutions and their respective resistance patterns among their outpatient population (Gupta et al., 2011). The guidelines consider TMP/SMX to remain highly effective for uncomplicated cystitis when the resistance rate is less than 20% and yield early clinical and microbiological cure rates (90%–100%). Although TMP/SMX use is associated with increased antimicrobial resistance and has a significant impact on intestinal flora, it is not considered to have the same propensity to contribute to community resistance as cephalosporins or fluoroquinolones (Gupta

et al., 2011). A more recent review of the literature found three randomized controlled trials that investigated TMP/SMX in this population, and it demonstrated cure rates of 85%–100% (Arredondo-Garcia et al., 2004; Grigoryan et al., 2014; Gupta, Hooton, Roberts, & Stamm, 2007; Kavatha et al., 2003). They did note a potentially high rate of adverse events ranging from 1% to 31%, most frequently nausea, diarrhea, headache, and dizziness. The authors recommended that TMP/SMX 160/800 mg twice a day for 3 days is an appropriate regimen if susceptibility patterns support its use (Grigoryan et al., 2014).

The IDSA guidelines note that nitrofurantoin has similar clinical cure rates to that of TMP/SMX, ciprofloxacin, and fosfomycin in the studies reviewed (88%–93%) (Gupta et al., 2011). A further meta-analysis of four trials comparing the clinical cure rates of nitrofurantoin and TMP/SMX has also demonstrated equivalence (Gupta et al., 2011). An additional literature review identified that a course of nitrofurantoin therapy was comparable to other antimicrobial agents (Grigoryan et al., 2014; Iravani et al., 1999; Spencer, Moseley, & Greensmith, 1994; Stein, 1999; Van Pienbroek, Hermans, Kaptein, & Mulder, 1993). The authors concluded that nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for 5–7 days is an acceptable empiric regimen (Grigoryan et al., 2014). Nitrofurantoin is distinctive in that it has the additional advantage of having a low propensity for collateral damage secondary to its pharmacologic profile; however, it is not effective for the treatment of pyelonephritis (Gupta et al., 2011).

Fosfomycin is an agent with a unique mechanism of agent that has been increasing in usage secondary to data showing its efficacy in resistant UTIs, its stable susceptibility pattern over time, and its convenient single-dosing regimen (Bader, Loeb, & Brooks, 2017; Gupta et al., 2011; Vardakas, Legakis, Triarides, & Falagas, 2016). The IDSA guidelines support its use in this setting despite its bacterial efficacy being potentially lower than other agents but with equivalent clinical efficacy. Another detailed review of the available studies also echoes these recommendations and suggests that 3 g as a single dose is an appropriate empiric option (Boerema & Willems, 1990; Ceran et al., 2010; Elhanan, Tabenkin, Yahalom, & Raz, 1994; Grigoryan et al., 2014; Minassian et al., 1998; Stein, 1999; Van Pienbroek et al., 1993). Some institutions may not have the capability to do susceptibility testing of certain pathogens to this agent; however, based on its guideline recommendation, broad spectrum, and its high clinical efficacy, its use should still be considered. Similar to nitrofurantoin, this agent has a limited likelihood of causing collateral damage and should not be used to treat pyelonephritis, but it is unique in that the convenience of its single-dose regimen is a quite attractive option in the setting of the ED (Gupta et al., 2011). This can be a challenging agent for patients to utilize outside of the ED secondary to cost and availability, and so administration prior to ED discharge might be necessary.

Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) are well-studied agents in the treatment of acute cystitis but with a wide variety of different agents along with varying doses and durations (Gupta et al., 2011). The IDSA guidelines note that these are very effective for this presentation despite the continually increasing resistance among urinary pathogens. They recommend that these agents should not be used as a primary agent but rather an alternative when other options are not possible (Gupta et al., 2011). The primary concern with the use of fluoroquinolones is the promotion of resistance, not necessarily among the bacteria that are being treated, but rather in other organisms and the association between fluoroquinolone use and increased rates of methicillin-resistant *Staphylococcus aureus* (Gupta et al., 2011). Another review of the literature comes to a similar conclusion: these agents are needed for the treatment of more severe infections at other sites and should be reserved if possible (Grigoryan et al., 2014). If these agents are to be used, however, they should be used for the shortest duration possible (3–7 days).

Multiple investigations have demonstrated that a 3-day regimen of fluoroquinolones is equivalent to a 7-day regimen in this setting (Auquer et al., 2002; Vogel et al., 2004). Although some have advocated for a 7-day regimen in the setting of women with diabetes, this has not been demonstrated in the available literature to date (Grigoryan et al., 2014).

