Evaluation of cefazolin as a surrogate marker for cefpodoxime susceptibility for urinary tract isolates

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Of the cephalosporins, cefpodoxime has the most published clinical data for the treatment of urinary tract infections. In 2014, the Clinical and Laboratory Standards Institute (CLSI) guidelines recommended that cefazolin should be used as the surrogate marker for cefpodoxime among urinary tract isolates, replacing cephaplothin. This study attempted to determine how well cefazolin serves as the surrogate marker. Additionally, it investigated how cefuroxime compared with cefpodoxime as a surrogate marker. The MicroScan Walkaway Plus system was used to determine susceptibility for cefazolin and cefuroxime on consecutive urine cultures with a colony count of ≥50 000 organisms. Only Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis isolates were included, following CLSI guidelines. Simultaneously, an Etest for cefpodoxime was conducted. The cefpodoxime interpretation was compared with that of the other two agents, and the categorical agreement was calculated, defined as the percentage of identical susceptibility interpretations. Cefazolin (92 %) had a significantly higher categorical agreement than cefuroxime (85 %) among 284 isolates (P=0.011). The major error rate was 4.4 % for cefazolin and 1.1 % for cefuroxime. The very major error rate was 64 % for cefazolin and 18 % for cefuroxime among the 11 cefpodoxime-resistant isolates. Cefazolin was a better predictor of cefpodoxime susceptibility than the previously recommended agent, cephaplothin. However, cefuroxime had better major and very major error rates than cefazolin.

INTRODUCTION

Cephalosporins are considered to be alternative agents to fluoroquinolones or trimethoprim/sulfamethoxazole for the treatment of urinary tract infections (Gupta et al., 2011). Fluoroquinolone resistance among urinary tract isolates is increasing (Johnson et al., 2008; Olson et al., 2009), and decreasing their use may slow this trend (Gottesman et al., 2009). Resistance to trimethoprim/sulfamethoxazole is also common (Brown et al., 2002). Cefpodoxime has the most published clinical trial data for the treatment of urinary tract infections among the oral cephalosporins (Hooton et al., 2012; Kavatha et al., 2003). However, cefpodoxime is not available on a susceptibility panel for MicroScan automated testing systems used in many hospitals. The Clinical and Laboratory Standards Institute (CLSI) recently changed their recommendation to state that cefpodoxime susceptibility among urinary isolates can be inferred from the result for cefazolin, replacing cephaplothin as the surrogate marker (CLSI, 2015). However, they do include a caveat that isolates may test resistant to cefazolin but are actually sensitive to cefpodoxime. The purpose of this study was to determine how well cefazolin served as a surrogate marker for cefpodoxime, and how it compared with cefuroxime, which has been shown to be superior to the previously recommended surrogate marker, cephaplothin (Bookstaver et al., 2014; CLSI, 2013).

METHODS

The study was conducted at a US army hospital in Augusta, GA, USA. Automated bacterial identification and susceptibility testing for cefazolin, cefuroxime, levofloxacin, trimethoprim/sulfamethoxazole and nitrofurantoin was conducted on consecutive positive urine cultures obtained in the course of regular medical care with a colony count of at least 50 000 organisms via the MicroScan™ Walkaway Plus System (Siemens). Cultures were excluded if they were positive for more than three organisms, as this was suggestive of contamination. Isolates from a previous study comparing cephaplothin with cefuroxime were utilized (Bookstaver et al., 2014); however, only Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis isolates were included, following the CLSI guidelines (CLSI, 2015). Simultaneously, a manual Etest (bioMérieux) for cefpodoxime was conducted following 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, 2015).
The susceptibility interpretations for cefpodoxime were compared with those of cefazolin and cefuroxime by using the CLSI breakpoints for the three agents (CLSI, 2015). 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 *E. coli* individually and the other two organisms combined were also determined. The rates for cefazolin were then compared with the corresponding rates for cefuroxime. Major, very major and minor error rates were also calculated as defined by the US Department of Health and Human Services Food and Drug Administration (US FDA, 2007).

