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# *In Vitro* Activity of Sulopenem, an Oral Penem, against Urinary Isolates of *Escherichia coli*

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**ABSTRACT** The *in vitro* activity of sulopenem was assessed against a collection from 2014 to 2016 of 539 urinary isolates of *Escherichia coli* from Canadian patients by using CLSI-defined broth microdilution methodology. A concentration of sulopenem 0.03 $\mu$g/ml inhibited both 50% ($MIC_{50}$) and 90% ($MIC_{90}$) of isolates tested; sulopenem MICs ranged from 0.015 to 0.25 $\mu$g/ml. The *in vitro* activity of sulopenem was unaffected by nonsusceptibility to trimethoprim-sulfamethoxazole and/or ciprofloxacin, multidrug-resistant phenotypes, extended-spectrum $\beta$-lactamases, or AmpC $\beta$-lactamases.

**KEYWORDS** *Escherichia coli*, penem, sulopenem, urinary

Infections of the urinary tract are among the most common infections of humans (1–3). *Escherichia coli* is the etiological agent of 75% to 95% of uncomplicated urinary tract infections and ~50% of complicated, recurrent, and hospital-acquired urinary tract infections (1–5). The Infectious Diseases Society of America recommends a 3-day course of double-strength trimethoprim-sulfamethoxazole (SXT) (160 mg trimethoprim/800 mg sulfamethoxazole twice daily) in settings where the prevalence of SXT resistance is <10% to 20%, a 5-day course of nitrofurantoin (100 mg twice daily), or a single dose of fosfomycin (3 g) as empirical treatment for acute uncomplicated bacterial cystitis in otherwise healthy adult nonpregnant women; fluoroquinolones and $\beta$-lactams (e.g., amoxicillin-clavulanate, cephalosporins) are recommended as second-line therapies (1). However, in North America and elsewhere, urinary isolates of *E. coli* commonly demonstrate rates of resistance to SXT that exceed 20% (5–8). SXT (e.g., enterococci) and nitrofurantoin (e.g., enterococci, *Proteus* spp.) do not possess activity against all bacterial species commonly identified as pathogens in urinary tract infections, and access to *in vitro* susceptibility testing results for fosfomycin is frequently limited, although most urinary isolates of *E. coli* and *Enterococcus faecalis* are susceptible *in vitro* to fosfomycin (9). Furthermore, 10% to 20% of urinary isolates of *E. coli* carry extended-spectrum $\beta$-lactamases (ESBLs) (5–8). The emergence and dissemination of *E. coli* sequence type 131 (ST131), which harbors an ESBL (CTX-M-14 or CTX-M-15) and fluoroquinolone resistance conferring mutations (in its *gyrA*/*gyrB* genes), has been responsible for most increases in resistance noted for these two antimicrobial classes in patients with community-onset and hospital-acquired disease (5–8, 10, 11).

The availability of an oral carbapenem may complement our current antimicrobial armamentarium and provide an efficacious oral treatment alternative for outpatients with infections caused by ESBL-producing pathogens, especially when isolates are not susceptible to first- or second-line agents, as well as offering potential avoidance of hospitalization or outpatient intravenous antimicrobial therapy. In the hospital setting, an oral carbapenem may provide flexibility and simplify selection of effective stepdown

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therapy in more serious infections (e.g., mixed aerobic/anaerobic infections), permitting hospital discharge of patients and potentially reducing the length of hospitalization.

Sulopenem, formerly CP-70,429, is an investigational thiopenem currently under development for the treatment of uncomplicated and complicated urinary tract infections and intra-abdominal infections (12), including multidrug-resistant (MDR) infections and infections attributable to quinolone-nonsusceptible and/or ESBL-producing Gram-negative bacilli (10). Sulopenem is in development in both parenteral and oral prodrug (sulopenem-etzadroxil) formulations, may be combined with probenecid, and has a safety and efficacy profile similar to those of other penems and $\beta$-lactams (10). Sulopenem is stable to renal dehydropeptidase I, unlike imipenem (13), and has been reported to be stable against hydrolytic attack by many $\beta$-lactamases, including ESBLs and AmpC enzymes, which confer resistance to third-generation cephalosporins (10). The activity of sulopenem addresses several of the most urgent, serious, and concerning drug-resistant antimicrobial threats defined by the CDC, including ESBL-producing *Enterobacteriaceae* (14).

(This work was presented in part as an abstract at ASM Microbe 2018, 7 to 11 June 2018, Atlanta, GA [15].)

