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Short Communication

Looking Beyond: Expanding the Utility of Cefazolin as a Surrogate Marker

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ABSTRACT

For uncomplicated urinary tract infections caused by *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*, CLSI recommends the use of cefazolin as a surrogate marker for the oral third-generation cephalosporins cefpodoxime and cefdinir. However, they do not comment on cefixime, which has emerged as an alternate treatment option, especially in the pediatric population. Our aim is to determine whether the susceptibility results of cefazolin can predict susceptibility results to cefixime. We included 39 urinary isolates of *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis* isolated from patients with uncomplicated urinary tract infections. On comparing cefazolin and cefixime susceptibilities, it was observed that there was a categorical agreement in 36/39 isolates (92.3%), with Major Errors (ME) seen in 3 isolates. There were no Very Major Errors (VME) or Minor Errors (mE). In all three occasions of discrepancies, the isolate was susceptible to cefixime but resistant to cefazolin. Thus, similar to the other third-generation oral cephalosporins, a susceptible cefazolin result indicates susceptibility to cefixime, but if the isolate is resistant to cefazolin, cefixime needs to be tested individually.

KEYWORDS: Cefazolin; Surrogate marker; Cefixime; Uncomplicated; Urinary tract; Infections

INTRODUCTION

For uncomplicated urinary tract infections (uUTIs) caused by *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*, the increasing resistance patterns observed to oral antibiotics i.e. trimethoprim-sulfamethoxazole and fluoroquinolones has prompted oral third-generation cephalosporins (3GCs), namely cefpodoxime, cefdinir and cefixime, as viable alternative treatment options.[1] Thus, timely reporting of oral 3GC susceptibility may avoid usage of other broad-spectrum antibiotics or intravenous therapy. However, many oral cephalosporin agents are unavailable for testing in automated susceptibility systems, and breakpoints for some oral cephalosporins still need to be elucidated. Surrogate testing allows clinicians to use the preferred oral cephalosporin without requiring the clinical laboratory to perform additional susceptibility testing separately.[2]

For *E.coli, K. pneumoniae*, and *P. mirabilis* isolates from uUTIs, CLSI (Clinical and Laboratory Standards Institute) recommends using cefazolin as a surrogate marker to predict susceptibility to seven oral cephalosporins, including the 3GCs cefpodoxime and cefdinir; however, it does not provide guidance for cefixime.[3] Our aim was to determine whether cefazolin's susceptibility results can predict susceptibility to cefixime amongst urinary isolates of *E. coli, K. pneumoniae*, and *P. mirabilis* isolated from cases of uUTIs.

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METHODOLOGY

Urine cultures from patients suspected of uUTIs submitted to the Bacteriology Laboratory, Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India, were collected between August 2023 and November 2023. Specifically, the isolates of *E. coli, K. pneumoniae*, and *P. mirabilis* with pure growth of ≥ 1,00,000 CFU/mL from these urine cultures were included in the study. Routine antimicrobial susceptibility testing (AST) was performed by Kirby-Bauer disc diffusion technique for discs of gentamicin (10 µg), cefixime (5 µg), cefepime (30 µg), ceftazidime (30 µg), cefuroxime (30 µg), ciprofloxacin (5 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), fosfomycin (200 µg), nitrofurantoin (300 µg), norfloxacin (10 µg), and cefazolin (30 µg). Categorical agreement and error rates were calculated using cefazolin as the surrogate drug for cefixime. Discrepancies in categorical agreement are defined as minor errors (mE), major errors (ME), and very major errors (VME). A minor error was an intermediate test result reported as susceptible or resistant and vice versa. Very major errors are resistant isolates reported as susceptible, and major errors are susceptible isolates reported as resistant.[4]

RESULTS

Table 1: Agreement and error rate analysis comparing cefixime and cefazolin breakpoints

Organisms (n=number of isolates)	Cefixime			Cefazolin			Categorical agreement	Very major error	Major error	Minor error
	S	I	R	S	I	R				
E. coli (n=31)	12/31	0/31	19/31	9/31	0/31	22/31	28/31	0/19	3/12	0/31
K. pneumoniae (n=6)	3/6	0/6	3/6	3/6	0/6	3/6	6/6	0/3	0/3	0/6
P. mirabilis (n=2)	1/2	0/2	1/2	1/2	0/2	1/2	2/2	0/1	0/1	0/2
TOTAL	16/39	0/39	23/39	13/39	0/39	26/39	36/39 (92.3%)	0/23(0%)	3/16(18.8 %)	0/39(0%)

We included 31 *E. coli*, six *K. pneumoniae*, and two *P. mirabilis* urine isolates from patients aged three months to 74 years (median age = 42.5 years). Amongst 39 total isolates, 26 (66.7%) tested resistant to cefazolin. On comparing cefazolin and cefixime, it was observed that there was a categorical agreement in 36/39 isolates (92.3%) with ME seen in 3 isolates (18.8%). (Table 1) There were no VME or mE. In all three occasions of discrepancies, the isolate was susceptible to cefixime but resistant to cefazolin. Thus, using cefazolin as a surrogate marker yielded a 100% positive predictive value of susceptibility to cefixime.

