Correlation of cefpodoxime susceptibility with cephalothin and cefuroxime for urinary tract isolates

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This study attempted to determine whether cefuroxime was superior to cephalothin as a surrogate marker for cefpodoxime among urinary tract isolates. The MicroScan system (Siemens) was used to determine susceptibility for cephalothin and cefuroxime on consecutive cultures with a colony count of ≥50 000 organisms. Simultaneously, an Etest (bioMérieux) for cefpodoxime was conducted. The cefpodoxime interpretation was compared to that of the other two agents, and the categorical agreement was calculated, defined as the percentage of identical susceptibility interpretations. Cefuroxime (83%) had a significantly higher categorical agreement than cephalothin (63%) among 300 isolates (P<0.01). The major error rate was 16% for cephalothin and 3% for cefuroxime. The very major error rate was 7% for cephalothin and 14% for cefuroxime among the 14 cefpodoxime-resistant isolates. For Escherichia coli, the major error rates were 15% and 1% for cefalothin and cefuroxime, respectively. Very major error rates were 9% for both agents. Cefuroxime was a better predictor of cefpodoxime susceptibility than cefalothin, and appears to be the preferred surrogate agent for the MicroScan system, particularly for E. coli.

INTRODUCTION

Resistance to fluoroquinolones among urinary tract isolates is increasing (Johnson et al., 2008; Olson et al., 2009), and limiting their use may be beneficial in slowing this trend (Gottesman et al., 2009). Pathogens are frequently resistant to trimethoprim/sulfamethoxazole (Brown et al., 2002), and nitrofurantoin is not recommended for patients with diminished renal function (Product Information, 2006). Cephalosporins can be considered as alternative agents (Gupta et al., 2011), and cefpodoxime has the most published data among the oral cephalosporins (Hooton et al., 2012; Kavatha et al., 2003). However, cephalosporin is not available on a susceptibility panel for the MicroScan (Siemens) automated testing system used in many hospitals. The Clinical and Laboratory Standards Institute (CLSI) recommends that cefpodoxime susceptibility among urinary isolates can be inferred from the result for cephalothin (CLSI, 2013). However, these agents have significantly different spectra of antibacterial activity. The purpose of this study was to determine whether cefuroxime was superior to cephalothin as a surrogate marker.

METHODS

The study was conducted at a United States Army hospital in Augusta, Georgia. The hospital and clinics serve active duty personnel, United States Army retirees and their dependents. Automated susceptibility testing for cephalothin and cefuroxime was conducted on consecutive positive urine cultures with a colony count of at least 50000 organisms via the MicroScan WalkAway System (Siemens). Cultures were excluded if they were positive for greater than three organisms due to this being suggestive of contamination. Also, Pseudomonas, Enterococcus and Acinetobacter isolates were excluded due to inherent resistance to the agents studied. Streptococcus agalactiae isolates were also excluded because they are not routinely tested against cephalosporins, and Staphylococcus isolates were excluded since cephalothin is not recommended as a surrogate for susceptibility testing (CLSI, 2013).

Simultaneously, a manual Etest (bioMérieux) for cefpodoxime was conducted per standard procedures. The MIC was determined by a technician, and a second reading was done by the microbiology supervisor who was blinded to the prior result. The highest MIC was chosen if a discrepancy occurred between the two reviewers. Cefpodoxime susceptibility was then determined based on CLSI breakpoints (CLSI, 2013).

The susceptibility interpretations for cefpodoxime were compared to those of cephalothin and cefuroxime by using the CLSI breakpoints for the three agents (CLSI, 2013). The categorical agreement rate was calculated, defined as the percentage of identical susceptibility interpretations between cefpodoxime and each of the other agents. The categorical agreement for Escherichia coli individually and all other organisms combined were also determined. The rates for cephalothin were then compared to the corresponding rates for cefuroxime. Major, very major, and minor error rates were also calculated.
The rates were compared via the $\chi^2$ test. A sample size calculation determined that 300 isolates were needed to assess whether the rates differed by more than 5% with an $\alpha$-error of 0.05 and a power of 80%.

RESULTS

A total of 301 isolates were evaluated; *E. coli* (66%) and *Klebsiella pneumoniae* (20%) were the most common organisms. Cefpodoxime (94%) had the highest overall susceptibility rate, followed by cefuroxime (83%) and cefalothin (59%). For comparison, the susceptibility rate of levofloxacin was 90%, and those of trimethoprim/sulfamethoxazole and nitrofurantoin were 85% and 79%, respectively. There was minimal disagreement between the two reviewers in reading the Etests as 97% were within one two-fold dilution. No discrepancies yielded different interpretations.

The cefpodoxime categorical agreement rate was 83% for cefuroxime, which was significantly greater than the rate of 63% for cefalothin ($P<0.01$). Among *E. coli* isolates, the rate was also significantly higher for cefuroxime (83%) compared to 56% for cefalothin ($P<0.01$). However, there was no significant difference in the rates for all other organisms combined [83% versus 77%, respectively, ($P=0.38$)].