The purpose of the current study was to assess the *in vitro* activity of sulopenem against recent (2014 to 2016) urinary tract infection isolates of *E. coli*. The isolates tested were collected as part of the CANWARD surveillance study, an annual (since 2007) national study designed to assess antimicrobial resistance and pathogen prevalence in patients receiving care at hospitals in major population centers across Canada (16) (www.can-r.ca). All isolates collected by the CANWARD surveillance study are shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Manitoba, Canada), where they are subcultured; their identities are confirmed by colonial appearance, spot testing (17), and/or MALDI-TOF (matrix-assisted laser desorption ionization-time of flight) mass spectrometry (Bruker Daltonics, Billerica, MA, USA); and antimicrobial susceptibility testing is performed according to CLSI-defined broth microdilution methodology (18, 19). Cation-adjusted Mueller-Hinton II broth (BD BBL; Becton, Dickinson and Company, Sparks, MD) was used in 96-well broth microdilution panel production. The antimicrobial agents tested were acquired as laboratory-grade powders from their respective manufacturers or from a commercial source. All antimicrobial agents were tested against the same inoculum of each isolate of *E. coli*.

In total, 539 urinary isolates of *E. coli* were tested. Sulopenem MIC interpretative criteria have not been established to date. MICs of comparator antimicrobial agents were interpreted by using current CLSI M100 breakpoints (19). ESBL-producing isolates of *E. coli* were screened for and confirmed phenotypically following the CLSI method (19). Isolates of *E. coli* demonstrating an MIC of $\geq$1 $\mu$g/ml for ceftriaxone and/or ceftazidime (data not shown) and/or aztreonam (data not shown), having an MIC of $\geq$32 $\mu$g/ml for cefoxitin (data not shown), and testing phenotypically negative for ESBL production were considered putative AmpC producers (20). Putative AmpC-producing *E. coli* were then screened for $bla_{ENT}$, $bla_{DHA}$, $bla_{FOX}$, $bla_{CIT}$, and $bla_{CMY}$ as previously described (21). All four isolates of *E. coli* putatively identified as producing AmpC were positive for a CMY-type $\beta$-lactamase by PCR. MDR isolates of *E. coli* were defined by using a published guideline (22). In this study, MDR was defined as nonsusceptible to $\geq$3 agents from different antimicrobial classes (ceftriaxone, amoxicillin-clavulanate, SXT, nitrofurantoin, ciprofloxacin, and gentamicin).

Sulopenem demonstrated a narrow (four doubling dilution) MIC range of 0.015 to 0.12 $\mu$g/ml, an $MIC_{50}$ of 0.03 $\mu$g/ml, and an $MIC_{90}$ of 0.03 $\mu$g/ml against all 539 urinary isolates of *E. coli* tested (Table 1). The *in vitro* activity of sulopenem (minimum MIC, maximum MIC, $MIC_{50}$, and $MIC_{90}$) was unaffected ($\leq$1 doubling-dilution difference from comparator-susceptible subsets) by nonsusceptibility to trimethoprim-sulfamethoxazole, ciprofloxacin, or both, as well as isolates with MDR, ESBL-positive, and AmpC-positive phenotypes. The maximum MICs observed for sulopenem and meropenem against *E. coli* were both 0.12 $\mu$g/ml.

To date, publication of data describing the *in vitro* activity of sulopenem has been

**TABLE 1** *In vitro* activity of sulopenem and comparator antimicrobial agents against *E. coli* isolated from urine specimens of Canadian patients from 2014 to 2016

