Urinary Breakpoints for Cefazolin	Rationale for the CLSI Clinical Breakpoints	Date: June 11, 2014

1. Background/Introduction

The purpose of this assessment was to identify an antimicrobial agent which could be tested as a surrogate for accurate prediction of the activity of oral cephalosporins for the treatment of uncomplicated urinary tract infections (uUTIs) due to *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. Testing of cephalothin has been suggested to predict results to certain oral cephalosporins; however, recent susceptibility data indicate that testing of cefazolin, though not an oral agent, is a more accurate predictor than cephalothin of activity of certain oral cephalosporins for treatment of uUTIs.

2. Standard Adult Dosages

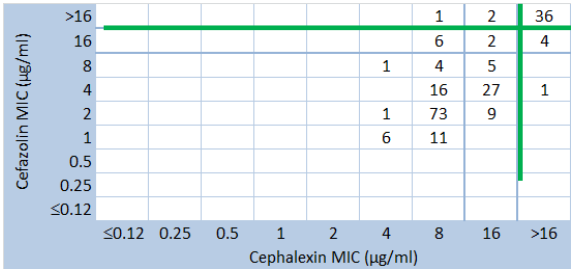
Cefazolin: 1-2 g q 8 hrs (1 g q 12 hours for uncomplicated UTI) (administered IM or IV)

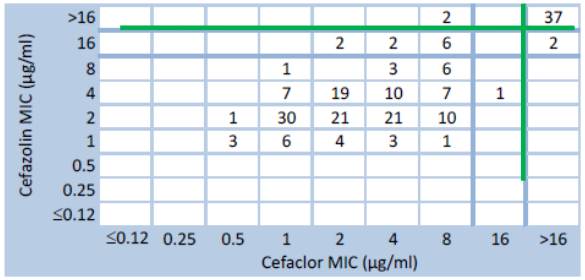
Oral agents for which cefazolin testing is proposed as a surrogate test:
Cefaclor: 0.25 – 0.5 g q 8 hrs
Cefdinir: 100 mg q 12 hrs
Cefpodoxime: 0.1 – 0.2 g q 12 hrs
Cefprozil: 250-500 mg q 12 hrs
Cefuroxime axetil: 0.125 – 0.5 g q 12 hrs
Cephalexin: 0.25 – 1 g q 6 hrs
Loracarbef: 200 to 400 mg q 12 to q 24 hrs (200 mg q 24 hrs for uncomplicated UTI)

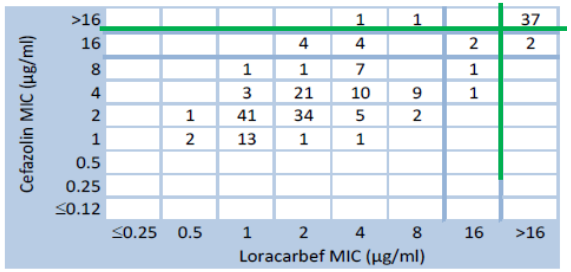
3. MIC Distribution Data

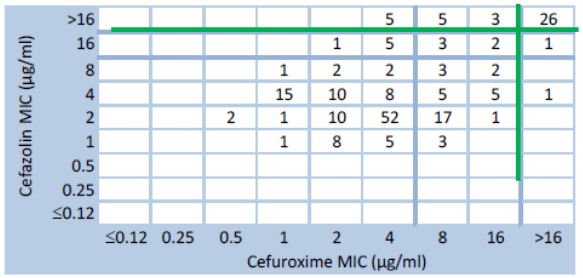
Cross susceptibility MIC data for cefazolin against 9 oral cephalosporins were generated by Dr. Ron Jones on a defined collection of 186 isolates of Enterobacteriaceae: 93 *E. coli* (40% with acquired β-lactamases), 62 *K. pneumoniae*, 31 *P. mirabilis* (10% with acquired β-lactamases). The MIC distribution data and cross susceptibility tables demonstrate that the cefazolin MIC of ≤ 16 µg/mL correlates with the PO cephalosporin MICs at ≤ 16 µg/mL. Thus, based on available data discussed in Section 4 of this document, the concentrations of oral cephalosporins in urine and the percent recovery of antimicrobial agents in urine suggest high urinary recovery, well above the 16 µg/mL cutoff. Setting a susceptible cefazolin MIC of ≤16 µg/mL shows high predictive value for the oral agents tested. Cross-susceptibility and cross-

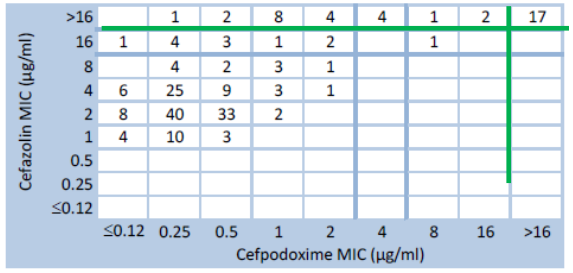
resistance tables are included below, as are agreement calculations.

