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9-2015

## Impact of an Antimicrobial Stewardship Intervention on Urinary Tract Infection Treatment in the Emergency Department

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### Recommended Citation

Percival, Kelly M.; Valenti, Kristine M.; Scmittling, Stacy E.; Strader, Brandi D.; Lopez, Rebecka R.; and Bergman, Scott, "Impact of an Antimicrobial Stewardship Intervention on Urinary Tract Infection Treatment in the Emergency Department" (2015). *SIUE Faculty Research, Scholarship, and Creative Activity*. 31.

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No financial support to disclose

Meetings: ICAAC 2014, Washington D.C.

Key Words: Urinary tract infections; antimicrobial stewardship; Emergency Department; cystitis; pyelonephritis; nitrofurantoin

## **Abstract**

**Study objective:** To assess changes in treatment of uncomplicated urinary tract infections (UTIs) following implementation of recommendations based on national guidelines and local resistance rates.

**Methods:** This pre- and post-intervention study included patients discharged home from the Emergency Department (ED) with an uncomplicated UTI at a 439-bed teaching hospital. ED prescribers were educated on how local antimicrobial resistance rates impact UTI practice guidelines. Empiric treatment according to recommendations was assessed as the primary outcome. Agreement between chosen therapy and isolated pathogen susceptibility was compared before and after education. Reevaluation in the ED or hospital admission within 30 days for a UTI was also evaluated.

**Results:** A total of 350 patients were studied (174 before and 176 after education). Of those, 255 had cystitis and 95 had pyelonephritis. Following education, choice of therapy consistent with recommendations increased from 44.8% to 83% (difference 38.2%, 95% CI 33% to 43%;  $P < 0.001$ ). The change was predominately driven by an increase in nitrofurantoin use for cystitis from 12% to 80% (difference 68%, 95% CI 62% to 73%;  $P < 0.001$ ). Agreement between empiric treatment and the isolated pathogen susceptibility improved for cystitis 74% to 89% ( $P = 0.05$ ), and no change occurred in 30-day repeat ED visits for a UTI.

**Conclusions:** After implementation of treatment recommendations for uncomplicated UTIs based on local resistance, empiric antibiotic selection improved in the ED. To further meet goals of antimicrobial stewardship, additional interventions are needed.

## 1. Introduction

### 1.1 Background

The Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases published updated practice guidelines for uncomplicated cystitis and pyelonephritis in women during 2011 [1]. Due to the large variance in *Escherichia coli* resistance to fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX) throughout the world, the guidelines place a large emphasis on the importance of using local resistance rates to determine the best empiric treatment [1, 2]. Specifically, the guidelines recommend that TMP-SMX no longer be used as first-line therapy for uncomplicated cystitis when local resistance for *E. coli* exceeds 20%. If patients are being discharged on oral therapy for pyelonephritis in areas where *E. coli* resistance to fluoroquinolones exceeds 10%, then it is also suggested that a one-time dose of a long-acting parenteral agent from a different antimicrobial class be used. Another addition to the guidelines is the concept of avoiding collateral damage, which includes the ecological adverse effects from antibiotic therapy, especially the selection of multi-drug resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci and *Clostridium difficile* [1, 3]. It emphasized that drugs with minimal impact on the microbiota, such as nitrofurantoin, should be utilized when possible while higher risk drugs, including fluoroquinolones, should be reserved for infections more severe than cystitis [1].

The public health threat of antimicrobial resistance and the need to prevent its spread is at the forefront of importance as demonstrated by the White House releasing an Executive Order and National Strategy to Combat Antibiotic-Resistant Bacteria in September 2014 [4]. The need for increased education on antimicrobial resistance and selection of therapy was demonstrated in a recent survey of healthcare providers that revealed antibiotic resistance was not commonly