| *E. coli* phenotype (no. of isolates tested) and antimicrobial agent | MIC data (μg/ml) | | | MIC interpretation (%) | | |
|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | Range | Susceptible | Intermediate | Resistant |
| All isolates (539) | | | | | | |
| Sulopenem | 0.03 | 0.03 | 0.015 to 0.12 | NA[a] | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.12 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | 1 | ≤0.25 to >64 | 90.4 | 0.1 | 9.5 |
| Amoxicillin-clavulanate | 4 | 16 | 0.5 to >32 | 81.3 | 14.6 | 4.1 |
| SXT[b] | ≤0.12 | >8 | ≤0.12 to >8 | 75.5 | NA | 24.5 |
| Nitrofurantoin | 16 | 16 | ≤1 to 256 | 97.8 | 1.5 | 0.7 |
| Ciprofloxacin | ≤0.06 | >16 | ≤0.06 to >16 | 76.3 | 0.1 | 23.6 |
| Gentamicin | ≤0.5 | 1 | ≤0.5 to >32 | 91.3 | 0.4 | 8.3 |
| Pansusceptible[c] isolates (309) | | | | | | |
| Sulopenem | 0.03 | 0.03 | 0.015 to 0.06 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.12 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25 to 1 | 100 | 0 | 0 |
| Amoxicillin-clavulanate | 4 | 8 | 0.5 to 8 | 100 | 0 | 0 |
| SXT | ≤0.12 | 0.25 | ≤0.12 to 2 | 100 | NA | 0 |
| Nitrofurantoin | 16 | 16 | 2 to 32 | 100 | 0 | 0 |
| Ciprofloxacin | ≤0.06 | ≤0.06 | ≤0.06 to 0.5 | 100 | 0 | 0 |
| Gentamicin | ≤0.5 | ≤0.5 | ≤0.5 to 2 | 100 | 0 | 0 |
| SXT-susceptible isolates (407) | | | | | | |
| Sulopenem | 0.03 | 0.03 | 0.015 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.12 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25 to >64 | 94.3 | 0 | 5.7 |
| Amoxicillin-clavulanate | 4 | 16 | 0.5 to >32 | 88.0 | 9.1 | 2.9 |
| SXT | ≤0.12 | 0.25 | ≤0.12 to 2 | 100 | NA | 0 |
| Nitrofurantoin | 16 | 16 | ≤1 to 128 | 98.3 | 1.2 | 0.5 |
| Ciprofloxacin | ≤0.06 | >16 | ≤0.06 to >16 | 85.3 | 0 | 14.7 |
| Gentamicin | ≤0.5 | 1 | ≤0.5 to >32 | 95.1 | 0.5 | 4.4 |
| SXT-nonsusceptible isolates (132) | | | | | | |
| Sulopenem | 0.03 | 0.06 | 0.015 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.06 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | >64 | ≤0.25 to >64 | 78.0 | 0.8 | 21.2 |
| Amoxicillin-clavulanate | 8 | 16 | 2 to >32 | 60.6 | 31.8 | 7.6 |
| SXT | >8 | >8 | 4 to >8 | 0 | NA | 100 |
| Nitrofurantoin | 16 | 32 | ≤1 to 256 | 96.2 | 2.3 | 1.5 |
| Ciprofloxacin | 16 | >16 | ≤0.06 to >16 | 48.5 | 0.7 | 50.8 |
| Gentamicin | ≤0.5 | 32 | ≤0.5 to >32 | 79.5 | 0 | 20.5 |
| Ciprofloxacin-susceptible isolates (411) | | | | | | |
| Sulopenem | 0.03 | 0.03 | 0.015 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.12 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25 to >64 | 96.6 | 0.2 | 3.2 |
| Amoxicillin-clavulanate | 4 | 16 | 0.5 to >32 | 86.9 | 10.2 | 2.9 |
| SXT | ≤0.12 | >8 | ≤0.12 to >8 | 84.4 | NA | 15.6 |
| Nitrofurantoin | 16 | 16 | ≤1 to 128 | 99.8 | 0 | 0.2 |
| Ciprofloxacin | ≤0.06 | 0.12 | ≤0.06 to 1 | 100 | 0 | 0 |
| Gentamicin | ≤0.5 | 1 | ≤0.5 to >32 | 95.9 | 0.2 | 3.9 |
| Ciprofloxacin-nonsusceptible isolates (128) | | | | | | |
| Sulopenem | 0.03 | 0.06 | 0.015 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.06 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | >64 | ≤0.25 to >64 | 70.3 | 0 | 29.7 |
| Amoxicillin-clavulanate | 8 | 16 | 1 to >32 | 63.3 | 28.9 | 7.8 |
| SXT | >8 | >8 | ≤0.12 to >8 | 46.9 | NA | 53.1 |
| Nitrofurantoin | 16 | 32 | ≤1 to 256 | 91.4 | 6.3 | 2.3 |
| Ciprofloxacin | >16 | >16 | 2 to >16 | 0 | 0.8 | 99.2 |
| Gentamicin | ≤0.5 | >32 | ≤0.5 to >32 | 76.6 | 0.7 | 22.7 |
| SXT- and ciprofloxacin-susceptible isolates (347)[d] | | | | | | |
| Sulopenem | 0.03 | 0.03 | 0.015 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.12 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25 to >64 | 97.7 | 0 | 2.3 |

(Continued on next page)