Beta-lactams are a diverse group of agents that include cephalosporins (e.g., cefpodoxime, cephalexin, and cefdinir) and penicillins (e.g., amoxicillin/clavulanate) with moderate variations in their individual antimicrobial spectrum. The overall efficacy of beta-lactams in this setting has been shown to be inferior to that of fluoroquinolones, although the broader-spectrum agents such as cefpodoxime have shown equivalent efficacy to TMP/SMX (Gupta et al., 2011). The IDSA guidelines do not recommend broad-spectrum beta-lactams as first-line agents because of concern over the promotion of gram-negative resistance and acknowledge that there are limited data to support the use of narrower-spectrum cephalosporins (e.g., cephalexin) (Gupta et al., 2011). A more recent review of the literature supports this recommendation, suggesting that beta-lactam agents have inferior efficacy compared with other agents in this setting (Grigoryan et al., 2014).

PRACTICAL IMPLEMENTATION

In the course of treating over 100 million people annually, 15.7% of ED patients are prescribed an antimicrobial agent, making it imperative that a more structured approach to the care of these patients be undertaken (Dumkow et al., 2014). The clinical implications of inappropriate antibiotic prescribing have been demonstrated by higher revisits to the ED and hospital admissions (Micek et al., 2011; Ramphal, 2005). Through the development of institution-specific ED antibiograms, it is possible to develop pathways to ensure that empiric therapy selections are appropriate and data-driven. One study demonstrated that, through the development of an ED-specific order pathway, they were able to significantly increase guideline adherence for the treatment of cystitis from 44% to 82%, significantly decrease the duration of therapy from 5.6 to 3.6 days, and significantly decrease the use of fluoroquinolones from 44.4% to 12.9% (Hecker et al., 2014). These pathways should consider susceptibility patterns, potential complications, patient-specific factors such as organ function, as well as pharmacoeconomic factors of both the institution and the patient. Furthermore, patient compliance, tolerance, and concomitant medication therapy are also key factors that can impact antimicrobial selection. As such, the development of a comprehensive process for developing and revising such pathways, as well as implementing a reliable patient follow-up process when culture susceptibilities are available, is a multidisciplinary endeavor (Dumkow et al., 2014). The integration of prescribers, nurses, the hospital antimicrobial stewardship service, and emergency medicine (EM) pharmacists has the potential to yield a diverse and highly skilled team to assist in the overall management of this population. Studies have demonstrated that, with this multidisciplinary collaboration, significant reductions in revisits to the ED within 72 hr were seen (Dumkow et al., 2014). A sample uncomplicated UTI pathway is provided in Figure 1 (Grigoryan et al., 2014; Gupta et al., 2011).

It has been noted that many patients will require a modification of their initial empiric antimicrobial therapy, up to a quarter of patients in some studies (Dumkow et al., 2014). It is imperative that a process be put into place that ensures these patients receive timely follow-up with appropriate modifications to their therapy. Research has clearly demonstrated that this is a multidisciplinary process that can be a collaboration between prescribers, nurses, and EM pharmacists. The key is that a process be implemented. For example, one study demonstrated that, when such a process was staffed by advanced practice providers, the authors found significant reductions in the amount of time to follow-up

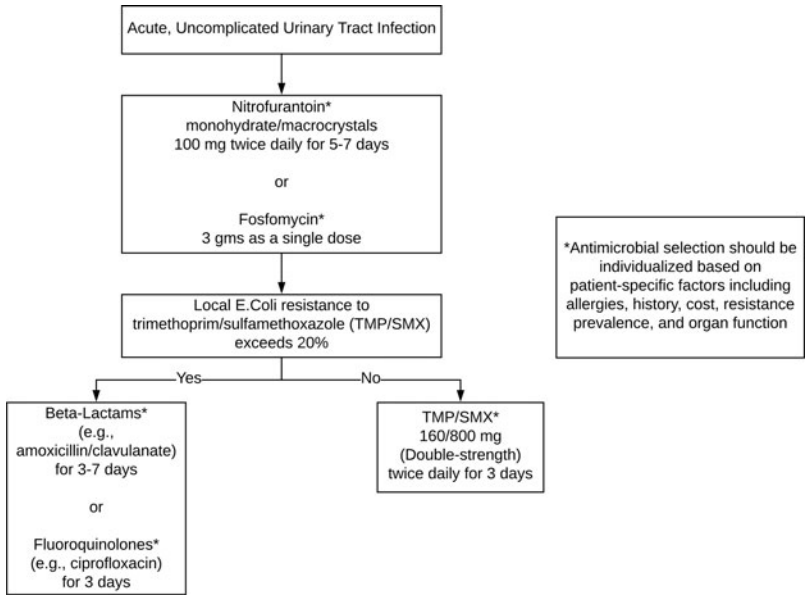

Figure 1. Sample uncomplicated urinary tract infection treatment pathway. From Gupta et al. (2011).

and increased the number of follow-up calls to discontinue antibiotics when cultures were negative (Burchett, Harpin, Petersen-Smith, & Emery, 2015). Additional literature has shown that when EM pharmacists were tasked with follow-up there was a reduced time to positive culture review and patient notification as well as up to a 30% improvement in the identification and resolution of inappropriate empiric regimens (Baker et al., 2012; Davis, Covey, Weston, Hu, & Laine, 2016; Miller et al., 2014). A sample ED culture follow-up process is provided in Figure 2.