considered when prescribing antimicrobials despite the widespread concern for resistance [5]. The definition of antimicrobial stewardship according to guidelines from IDSA and the Society of Healthcare Epidemiology of America is “to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*), and the emergence of resistance” [6]. Antimicrobial stewardship programs have successfully demonstrated the ability to safely reduce resistance by emphasizing use of narrow-spectrum antimicrobials, but these efforts have largely focused on inpatient settings despite the majority of prescribing for antibiotics occurring in outpatients. A call to action has been expressed for antimicrobial stewardship in the ED as this clinical setting can impact antibiotic use in both inpatients and outpatients [7]. Literature regarding antimicrobial stewardship in the ED has been minimal, possibly due to the difficulties of implementation in this setting. Some of these challenges include rapid patient turnover, the diverse needs of those destined for either inpatient or outpatient care, a varied mix of providers, and high staff turnover. A few of the inter-professional antimicrobial stewardship processes that have led to positive patient outcomes in the ED include development of ED-specific antibiograms as well as post-prescription culture follow-up [7-9]. The educational intervention in this study was designed to assist prescribers in making the best choice of therapy for uncomplicated UTIs, the infectious disease requiring the most frequent culture review.

## 1.2 Goals of This Investigation

The purpose of this study was to assess changes in treatment of uncomplicated UTIs following implementation of recommendations derived from applying local antimicrobial resistance patterns to national practice guidelines. It is hypothesized that increasing adherence to

the guidelines will result in a higher rate of isolated pathogens being susceptible to the prescribed therapy.

## **2. Methods**

### **2.1 Study Design and Setting**

This was a quasi-experimental study comparing two separate time periods before and after an educational intervention in November 2013. It was conducted at a 439-bed tertiary-care teaching center with more than 57,000 ED visits annually and approximately 100 visits per month for the diagnosis of any UTI. The facility has had an antimicrobial stewardship service since 2011, but no previous attempts have been made to implement outpatient interventions. Clinical pharmacists are present in the ED 24 hours each day. They verify patient medication orders during their stay but do not evaluate outpatient prescriptions unless requested. A post-prescription review program is in place to follow-up with patients who have positive culture results after discharge. Outcome measures were compared for the months following November 2012 and November 2013. The institutional review board approved the study prior to beginning research and provided a waiver of the requirement for informed consent as the intervention was deemed to be of minimal risk to subjects.

### **2.2 Selection of Participants**

Patients evaluated for a UTI by any ED provider during the specified time periods were eligible for the study. This included exams by resident physicians, mid-level practitioners, and attending physicians. Patients were identified through ED visit reports by diagnosis and were included if they were female, 12-70 years old, discharged home from the ED with an uncomplicated UTI, and received an antibiotic prescription. Exclusion criteria included patients



who were admitted for inpatient treatment, pregnant, catheterized, or diagnosed with a complicated UTI for any other reason.

### 2.3 Interventions

With the help of the microbiology laboratory, an ED-specific antibiogram was constructed to determine the rate of *E. coli* resistance to TMP-SMX, ciprofloxacin, nitrofurantoin, and cefazolin locally. For outpatients, the antibiogram revealed susceptibilities for these drugs of 75%, 80%, 99%, and 96% respectively. Based on this and the IDSA guidelines, institution-specific recommendations were developed for the empiric treatment of uncomplicated UTIs in the ED as shown in table 1.

After being endorsed by our local antimicrobial stewardship committee, institution-specific recommendations were implemented through education by a pharmacist in the ED and to resident physicians during their monthly meeting. In addition, all ED providers were delivered education by email from the medical director of the ED reinforcing the recommendations and their justification. Pharmacists did not actively review outpatient prescriptions during the study. A preliminary audit of empiric prescribing was performed two months into the post-education study period and then feedback on results was provided by email to all ED providers as a reminder of the recommendations. The remaining patient charts were reviewed at the end of the study period.

### 2.4 Methods and Measurements

All data were extracted systematically from the electronic medical record by one trained investigator using a standardized data collection form with definitions of each variable.