**TABLE 1** (Continued)

| *E. coli* phenotype (no. of isolates tested) and antimicrobial agent | MIC data (μg/ml) | | | MIC interpretation (%) | | |
|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | Range | Susceptible | Intermediate | Resistant |
| Amoxicillin-clavulanate | 4 | 8 | 0.5 to >32 | 90.8 | 6.6 | 2.6 |
| SXT | ≤0.12 | ≤0.12 | ≤0.12 to 2 | 100 | NA | 0 |
| Nitrofurantoin | 16 | 16 | ≤1 to 32 | 100 | 0 | 0 |
| Ciprofloxacin | ≤0.06 | ≤0.06 | ≤0.06 to 0.5 | 100 | 0 | 0 |
| Gentamicin | ≤0.5 | 1 | ≤0.5 to >32 | 98.3 | 0.3 | 1.4 |
| SXT- and ciprofloxacin-nonsusceptible isolates (68)[d] | | | | | | |
| Sulopenem | 0.03 | 0.06 | 0.015 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.06 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | >64 | ≤0.25 to >64 | 66.2 | 0 | 33.8 |
| Amoxicillin-clavulanate | 8 | 32 | 2 to >32 | 55.9 | 33.8 | 10.3 |
| SXT | >8 | >8 | 4 to >8 | 0 | NA | 100 |
| Nitrofurantoin | 16 | 32 | ≤1 to 256 | 94.1 | 4.4 | 1.5 |
| Ciprofloxacin | >16 | >16 | 2 to >16 | 0 | 1.5 | 98.5 |
| Gentamicin | ≤0.5 | >32 | ≤0.5 to >32 | 76.5 | 0 | 23.5 |
| MDR[e] isolates (71) | | | | | | |
| Sulopenem | 0.03 | 0.06 | 0.015 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.06 | 100 | 0 | 0 |
| Ceftriaxone | 16 | >64 | ≤0.25 to >64 | 46.5 | 0 | 53.5 |
| Amoxicillin-clavulanate | 16 | 32 | 4 to >32 | 32.4 | 50.7 | 16.9 |
| SXT | >8 | >8 | ≤0.12 to >8 | 23.9 | NA | 76.1 |
| Nitrofurantoin | 16 | 64 | 2 to 256 | 87.3 | 8.5 | 4.2 |
| Ciprofloxacin | >16 | >16 | ≤0.06 to >16 | 11.3 | 0 | 88.7 |
| Gentamicin | 1 | >32 | ≤0.5 to >32 | 56.3 | 1.4 | 42.3 |
| ESBL-negative isolates (490) | | | | | | |
| Sulopenem | 0.03 | 0.03 | 0.03 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.12 | 100 | 0 | 0 |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25 to >64 | 99.2 | 0 | 0.8 |
| Amoxicillin-clavulanate | 4 | 16 | 0.5 to >32 | 83.9 | 12.8 | 3.3 |
| SXT | ≤0.12 | >8 | ≤0.12 to >8 | 78.8 | NA | 21.2 |
| Nitrofurantoin | 16 | 16 | ≤1 to 256 | 98.2 | 1.4 | 0.4 |
| Ciprofloxacin | ≤0.06 | >16 | ≤0.06 to >16 | 81.4 | 0.2 | 18.4 |
| Gentamicin | ≤0.5 | 1 | ≤0.5 to >32 | 93.7 | 0 | 6.3 |
| ESBL-positive isolates (49) | | | | | | |
| Sulopenem | 0.03 | 0.06 | 0.03 to 0.12 | NA | NA | NA |
| Meropenem | ≤0.03 | ≤0.03 | ≤0.03 to 0.06 | 100 | 0 | 0 |
| Ceftriaxone | >64 | >64 | 1 to >64 | 2.0 | 2.1 | 95.9 |
| Amoxicillin-clavulanate | 8 | 32 | 4 to >32 | 55.1 | 32.7 | 12.2 |
| SXT | >8 | >8 | ≤0.12 to >8 | 42.9 | NA | 57.1 |
| Nitrofurantoin | 16 | 16 | 2 to 256 | 93.9 | 2.0 | 4.1 |
| Ciprofloxacin | >16 | >16 | ≤0.06 to >16 | 24.5 | 0 | 75.5 |
| Gentamicin | ≤0.5 | >32 | ≤0.5 to >32 | 67.3 | 4.1 | 28.6 |
| AmpC-positive isolates (4) | | | | | | |
| Sulopenem | NA | NA | 0.03 to 0.12 | NA | NA | NA |
| Meropenem | NA | NA | ≤0.03 to 0.06 | 100 | 0 | 0 |
| Ceftriaxone | NA | NA | ≤0.25 to >64 | 25.0 | 0 | 75.0 |
| Amoxicillin-clavulanate | NA | NA | 32 to >32 | 0 | 0 | 100 |
| SXT | NA | NA | 0.25 to >8 | 50.0 | NA | 50.0 |
| Nitrofurantoin | NA | NA | 8 to 32 | 100 | 0 | 0 |
| Ciprofloxacin | NA | NA | ≤0.06 to >16 | 50.0 | 0 | 50.0 |
| Gentamicin | NA | NA | ≤0.5 to 1 | 100 | 0 | 0 |