Percival et al. (2015) operationalized these concepts through collaboration with the microbiology laboratory to build an ED-specific antibiogram, partnered with the local antimicrobial stewardship committee to develop institution-specific recommendations, increased provider education by EM pharmacists, set up a system for routine follow-up education to providers, and conducted follow-up patient contact when a revision in therapy was necessary (Percival et al., 2015). The investigators found that, after education, antimicrobial selection that was consistent with recommendations increased from 44.8% to 83% ($p < .001$)—largely due to an increase in the use of nitrofurantoin for cystitis (12% vs. 80%; $p < .001$). They also noted an improvement in the subsequent agreement between the initial antibiotic chosen and the pathogen susceptibility for cystitis from 74% to 89% ($p = .05$). Hence, through the development of institution-specific pathways to guide empiric medication selection by prescribers and ensuring appropriate and timely follow-up with patients, significant improvements in the provision of care to patients can be achieved.

CONCLUSION

Although health care providers often prescribe a wide array of antibiotics for patients presenting with acute, uncomplicated UTIs, the available literature supports the practice of reserving broad-spectrum agents for complex inpatient care and narrower-spectrum antibiotics for uncomplicated outpatient care (Grigoryan et al., 2014; Gupta et al., 2011). Specifically, TMP/SMX, fosfomycin, and nitrofurantoin are found to be consistently reliable antibiotics for uncomplicated UTIs in patients who present to the ED and that can safely be treated in an outpatient setting. Furthermore, the development of

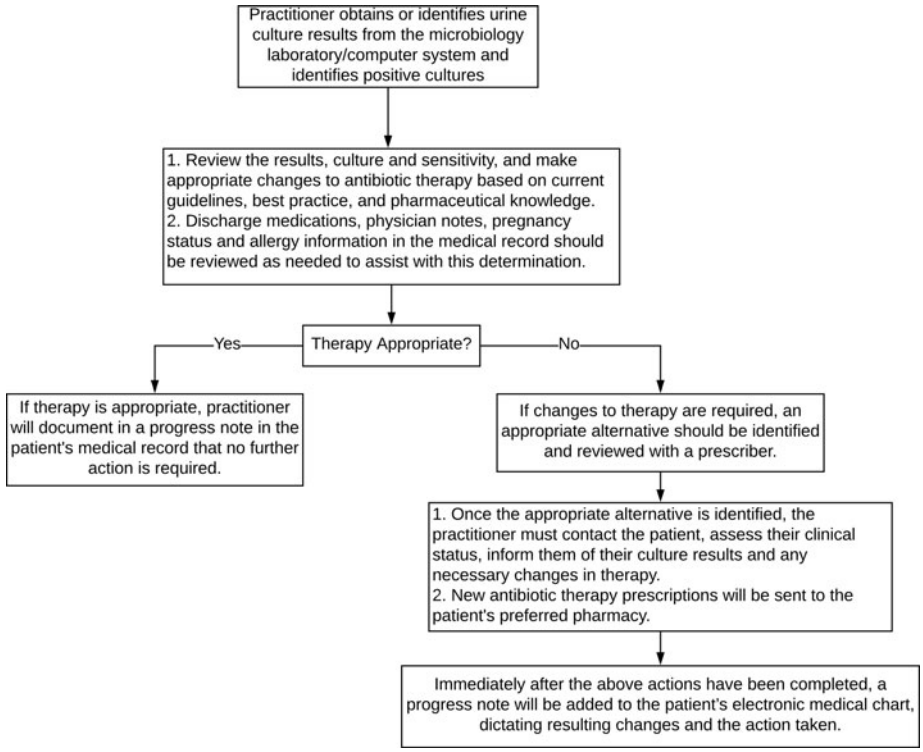

Figure 2. Sample emergency department culture follow-up process.

institution-specific antibiograms, treatment pathways, and culture follow-up procedures for discharged patients can help ensure that not only is empiric antimicrobial selection optimal but that significantly more patients will receive appropriate care even in the age of increasing antibiotic resistance.

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