All rates were compared using a $\chi^2$ test. A sample size calculation prior to the initial study (Bookstaver *et al.*, 2014) determined that 300

![Fig. 1. Scattergram analysis for cefazolin compared with cefpodoxime. Breakpoints are indicated by vertical and horizontal lines. Numbers represent the number of strains denoted by each point.](http://jmm.microbiologyresearch.org)

![Fig. 2. Scattergram analysis for cefuroxime compared with cefpodoxime. Breakpoints are indicated by vertical and horizontal lines. Numbers represent the number of strains denoted by each point.](http://jmm.microbiologyresearch.org)
Table 1. Error rates determined in this study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major</th>
<th>Very major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>4.4 %</td>
<td>63.6 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1.1 %</td>
<td>18.2 %</td>
<td>13.4 %</td>
</tr>
<tr>
<td>P value</td>
<td>0.033</td>
<td>0.08</td>
<td>&lt;0.001</td>
</tr>
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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 284 isolates were evaluated. \( E. \) coli comprised 71 % of the isolates, while \( K. \) pneumoniae and \( P. \) mirabilis accounted for 22 and 7 %, respectively. Cefpodoxime (95 %) had the highest overall susceptibility rate, followed by cefazolin (94 %) and cefuroxime (86 %). For comparison, the susceptibility rate of levofloxacin was 90 %, and those of trimethoprim/sulfamethoxazole and nitrofurantoin were 85 and 82 %, respectively. There was minimal disagreement between the two reviewers in reading the Etests, as 97 % were within one twofold dilution. No discrepancies yielded different interpretations.

The categorical agreement rate was 92 % for cefazolin, which was significantly greater than the rate of 85 % for cefuroxime (\( P=0.011 \)). Among \( E. \) coli isolates, the rate was also significantly higher for cefazolin at 92 % compared with 84 % for cefuroxime (\( P=0.014 \)). However, there was no significant difference in the rates for the other two organisms combined, 93 versus 88 %, respectively (\( P=0.43 \)).

The patterns of discordance are presented in Figs. 1 and 2. Of 22 discordant isolates, 12 were resistant to cefazolin but tested susceptible to cefpodoxime. Conversely, seven isolates were resistant to cefpodoxime, but were susceptible to cefazolin. Four isolates susceptible to cefuroxime were either resistant (\( n=2 \)) or intermediate (\( n=2 \)) to cefpodoxime. However, 31 isolates susceptible to cefpodoxime were either resistant (\( n=3 \)) or intermediate (\( n=28 \)) to cefuroxime.

The error rates are listed in the Table 1. Cefazolin had the highest rate of major and very major errors but the lowest minor error rate. The major error rate for cefuroxime was below the \( \leq 3 \% \) threshold recommended by the FDA. Both drugs exceeded the threshold for the very major error rate (\( \leq 1.5 \% \)); however, this calculation was based on only 11 cefpodoxime-resistant isolates (US FDA, 2007). For \( E. \) coli, the error rate patterns were similar to that of the entire population (data not shown).

DISCUSSION

Our results showed that using cefazolin as a surrogate marker for cefpodoxime resulted in a high categorical agreement rate. It performed much better than the previously recommended surrogate, cephalothin, which produced a categorical agreement rate of 63 % and a major error rate of 16 % in a prior study (Bookstaver et al., 2014; CLSI, 2013). However, major error and very major error rates for cefazolin were above the thresholds set by the FDA. Extrapolating cefpodoxime susceptibility from cefazolin may lead to the presumption of an inaccurately high rate of non-susceptibility. Additionally, a high rate of incorrectly predicting susceptibility to cefpodoxime may also occur.

Cefuroxime had a lower categorical agreement rate than cefazolin but overall may be a better surrogate marker for cefpodoxime susceptibility. The major error rate was in the acceptable range, and was fourfold lower than the rate for cefazolin. It also had a much lower very major error rate, which approached statistical significance. However, 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 11 isolates.

To the best of our knowledge, this is the first study to assess cefazolin as a surrogate marker for cefpodoxime susceptibility. Clinical use of cefpodoxime as a fluoroquinolone-sparing agent for acute cystitis would require the ability to determine susceptibility more accurately from automated testing via the MicroScan system. Etest antimicrobial susceptibility testing is time consuming, and the cefpodoxime Etest is only available from the manufacturer for research purposes.

A limitation of our study was 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 \( \leq 40 \) years old. Also, the level of fluoroquinolone and cefpodoxime resistance in the isolates tested was fairly low. Additionally, the power of the study was diminished because 300 isolates of the relevant organisms were not present in the data from the original study.

In summary, our results showed that cefazolin is a better surrogate marker for cefpodoxime than the previously recommended agent, cephalothin, among urinary isolates on automated testing using the MicroScan system. However, cefuroxime had better major and very major error rates. Further study in hospitals with higher rates of cefpodoxime and fluoroquinolone resistance would be valuable.

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REFERENCES