Diagnosis of UTI was based on provider documentation and the ICD-9-CM codes assigned to the visit. If the type of UTI was not specified, classification was based on evidence-based definitions

[10]. Patients were determined to have cystitis if there was no documentation of flank pain, fever, leukocytosis ( $\text{WBC} \geq 12,000/\text{ml}$ ), or the prescriber recorded that there was no evidence for pyelonephritis. An infection was defined as uncomplicated if it occurred in non-pregnant woman with no known urological abnormalities. If documentation was not clear, the abstractor reviewed the available data with the senior investigator. If there was a discrepancy, then a third investigator was consulted for interpretation. The study team met regularly to review progress. The drug, dose, frequency, duration and use of one-time parenteral injection, if warranted, were assessed according to the recommendations in Table 1. After nitrofurantoin and cephalexin, the use of TMP-SMX was considered appropriate in patients' with a creatinine clearance ( $\text{CrCl}$ ) 15-60 ml/min and a beta-lactam allergy. The fluoroquinolones, ciprofloxacin and levofloxacin, were appropriate in those with  $\text{CrCl}$  less than 60ml/min and a contraindication to both a beta-lactam and sulfa drug. These fluoroquinolones, TMP-SMX, or cephalosporins were considered appropriate therapy in pyelonephritis in that order. Isolated pathogen susceptibilities were compared to empiric therapy, and reevaluation for a UTI in the ED or hospital admission within 30 days was assessed to determine treatment failure.

## 2.5 Outcomes

The primary outcome of this study was to assess adherence to recommendations for the treatment of uncomplicated UTIs based on local resistance rates. Secondary outcomes included the agreement between empiric antibiotics prescribed and isolated pathogen susceptibilities, and reevaluation in the ED or hospital admission for a UTI within 30 days.

## 2.6 Analysis

Primary and secondary outcomes were analyzed statistically according to data type. Nominal data was assessed with Chi-square tests using GraphPad Prism version 5.00 for

Windows (GraphPad Software, San Diego California USA [www.Graphpad.com](http://www.Graphpad.com)). Continuous data was analyzed with a Student's t-test performed utilizing Microsoft Excel 2010 (Microsoft, Redmond Washington USA). For the primary outcome, a sample size of 343 patients was determined necessary to detect a 15% difference with an 80% power. A p-value of 0.05 was considered statistically significant.

### **3. Results**

#### **3.1 Characteristics of Study Subjects**

The flowchart of patients evaluated in the study is shown in Figure 1. The most common diagnosis code was for "Nonspecific UTI." Upon review, 255 patients were classified as having cystitis and 95 with pyelonephritis. There were no meaningful differences in the demographics of patients before and after education. Baseline characteristics are shown in Table 2. *E. coli* was the most common pathogen in positive urine cultures for both pre-and post-education patients with cystitis (73% and 71%,  $P=0.75$ ), and pyelonephritis (75% and 58%,  $P=0.23$ ), respectively.

#### **3.2 Main Results**

Antibiotics prescribed at discharge changed significantly following education (table 3). Before the intervention, the choice of empiric therapy was consistent with recommendations 44.8% of the time compared to 83% after (difference 38.2%, 95% CI 33% to 43%;  $P<0.001$ ). This change was driven by significant decreases in TMP-SMX and fluoroquinolone use for cystitis balanced with increases in prescribing of nitrofurantoin for cystitis and fluoroquinolones for pyelonephritis. Overall prescribing according to institution-specific recommendations for the treatment of UTIs in regard to antibiotic choice, dose, frequency, duration, and a 1-time parenteral antibiotic dose for pyelonephritis pre- and post-education increased from 2.3% to 20% (difference 17.7%, 95% CI 14% to 22%;  $P<0.001$ ) (table 4). The lowest rate of adherence to recommendations was in duration of therapy which changed from 16 % to 25.5 % (difference

9.5%, 95% CI 6% to 13%;  $P=0.029$ ) and administration of a long-acting parenteral agent for pyelonephritis different from the treatment at discharge. There was no further change in prescribing observed after feedback was delivered via e-mail to providers following the initial audit of empiric treatment halfway through the prospective study period.