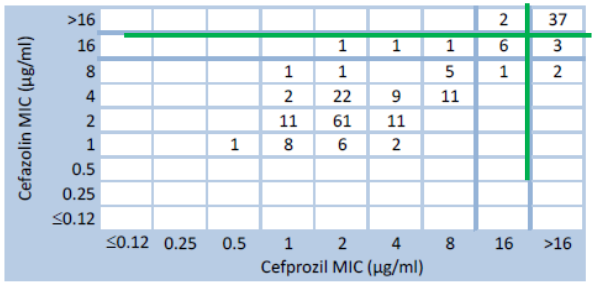


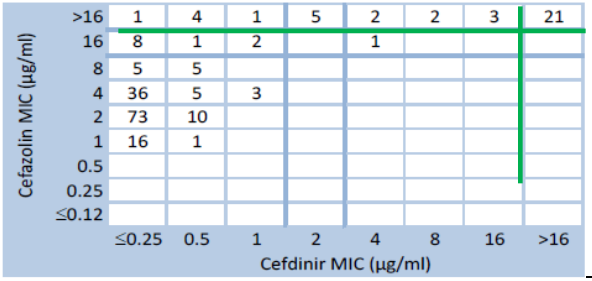












The thick green lines in the tables above highlight the 16 µg/mL breakpoints. The thick blue lines in the tables highlight the current CLSI (or EUCAST – cephalexin) S/I/R breakpoints for each antimicrobial agent (excluding cefazolin) for infections other than uUTIs. Since the working group considered a breakpoint of 8 µg/mL for cefazolin for surrogate testing, cefazolin is also marked with a thick blue line at 8 µg/mL.

Accuracy of Cefazolin as a Surrogate Marker at a Breakpoint of 16 µg/mL

- For predicting:
  - Cephalexin (97.0%)[a], 1.5%[b]
  - Cefadroxil (91.6%), 1.0%
  - Cefaclor (98.8%), 1.2%
  - Loracarbef (98.8%), 1.2%
  - Cefuroxime axetil (98.8%), 6.3%
  - Cefpodoxime (100.0%), 10.7%
  - Cefadrine (80.1%), 2.0%
  - Cefprozil (97.0%), 1.2%
  - Cefdinir (100.0%), 8.8%

a. For all drugs, percent categorical agreement
b. For all drugs, percentage that cefazolin calls resistant or intermediate when other drug calls susceptible

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4. Pharmacokinetic Data

PK data from several oral cephalosporins have been collated from the published literature (references are listed below) and from a review of the USA-FDA product package inserts (see table below). Pharmacokinetic data of the listed oral cephalosporins indicate that the drugs reach high concentrations in the urine.

Review of USA-FDA Product Package Insert and Comprehensive Review Articles:

Oral cephalosporin	*UTI indication*	*Indicated enteric species*	*S Breakpoint*	*Typical Dosage*	*Product PI Pharmacology*	*Other PK Data from review articles in Drugs*
Cephalexin	*Yes*	*E. coli* *K. pneumoniae* *P. mirabilis*	*≤8 µg/ml for cephalothin*	*0.25 – 1 g q 6 hrs*	*Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period, peak urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 1000, 2200, and 5000 µg/ml, respectively.*	*On average, 70-100% of administered doses are recovered unchanged in urine within 6-8h. Urinary peak concentrations as noted in PI. Mean urinary concentrations of 150 mg/L were noted in the second 4h period (i.e. 4-8h) after a 500 mg dose. Urinary concentrations are lower and less overall drug is recovered in patients with renal failure, but prolonged low levels of drug were observed (Cmin =32mg/L between 4-18h after single 500mg dose).*
Cefradine	*Yes*	*E. coli* *Klebsiella spp.*	*≤8 µg/ml for cephalothin*	*500 q12 hrs for UTI. range: 500 to 1000 q6 or q12 hrs*	*Over 90% of the drug is excreted unchanged in the urine within 6 hours. Peak urine concentrations are approximately 1600 µg/ml following a 250 mg dose and 3200 µg/ml following a 500 mg dose.*	