The patterns of discordance are presented in Figs 1 and 2. Of 111 discordant isolates, 96% were intermediate or resistant to cefalothin, but tested susceptible to cefpodoxime. Five isolates susceptible to cefuroxime were either resistant (two) or intermediate (three) to cefpodoxime. Conversely, 37 isolates susceptible to cefpodoxime were either resistant (eight) or intermediate (29) to cefuroxime.

Error rates are listed in Table 1. Cefalothin had the highest rate of major and minor errors, but the lowest very major error rate. The major error rate for cefuroxime was at the $\leq 3\%$ threshold recommended by the US Food and Drug Administration. Both drugs exceeded the threshold for the very major error rate (≤1.5%); however, this calculation was based on only 14 cefpodoxime-resistant isolates. For *E. coli*, the major and minor error rates were significantly better for cefuroxime than cefalothin, and the very major error rates were the same.

DISCUSSION

Our results suggest that using cefalothin as a surrogate marker for cefpodoxime would lead to the presumption of an inaccurately high rate of non-susceptibility. It was especially poor at predicting susceptibility for *E. coli*. Continuing to use this extrapolation would limit the use of cefpodoxime as a treatment option for urinary tract infections.

Cefuroxime was significantly better as a surrogate marker for cefpodoxime susceptibility than cefalothin. The major error rate was in the acceptable range and was five-fold lower than that of cefalothin.
lower than the rate for cephalothin. However, it had a higher very major error rate than cephalothin, which also exceeded the recommended threshold. The low rate of cefpodoxime resistance in our study makes it difficult to adequately compare the very major error rates as the calculation included only 14 isolates. Among *E. coli* isolates, cefuroxime had an identical very major error rate, and a 15-fold lower major error rate than cephalothin.

To our knowledge, this is the first study to directly compare cefpodoxime to cephalothin and cefuroxime. An abstract presented at the Society for Healthcare Epidemiology of America meeting in April 2011 reported that 23 of 26 isolates susceptible to ceftriaxone were also susceptible to cefpodoxime and cefuroxime. All isolates tested were *E. coli* (Mehta *et al.*, 2011). Clinical use of cefpodoxime as a fluoroquinolone-sparing agent for acute cystitis would require the ability to more accurately determine susceptibility from automated testing via the MicroScan system. The use of Etests is time consuming, and the cefpodoxime Etests are not readily available for clinical use.

To date, there are only two trials of significant size evaluating the efficacy of cefpodoxime. A 3-day regimen

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**Table 1.** Major, very major and minor error rates for cephalothin and cefuroxime

<table>
<thead>
<tr>
<th></th>
<th>Major error rate(%)</th>
<th>Very major error rate(%)</th>
<th>Minor error rate(%)</th>
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<tbody>
<tr>
<td><strong>Overall (n=300)</strong></td>
<td></td>
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<tr>
<td>Cephalothin</td>
<td>15.7</td>
<td>7.1</td>
<td>21.4</td>
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<tr>
<td>Cefuroxime</td>
<td>2.9</td>
<td>14.2</td>
<td>13.3</td>
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<td><strong>E. coli (n=200)</strong></td>
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<tr>
<td>Cephalothin</td>
<td>14.8</td>
<td>9.1</td>
<td>29.6</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1.1</td>
<td>9.1</td>
<td>15.5</td>
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<tr>
<td><strong>Non-E. coli (n=100)</strong></td>
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<tr>
<td>Cephalothin</td>
<td>17.4</td>
<td>0.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>6.6</td>
<td>33.3</td>
<td>9.0</td>
</tr>
</tbody>
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**Fig. 2.** Scattergram analysis for cefuroxime compared to cefpodoxime. Breakpoints are indicated by vertical and horizontal lines. Numbers represent the number of strains denoted by each point.
produced equivalent clinical cure and bacteriological eradication to trimethoprim/sulfamethoxazole (Kavatha et al., 2003). However, a recent 3-day study showed that cefpodoxime produced a lower clinical cure rate (82 %) than ciprofloxacin (93 %) in 300 women with acute cystitis (Hooton et al., 2012). It is uncertain whether cefpodoxime would fare better if given for a longer treatment course since β-lactam agents have typically produced better results with longer durations of therapy (Milo et al., 2005).

A limitation of our study is that it was conducted at a single centre. The patient population may have included a higher rate of younger patients than many community hospitals given that approximately 45 % were ≤ 40 years old. Also, the level of fluoroquinolone resistance in the isolates tested was fairly low. A post hoc analysis of fluoroquinolone-resistant isolates showed a categorical agreement of 43 % for cephalothin and 71 % for cefuroxime.

In summary, our results suggest that cefuroxime is a better surrogate marker than cephalothin for cefpodoxime among urinary isolates on automated testing using the MicroScan system. A further study in hospitals with higher rates of cefpodoxime and fluoroquinolone resistance would be valuable. Notably, it has been reported that the CLSI has proposed that cefazolin should replace cephalothin as the surrogate marker for cephalosporins at the Antimicrobial Susceptibility Testing subcommittee meeting in June 2013. However, it was also noted that some isolates may be susceptible to cefpodoxime but resistant to cefazolin. It is unknown whether this will become an official recommendation, or whether cefazolin would be superior to cefuroxime as a surrogate marker for cefpodoxime.

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REFERENCES