When a urine culture was performed, the prescribed antibiotic was susceptible to the isolated pathogen more often in cystitis following education (74% vs. 89%,  $P=0.05$ ), but not in pyelonephritis patients (90% vs. 76%,  $P=0.23$ ). The rate of patients seeking follow-up care for a UTI at the institution within 30 days was unchanged at 4.6% compared to 7.4% ( $P=0.27$ ).

#### **4. Discussion**

We observed that the prescribing habits for treatment of uncomplicated UTIs changed to utilize narrower-spectrum antibiotics after implementation of antimicrobial stewardship recommendations in the ED. This is noteworthy because national guidelines were tied to local resistance rates and providers adjusted empiric prescribing accordingly following education. Since hospital pharmacists do not normally view the prescriptions patients are being discharged home on, and community pharmacists do not have access to the medical record, no other intervention was performed during the study period unless a provider asked for assistance. Our results demonstrated the largest differences before and after education in treatment for patients with cystitis, which is a very common diagnosis in emergency department patients being discharged home. Although we were able to show significant improvements in appropriate antibiotic choice, the results indicate further work can be done to optimize treatment.

Recently, outcomes have been published from another center replicating our improvement in guideline adherence for the treatment of uncomplicated UTIs, in their case through the utilization of an electronic order set. That intervention resulted in a 38% increase in adherence to guidelines, primarily from a reduction similar to ours in use of fluoroquinolones for

cystitis. In that study, unnecessary antibiotic days were decreased from 250 to 52 per 200 patients [11]. Although our education improved the days of therapy prescribed to be more consistent with guidelines, recommendations for treatment duration were only followed a minority of the time. This may have been because our education focused primarily on attributing rising resistance rates to empiric antibiotic selection as opposed to prolonged duration of therapy. This leads us to believe that future studies intending to improve antibiotic use should also incorporate utilization of order sets, custom-built with recommended agents based on local resistance and durations of therapy. At our institution, order sets have been difficult to implement during a time of transition between paper and electronic prescriptions so treatment recommendations were distributed through verbal education with paper handouts provided and e-mail. Although order sets were not included in this study, they will be considered for antimicrobial stewardship efforts in the future based on the success of this baseline study.

One of the alarming findings from our experience was that patients labeled as having pyelonephritis were being prescribed nitrofurantoin at discharge both before and after education. This is concerning because nitrofurantoin does not achieve adequate concentrations in the kidney tissue and is not appropriate to treat a potentially systemic infection. Although the retrospective nature of this analysis could have misclassified the infection, it is a point that necessitates further education to providers for the sake of patient safety. We have continued the practice of educating ED providers on UTI treatment recommendations upon the annual arrival of new medical residents.

The most commonly described antimicrobial stewardship intervention in the ED is post-prescription culture review, and there have previously been improvements in readmission rates for patients with this follow-up. One way pharmacists have assisted with these review programs

is to ensure that patients with positive test results are being treated appropriately after they have left the ED [9, 12, and 13]. Our intervention was intended to improve prescribing before the patient was discharged from the ED; subsequently leading to less follow-up that would be needed later. In our experience, there was a clinically relevant improvement in the number of times the isolated pathogen was susceptible to the prescribed antibiotic. We did not specifically evaluate the number of minutes spent on post-prescription review in this study but felt there was a meaningful decrease in the amount of follow-up needed for uncomplicated UTIs after the intervention because the therapy chosen was active against the isolated pathogen more often. This is especially important in an era of emphasis on cost-effective healthcare and limited reimbursement for treatment failures. Our findings did not show a difference in the number of reevaluations within 30-days between the two groups. This is most likely due to the fact that even in the pre-education group, culture follow-up was being performed and patients were contacted immediately if the organism was resistant to empiric treatment. They were then changed to appropriate treatment based on the urine culture and susceptibility report. In the meantime, even cystitis with organisms resistant to the prescribed therapy can sometimes be alleviated due to the high concentrations of most antibiotics in the urine. This would potentially limit the return of patients, even though it is not a reliable way to practice.

