To the Editor—Narrow-spectrum oral cephalosporins are currently not recommended as first-line options for the treatment of uncomplicated urinary tract infection (UTI) [1]. At present, there is a perception that these agents will result in poor outcomes due to increasing Enterobacteriaceae resistance, or, in the case of pyelonephritis, insufficient drug levels in parenchymal tissue. Older minimum inhibitory concentration (MIC) interpretative criteria (susceptibility breakpoints) have not accounted for the high concentrations that these agents can achieve in urine [2]. More recently, a better
understanding of pharmacokinetics/pharmacodynamics has led the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) to develop urinary cephalosporin breakpoints for Enterobacteriaceae that are more clinically relevant [3, 4]. These may help to “resurrect” the narrow-spectrum oral cephalosporins for greater use in the treatment of uncomplicated UTI.

As pointed out by Tamma et al [5], not all microbiology laboratories in the United States are implementing newer CLSI serum cephalosporin breakpoints. As a consequence, physicians may be incorrectly interpreting susceptibility reports. In their pooled antibiogram, 90% of urinary Escherichia coli isolates were sensitive to cefazolin when using a serum breakpoint of ≤8 µg/mL (pre-2011 CLSI) vs only 47% when using a breakpoint of ≤2 µg/mL (post-2011 CLSI). Whereas this analysis of uropathogens helps bring further attention to an important issue, we believe analyses focusing on the latest CLSI and EUCAST urinary (rather than serum) breakpoints would be even more informative. In 2014, CLSI established a urinary cefazolin breakpoint of ≤16 µg/mL as a surrogate to predict the susceptibilities of 7 oral cephalosporins (cephalexin, cefprozil, cefaclor, loracarbef, cefuroxime, cefpodoxime, and cefdinir) for use only in uncomplicated UTI [4]. Applying this urinary breakpoint of ≤16 µg/mL to Enterobacteriaceae isolates has demonstrated susceptibilities >97% [6].

CLSI (unlike EUCAST) still retains cefalothin interpretative criteria for uncomplicated UTI. We previously noted that current CLSI serum cefazolin and urinary cefalothin breakpoints do not reliably predict the susceptibilities of cephalexin and other cephalosporins [7]. According to CLSI, a urinary cefalothin breakpoint of ≤8 µg/mL can be used to predict the susceptibility (not resistance) of cephalexin, cefadroxil, loracarbef, and cefpodoxime [4]. This implies that cefalothin, as a surrogate predictor, tends to overcall resistance, potentially leading physicians to prescribe broad-spectrum antimicrobials. To avoid confusion, EUCAST has largely abandoned surrogate testing and has instead established unique urinary breakpoints for 7 oral cephalosporins [3].

Tamma et al also showed that the addition of clavulanate to amoxicillin increased E. coli susceptibility from 49% to 75% using the latest CLSI serum amoxicillin/clavulanic acid susceptible breakpoint of ≤8 µg/mL [5]. We believe CLSI should follow the lead of EUCAST and establish urinary breakpoints for amoxicillin/clavulanate against the Enterobacteriaceae. In 2014, EUCAST introduced a urinary amoxicillin/clavulanate susceptible breakpoint of ≤32 µg/mL for uncomplicated UTI [3]. Clinical evidence supporting the higher breakpoint includes a randomized trial of amoxicillin/clavulanate vs ciprofloxacin for uncomplicated UTI where cure rates with amoxicillin/clavulanate treatment were not significantly different when the pathogen was not susceptible according to the existing breakpoint (≤8 µg/mL) [8]. A higher breakpoint may also allow for consideration of amoxicillin/clavulanate as a treatment option for uncomplicated UTI caused by some extended-spectrum β-lactamase–producing Enterobacteriaceae that are resistant to other oral agents [9]. In an age of increasing antimicrobial resistance, any strategy that increases rather than decreases antimicrobial options deserves further examination.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest.

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Hien M. Nguyen, Matthew J. Labreche, and Christopher J. Graber

1Kaiser Permanente Northwest, Portland, Oregon; and
2Infectious Diseases Section, VA Greater Los Angeles Healthcare System and the David Geffen School of Medicine at the University of California

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Correspondence: Hien M. Nguyen, MD, Kaiser Permanente Northwest, 9800 SE Sunnyside Rd, Clackamas, OR 97015 (hien.m.nguyen@kp.org).

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