DISCUSSION

Cefazolin, a parenteral first-generation cephalosporin, has been extensively used as an alternative to penicillin for treating susceptible staphylococcal and streptococcal infections, most commonly skin soft tissue infections. In addition, cefazolin may be used to treat complicated urinary tract infections and systemic infections due to susceptible isolates of *Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis*.[5]

In clinical microbiology laboratories since 2014, cefazolin has found its utility as a surrogate marker when CLSI recommended its use to predict the susceptibility of seven oral antimicrobial agents in cases of uUTI caused by *E. coli*, *K. pneumoniae*, and *P. mirabilis.* These seven agents include cephalexin (a first-generation cephalosporin); cefaclor, cefprozil, cefuroxime axetil, loracarbef (second-generation cephalosporins); cefdinir and cefpodoxime (third-generation cephalosporins).[3,6] The breakpoints of cefazolin for various indications are included in Table 2. The peak urine concentrations attained after standard dosing of the above-mentioned seven oral cephalosporins are much higher than the cefazolin susceptible breakpoint MIC, i.e., ≤16 µg /ml, therefore supporting the use of cefazolin as the surrogate marker. CLSI has pointed out that some isolates may be susceptible to the more potent oral agents (cefuroxime, cefpodoxime, and cefdinir) while testing resistant to

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cefazolin. Thus, if the cefazolin test result is resistant and the clinician wishes to use the three drugs mentioned above, the applicable drug should be tested individually. [3,6]

Table 2: Cefazolin breakpoints as per CLSI M100 2023

	Zone diameter breakpoints and Interpretive categories (mm)			MIC breakpoints and Interpretive categories (µg/ml)		
	S	I	R	S	I	R
When cefazolin is used as a surrogate test to predict results for the seven oral agents in uUTIs due to E. coli, K. pneumoniae, and P. mirabilis	≥15	-	≤14	≤16	-	≥32
When cefazolin is used for therapy of uUTIs due to E. coli, K. pneumoniae, and P. mirabilis Dosage: 1g every 12 h	≥15	-	≤14	≤16	-	≥32
When cefazolin is used for therapy of infections other than uUTIs due to E. coli, K. pneumoniae, and P. mirabilis Dosage: 2g every eight hour	≥23	20-22	≤19	≤2	4	≥8
When cefazolin is used for Staphylococcal infections	Oxacillin or cefoxitin is the surrogate marker of cefazolin					
When cefazolin is used for Streptococcal infections	Penicillin is the surrogate marker of cefazolin					

Like the other oral 3GCs, such as cefpodoxime and cefdinir, cefixime has increased potency for *E. coli, K. pneumoniae, Enterobacter, Citrobacter,* and *Serratia* spp.[5] About 20% of cefixime is excreted by the kidneys as the active drug, thus making it an effective drug for treating UTIs.[7] Cefixime is a well-studied, guideline-concordant treatment option for pediatric UTIs,[8] and is among the alternative treatment choices for UTIs in adult guidelines.[9]

While CLSI recommends cefpodoxime and cefdinir susceptibility prediction using cefazolin as a surrogate marker, it has not commented on cefixime. Earlier studies have examined whether the susceptibility results of one oral 3GC (cefpodoxime, cefdinir, cefixime) can predict susceptibility results to other oral 3GCs.[2] They found >95% categorical agreement for oral 3GCs among the 194 urine isolates. Surrogate testing of cefpodoxime for cefdinir, and vice versa, resulted in no ME or VME, while combinations involving cefixime produced rare ME and VME. Hence, considering the lacunae in assigning a surrogate marker for cefixime, we aimed to determine whether cefazolin could predict susceptibility to cefixime among Indian isolates of the common uropathogens.

While comparing cefixime and cefazolin susceptibilities, it was observed that similar to the other oral 3GCs, susceptibility to cefazolin meant susceptibility to cefixime. However, an isolate resistant to cefazolin cannot be predicted to be resistant to cefixime. Individual susceptibility should be performed to confirm cefixime resistance.

A significant limitation of our study is that it was conducted on a limited number of isolates; testing multiple isolates would aid in supporting or refuting our argument. The lower number of isolates is the reason for the high major error rate despite the low number of overall errors. Moreover, further tests are required to elucidate the peak concentrations of cefixime in urine on oral administration. This would directly affect the use of cefazolin as a surrogate marker for cefixime. Nevertheless, this study throws light on the possible utility of cefazolin as a surrogate marker for cefixime, thus warranting further research on this matter.

CONCLUSIONS

The current recommendations by CLSI for cefazolin as a surrogate marker for oral third-generation cephalosporins do not comment on cefixime. This study shows promising results in arriving at cefixime susceptibility results based on cefazolin reports. Similar to the other third-generation oral cephalosporins, a susceptible cefazolin result indicates susceptibility to cefixime, but if the isolate is resistant to cefazolin, cefixime needs to be tested individually.

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CONFLICT OF INTERESTS STATEMENT

The authors declare no personal, financial, or institutional conflicts of interest in relation to the authorship and/or publication of this manuscript.

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ETHICS STATEMENT INCLUDING PATIENT CONSENT

Not applicable

AUTHORS' CONTRIBUTIONS

KPA: Conceptualization; Data curation; Analysis; Writing the draft

SM: Conceptualization; Supervision; Validation; Review and editing.

PK: Data curation

MN: Conceptualization; Analysis; Writing the draft; Review and editing.

BKD: Supervision; Validation

AI DECLARATION

No AI tool was used to generate research data, perform data analysis, interpret findings, formulate scientific conclusions, or make editorial decisions. All AI-assisted content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the accuracy, originality, integrity, and final content of the manuscript.

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