## **5. Limitations**

This was a single center observational experience without randomization. Recommendations were based on resistance rates that will differ in other geographic areas which limits external validity. Our study spanned four to five months, one year apart, and this is not long enough to determine whether cumulative resistance rates would change over time based on the improved adherence to guidelines. Only uncomplicated UTIs were analyzed for this study

and the number of patients with a diagnosis of pyelonephritis was small, especially in the post-education group, further limiting the applicability of results. The low number of pyelonephritis cases in both groups may have been due to the definition chosen, as few patients had a fever recorded. The majority of coding was for “non-specific UTIs”, and therefore, classification was based on chart documentation. Despite patients being enrolled prospectively in the second half of the study, all the charts were analyzed retrospectively and the authors had to apply definitions for pyelonephritis and cystitis themselves. The abstractor was not blinded to study group because of the nature of a before and after trial design. This leaves open the possibility that some patients may have been misclassified, even though every effort was made to accurately assess these patients without bias. Additionally, the report generated to identify patients evaluated for UTIs in the ED changed slightly from the pre- to post-education group. The pre-education report was able to identify all ICD-9 codes during the visit while the post-education report only identified patients by the primary diagnosis. This could have contributed to the discrepancy in the number of patients with pyelonephritis between the groups, although it seems unlikely that many patients would be discharged with pyelonephritis as a secondary diagnosis in our experience. Finally, there remains the possibility that patients initially evaluated in the ED could have sought follow-up care for their UTI at another site. This would lower our estimation of treatment failures both before and after the intervention. Furthermore, the study was powered to show a difference in treatment of 15%, but not reevaluation rates of 5%, so a larger trial would need to be conducted to detect if any difference existed in that outcome.

## **6. Conclusion**

In summary, outpatient prescribing in the ED changed significantly after implementation of treatment recommendations for uncomplicated UTIs based on local resistance patterns and

national practice guidelines. This resulted in achieving a goal of antimicrobial stewardship by decreasing use of broad spectrum agents for cystitis, specifically fluoroquinolones, and reserving them for more severe infections. Subsequently, there was an increase in isolated pathogens being susceptible to empiric therapy for cystitis following education. Additional studies of antimicrobial stewardship in the emergency department are needed to determine the impact interventions have on long-term resistance patterns, time required for post-prescription follow-up and patient outcomes. In the future, we advise implementing order sets focusing on recommended treatments including durations of therapy for urinary tract infections and appropriate use of one-time doses for long-acting parenteral agents prior to discharge with pyelonephritis.

### **Acknowledgments**

The authors acknowledge the assistance of McKenzie Ferguson, Pharm.D., BCPS in study design and statistical analysis.