Cefadroxil	*Yes*	*E. coli* *Klebsiella spp.* *P. mirabilis*	*≤8 µg/ml for cephalothin*	*0.5 – 1 g q 12 hrs*	*Over 90% of the drug is excreted unchanged in the urine within 24 hours. Peak urine concentrations are approximately 1800 µg/ml during the period following a single 500 mg oral dose. Increases in dosage generally produce a proportionate increase in cefadroxil urinary concentration. The urine antibiotic concentration, following a 1 g dose, was maintained well above the MIC of susceptible urinary pathogens for 20 to 22 hours.*	*88 to 93% of dose recovered in urine by 24 hours. Concentrations after 500mg dose of 1200-1800 mg/L @3h, 1100 mg/L @ 3-6h, and 167 mg/L @ 6-12h.*
Cefpodoxime	*Yes*	*E. coli* *K. pneumoniae* *P. mirabilis*	*≤2 µg/ml for cefpodoxime*	*0.1 – 0.2 g q 12 hrs*	*Over the recommended dosing range (100 to 400 mg), approximately 29 to 33% of the administered cefpodoxime dose was excreted unchanged in the urine in 12 hours.*	*Only IV urine recovery data are presented (80% recovered). No concentration-time data presented.*
Cefaclor	*Yes*	*E. coli* *Klebsiella spp.* *P. mirabilis*	*≤8 µg/ml for cefaclor*	*0.25 – 0.5 g q 8 hrs*	*Approximately 60 to 85% of the drug is excreted unchanged in the urine within 8 hours, the greater portion being excreted within the first 2 hours. During this 8-hour period, peak urine concentrations following the 250 mg, 500 mg and 1 g doses were approximately 600, 900 and 1,900 µg/ml, respectively.*	
Loracarbef	*Yes*	*E. coli*	*≤8 µg/ml for loracarbef*	*200 to 400mg q12 to q24 hrs (200 q24 for uncom. UTI)*		*60% recovery in urine from 7.5 to 15 mg/kg doses in pediatric patients (no time interval noted). 87 to 97% recovered in adults after 24 hours when given 200mg as single or multiple doses. Concentrations of 12-13 mg/L 6-12 hours after administration.*

Cefuroxime axetil	*Yes*	*E. coli* *K. pneumoniae*	*≤4 µg/ml for cefuroxime*	*0.125 – 0.5 g q 12 hrs for cefuroxime*	*Cefuroxime is excreted unchanged in the urine; in adults, approximately 50% of the administered dose is recovered in the urine within 12 hours.*	*Urinary recovery of approximately 50% after single doses and near 100% after multiple doses. One study recovered 52% in 12 hours after a 125 mg single dose. Most were evaluating 24 hours recovery.*
Cefprozil	*No*	-	*≤8 µg/ml for cefprozil*	*0.25 – 0.5 g q 12 hrs*	*Urinary recovery accounted for approximately 60% of the administered dose. During the first 4-hour period after drug administration, the average urine concentrations following 250 mg, 500 mg, and 1 g doses were approximately 700 µg/ml, 1000 µg/ml and 2900 µg/ml, respectively.*	*57 to 70% of dose recovered in urine over 24h following doses of 250 to 1000 mg. Peak concentrations (0 to 4h post-dose) ranged from 175 to 658 mg/L over the same dose range.*
Cefdinir	*No*	-	*≤1 µg/ml for cefdinir*	*300 mg q 12 hrs or 600 mg 2 24*	*Mean percent of dose recovered unchanged in the urine following 300- and 600-mg doses is 18.4% (±6.4) and 11.6% (±4.6), respectively.*	*Same data as in PI. Noted small % recovered in children (2.7 to 12.7%).*
Cefazolin	*Yes*	*E. coli* *Klebsiella spp.* *P. mirabilis*	*≤2 µg/ml for cefazolin*	*1 g q 12 hrs*	*In the first 6 hours, approximately 60% of the drug administered in the IM form is excreted in the urine and this increases to 70% to 80% within 24 hours. Peak urine concentrations of approximately 2,400 µg/mL and 4,000 µg/mL are seen following 500 mg and 1 gram intramuscular doses, respectively. Nearly all of a given dose can be recovered from the urine in 24 hrs.*	

5. Pharmacodynamic Data
There are no relevant PD data available.

6. Monte Carlo Simulations, PK/PD Breakpoints

There are no Monte Carlos simulation data or urinary tract models available.

