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# Efficacy of cephalexin for the treatment of uncomplicated urinary tract infections due to *E. coli* strains deemed resistant to cefazolin.

## A. Study Purpose and Rationale

A breakpoint is a minimum inhibitory concentration (MIC)[1] threshold below which an antimicrobial is considered efficacious against a particular microorganism. In January 2010, the Clinical and Laboratory Standards Institute (CLSI) revised the breakpoint for the first-generation cephalosporin, cefazolin, against Enterobacteriaceae from ≤8 μg/ml to ≤1 μg/ml. Prior to 2010, the susceptibility breakpoint of ≤8 μg/ml had been in use for over 30 years. Due to emerging drug-resistance, the CLSI revised the breakpoint for cefazolin using in vitro susceptibility data, pharmacokinetic-pharmacodynamic (PK-PD) analyses, and clinical outcome data. However there was concern that the new breakpoint may be too low for certain situations such as in urinary tract infections (UTIs).

The cefazolin susceptibility profile is commonly used to predict activity of cephalexin for UTIs since cephalexin is excreted in high concentration in the urine. However the revised cefazolin breakpoint would potentially steer clinicians away from treating UTIs with cephalexin when it could still be effective. This would lead to unnecessary use of broader spectrum antibiotics leading to increased costs, drug resistance and adverse side effects. After further review the CLSI again revised the breakpoint for cefazolin against Enterobacteriaceae in January 2011, increasing from ≤1 μg/ml to ≤2 μg/ml. Whether cephalexin is still effective in treating UTIs due to *E. coli* strains with cefazolin MICs above this new breakpoint is unknown.

## B. Study Design

This is a retrospective cohort study that will compare the efficacy of cephalexin for the treatment of uncomplicated urinary tract infections due to *E. coli* strains considered resistant versus susceptible to cefazolin based on CLSI criteria.

## C. Study Population

Patients hospitalized at Columbia University Medical Center from January 2011 to August 2012 who were treated with cephalexin for an uncomplicated UTI due to *E. coli*.

[1] MIC is the lowest concentration of an antimicrobial in the blood that will inhibit growth of a microorganism.

D. Inclusion Criteria

1. age 18-65
2. female

E. Exclusion Criteria

1. antibiotic use in the previous 4 weeks
2. concomitant use of other antibiotics besides cephalexin
3. complicated UTI (i.e. diabetes, pregnancy, hospital acquired infection, renal failure, urinary tract obstruction, presence of an indwelling urinary catheter, functional or anatomic abnormality of the urinary tract)

F. Study Outcomes

Primary outcome will be clinical cure within 7 days after the start of cephalexin. Clinical cure is defined by resolution of symptoms such as dysuria, frequency, urgency, suprapubic pain.

Secondary outcome will be bacteriological cure within 7 days after the start of cephalexin. Bacteriological cure is defined by negative urine culture.

G. Statistical analysis

Assuming 90% effectiveness of cephalexin in treating patients with E. coli UTIs susceptible to cefazolin (MIC $\leq 2$ μg/ml), 219 patients would be needed for each comparison group to detect a difference of greater than 10% with power set at 80% and $\alpha < 0.05$ considered statistically significance.

Odds ratios will be calculated by a logistic regression model adjusting for potential confounding variables such as dose of cephalexin used, duration of cephalexin use, and comorbidities.

H. Study Procedure: n/a

I. Study Drugs or Devices: n/a

J. Study Questionnaire: n/a

K. Recruitment: n/a

L. Confidentiality of Study Data: A unique code number will be used for all patients included in the study to protect patient identity. Data will be stored in a secure location, accessible only to the investigators.

M. Potential Risks: n/a

N. Potential Benefits: Avoiding unnecessary use of extended-spectrum antibiotics and associated cost, risk of antibiotic resistance, and risk of adverse side effects.

O. References

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4. Jenkins S; Recent Changes in Gram negative Resistance; 40th Annual Symposium of the Eastern Pennsylvania Branch of ASM - "Diagnostic and Clinical Challenges of 20th Century Microbes". Philadelphia, PA. Nov 18, 2010.

5. Estes L, et al. Impact of Cephalosporin and Carbapenem Breakpoint Revisions on Enterobacteriaceae Susceptibility Rates. Abstract #246. IDSA Annual meeting. Boston, MA. Oct 20-23, 2011.

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