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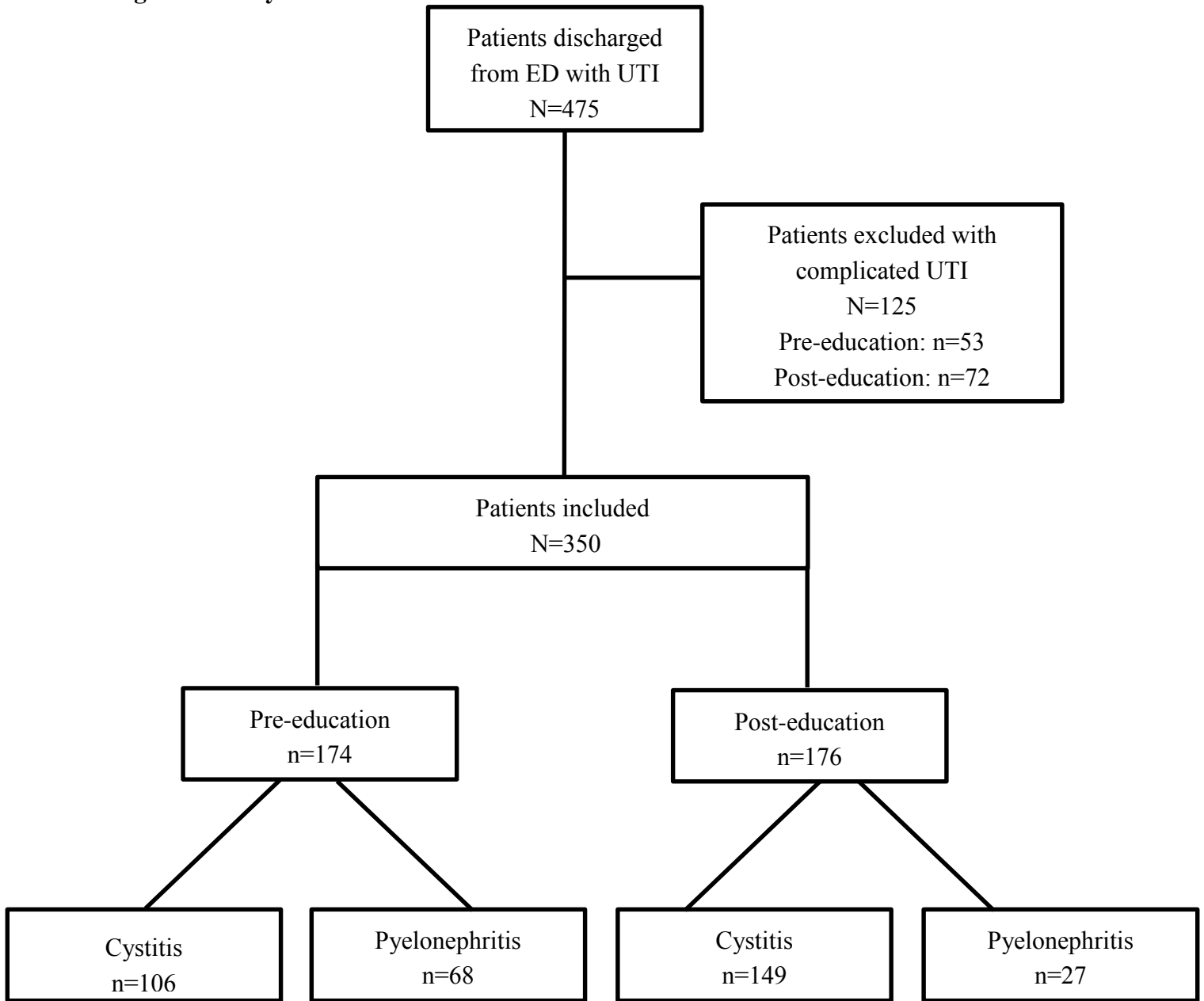
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**Figure 1. Study flowchart**



**Table 1. Empiric treatment recommendations for acute uncomplicated urinary tract infections**

**Cystitis**

- 1<sup>st</sup> choices
  - Nitrofurantoin monohydrate/macrocrystals 100 mg every 12 hours for 5 days
    - Only for patients with CrCl >60 ml/min
  - OR-
  - Cephalexin 500 mg every 12 hours for 7 days
- 2<sup>nd</sup> choice
  - Trimethoprim-sulfamethoxazole 160/800 mg every 12 hours for 3 days
    - Appropriate in patients with CrCl <60 ml/min and a beta-lactam allergy
- 3<sup>rd</sup> choice
  - Ciprofloxacin 250 mg every 12 hours or levofloxacin 250 mg daily for 3 days
    - Appropriate in patients with CrCl <60 ml/min plus a beta-lactam and sulfa allergy

**Pyelonephritis**

- A urine culture and susceptibility should always be performed
- Give 1 dose of a long acting parenteral agent in the ED
  - Ceftriaxone 1 g, gentamicin or tobramycin 5 mg/kg (Pharmacy to dose)
- Oral prescription for discharge
  - 1<sup>st</sup> choice
    - Ciprofloxacin 500 mg every 12 hours for 7 days or levofloxacin 750 mg daily for 5 days
  - 2<sup>nd</sup> choice
    - Trimethoprim-sulfamethoxazole 160/800 mg every 12 hours for 14 days
  - 3<sup>rd</sup> choice
    - Cephalexin 500 mg every 6 hours for 14 days

Note: Doses are for patients with normal renal function. Adjustment of therapy may be required for patients with kidney disease. CrCl = Creatinine clearance, ED = Emergency department.