7. Clinical Efficacy

Clinical trials of uUTIs against the oral cephalosporins are summarized below and listed in the reference section. Infectious Diseases Society of America (IDSA) clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women are also listed in the reference section (Gupta K et al., 2011).

Study	**Treatment Regimen, n (percentage)**	
Kavatha et al. (2003)	Cefpodoxime proxetil, 100 mg q 12 hrs for 3 days	
Early clinical cure	62/63 (98.4)	
Early bacterial cure	62/63 (98.4)	
Late clinical cure	42/50 (84)	
Adverse events, %	1.6	
Leigh et al. (2000)	Cefaclor, 250 mg q 8 hrs for 5 days	Cefdinir, 100 mg q 12 hrs for 5 days
Microbiologic cure rate by patient	149/187 (79.7)	166/196 (84.7)
Microbiologic cure rate by pathogen	161/200 (80.5)	183/213 (85.9)
Clinical cure by patient	174/187 (93.0)	179/196 (91.3)
Adverse events, %	17.0	23.0
Hooton et al. (2012)	Cefpodoxime proxetil, 100 mg q 12 hrs for 3 days	
Clinical cure rate intent-to-treat approach with patients lost to follow-up considered as clinical cure	123/150 (82)	
Clinical cure rate intent-to-treat approach with patients lost to follow-up considered as non-responders	106/150 (71)	
Microbiologic cure rate by patient	104/129 (81)	
Adverse events, %	23	

8. Breakpoints and Other Comments

1. A susceptible result for cefazolin at a breakpoint of ≤16 µg/mL was predictive of a susceptible result for the oral agents cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime axetil, cephalexin and loracarbef when testing *E. coli*, *K. pneumoniae* and *P. mirabilis*. Cefazolin uUTI MIC and disk diffusion breakpoints for these species were approved as follows: MIC, ≤16 µg/mL as susceptible and >16 µg/mL as resistant; disk diffusion ≥15 mm as susceptible and ≤14 mm as resistant. Since these breakpoints are only to be used for urine isolates, an intermediate category is unnecessary since an intermediate result indicates that an isolate from an uUTI that is interpreted as intermediate may be susceptible due to higher concentrations of drug attainable in urine.
2. Cefazolin (surrogate test for uncomplicated UTI) was added to the Oral Cephems section of Enterobacteriaceae Table 2A, with the breakpoints and disk correlates listed above. The following statement was added to the Comments box: "Cefazolin results predict results for the oral agents cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime axetil, cephalexin and loracarbef when used for therapy of uncomplicated UTIs due to *E. coli*, *K. pneumoniae*, and P. *mirabilis*. Cefpodoxime, cefdinir, and cefuroxime axetil may be tested individually because some isolates may be susceptible to these agents while testing resistant to cefazolin. To predict results for oral cephalosporins when used for therapy of uncomplicated UTIs, testing cefazolin is preferred to testing cephalothin." If cefpodoxime, cefdinir, and/or cefuroxime axetil are tested individually, refer to the drug's respective interpretive criteria.
3. The cephalothin comment as listed in M100-S23 was changed based on review of recent data to read "Cephalothin interpretive criteria can be used only to predict ~~results~~ **susceptibility** to the oral agents, cefadroxil, cefpodoxime, cephalexin, and loracarbef" (text in bold was added). In order to emphasize that cefazolin is preferred over cephalothin as a surrogate agent to predict results for oral cephalosporins, the following sentence was also added, "To predict results for oral cephalosporins when used for therapy of uncomplicated UTIs, testing cefazolin is preferred to testing cephalothin."
4. The parenteral breakpoints for cefazolin when cefazolin is used for treating infections other than uUTI due to members of the Enterobacteriaceae have not changed since 2011.
5. In bacteremic (complicated) UTI, the laboratory will have tested both a blood and a urine isolate. In these circumstances, it is recommended that the cefazolin interpretive criteria which should be applied for both isolates should be those for sources other than uUTI, namely susceptible ≤ 2 µg/mL, intermediate 4 µg/mL, and resistant ≥ 8 µg/mL.

9. References

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12) Cefazolin package insert 6/2/2004, available on FDA website at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Searched 1/9/2014.

13) Kucers A, Crowe SW, Grayson ML, Hoy JF. The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal and Antiviral Drugs. 5th edition. Jordan Hill, Oxford: Butterworth-Heinemann; 1997. p 285.