**Table 2. Patient characteristics**

	<b>Cystitis</b>			<b>Pyelonephritis</b>		
	Pre-Education	Post-Education	P-value	Pre-Education	Post-Education	P-value
<b>Characteristic</b>	n=106	n=149		n=68	n=27	
Mean age, years	31.8 (12.5)	29.5 (11.5)	0.14	34.4 (13.9)	32.1 (13)	0.47
Mean WBC, k/mL	9.5 (4.5)	8.9 (2.7)	0.44	10.7 (5.2)	12.3 (3.7)	0.19
Mean temperature, °C	36.7 (0.4)	36.8 (0.4)	0.48	36.9 (0.6)	36.9 (0.5)	0.84
Mean SCr	0.80 (0.2)	0.84 (0.1)	0.15	0.83 (0.2)	0.80 (0.1)	0.57
Mean CrCl	88.5 (12.7)	98 (26.2)	0.04	87.2 (17.3)	99.3 (25.7)	0.03
Urine culture performed (%)	58 (54.7)	103 (69.1)	0.02 <sup>¥</sup>	54 (79.4)	22 (81.5)	0.82 <sup>¥</sup>
Mean days of treatment	7 (2.8)	7.2 (2.2)	0.46	7.9 (2.9)	8.4 (2.8)	0.43

All values are number ( $\pm$ SD) unless specified. All p-values by Student's t-test unless noted. <sup>¥</sup>Chi-square test

**Table 3. Antibiotics prescribed at discharge**

	<b>Cystitis</b>			<b>Pyelonephritis</b>		
	Pre-Education n=106 (%)	Post-education n=149 (%)	P-value	Pre-Education n=68 (%)	Post-Education n=27 (%)	P-value
Cephalexin	1 (0.9)	2 (1.3)	0.77	0	1 (18.5)	0.11
FQs	35 (33)	16 (12.8)	<0.001	32 (47)	19 (70.4)	0.04
TMP-SMX	56 (52.8)	8 (5.4)	<0.001	29 (43)	2 (7.4)	0.001
Nitrofurantoin	13 (12.3)	119 (79.9)	<0.001	7(10)	5 (18.5)	0.28
Doxycycline	1 (0.9)	0	0.23	--	--	

FQs=fluoroquinolones: ciprofloxacin or levofloxacin, All p-values by Chi-square test.

**Table 4. Results of adherence to recommendations**

	<b>Pre-education N=174 (%)</b>	<b>Post-Education N=176 (%)</b>	<b>P-value</b>
<b>Combined cystitis and pyelonephritis overall</b>	<b>4 (2.3)</b>	<b>35 (20)</b>	<b>&lt;0.001</b>
<b>Cystitis</b>	<b>n=106 (%)</b>	<b>n=149 (%)</b>	
Discharge antibiotic	17 (16)	124 (83.2)	<0.001
Dose	87 (82)	138 (92.6)	0.02
Frequency	105 (99)	146 (97.9)	0.64
Duration	22 (20.8)	35 (23.2)	0.65
Overall adherence	3 (2.8)	32 (21.5)	<0.0001
<b>Pyelonephritis</b>	<b>n=68 (%)</b>	<b>n=27 (%)</b>	
Parenteral antibiotic in ED	6 (8.8)	3 (11.1)	0.73
Discharge antibiotic	61 (89.7)	22 (81.5)	0.28
Dose	55 (80.9)	22 (81.5)	0.95
Frequency	62 (91.2)	22 (81.5)	0.18
Duration	6 (8.8)	10 (37)	<0.001
Overall adherence	1 (1.5)	3 (11)	0.03

ED = Emergency department, All p-values by Chi-square test.