[a]NA, there are no MIC breakpoints defined for this antimicrobial agent or no intermediate MIC breakpoint for this antimicrobial agent, or there were <30 isolates tested and an $MIC_{50}$ and $MIC_{90}$ could not be generated.

[b]SXT, trimethoprim-sulfamethoxazole.

[c]Pansusceptible isolates were susceptible to meropenem, ceftriaxone, amoxicillin-clavulanate, SXT, nitrofurantoin, ciprofloxacin, and gentamicin and excluded MDR isolates and isolates resistant to one ($n = 89$) and two ($n = 70$) of the aforementioned list of antimicrobial agents.

[d]There were 124 isolates of *E. coli* that were SXT susceptible and ciprofloxacin nonsusceptible or SXT nonsusceptible and ciprofloxacin susceptible that were excluded from this analysis.

[e]MDR was defined as nonsusceptible to ≥3 agents from different antimicrobial classes (ceftriaxone, amoxicillin-clavulanate, SXT, nitrofurantoin, ciprofloxacin, and gentamicin). The most common MDR phenotypes were isolates nonsusceptible to amoxicillin-clavulanate, ciprofloxacin, and SXT ($n = 13$; 18.3% of MDR isolates); isolates nonsusceptible to ceftriaxone, ciprofloxacin, and SXT ($n = 9$; 12.7% of MDR isolates); isolates nonsusceptible to amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, and SXT ($n = 7$; 9.9% of MDR isolates); isolates nonsusceptible to ciprofloxacin, SXT, and gentamicin ($n = 6$; 8.5% of MDR isolates); isolates nonsusceptible to amoxicillin-clavulanate, ceftriaxone, and ciprofloxacin ($n = 4$; 5.6% of MDR isolates); and isolates nonsusceptible to amoxicillin-clavulanate, ciprofloxacin, SXT, and gentamicin ($n = 4$; 5.6% of MDR isolates).

limited. Sulopenem has been reported to inhibit the growth of most isolates of aerobic and anaerobic Gram-positive and Gram-negative bacteria, including methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae* (penicillin-susceptible and -resistant isolates), group A and B β-hemolytic streptococci, *Listeria monocytogenes*, *Enterobacteriaceae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* but excluding *P. aeruginosa* and *Stenotrophomonas maltophilia*, at a concentration of ≤1 μg/ml (10, 13, 23–27).

Data generated by the current study (Table 1) confirm previously published data describing the *in vitro* activity of sulopenem against *E. coli*, including ESBL- and AmpC-positive isolates (10, 13, 23, 24, 28, 29). Puttagunta et al. (10) reported sulopenem $MIC_{90}$s of 0.03 and 0.06 μg/ml, respectively, for ESBL-negative ($n = 169$) and ESBL-positive ($n = 20$) *E. coli* (all MICs were ≤0.12 μg/ml). In the same study, the sulopenem $MIC_{90}$s were 0.06 and 0.25 μg/ml, respectively, for ESBL-negative ($n = 108$) and ESBL-positive ($n = 16$) *Klebsiella* spp. (all MICs were ≤0.25 μg/ml), and 97.9% of all isolates of *Enterobacteriaceae* tested ($n = 682$) had sulopenem MICs of ≤1 μg/ml. Aronin et al. (24) reported $MIC_{50}$ and $MIC_{90}$ of 0.03 and 0.06 μg/ml, respectively, for 32 ESBL-positive *E. coli* urinary isolates from the United States and Europe, whereas Duignan et al. (28) reported that sulopenem had an $MIC_{90}$ of 0.03 μg/ml and an MIC range of 0.015 to 0.25 μg/ml for 17 isolates of ESBL-positive *E. coli*. Minamimura et al. (13) reported a sulopenem $MIC_{90}$ of 0.05 μg/ml when tested against 100 isolates of *E. coli*. The repeated observation of one-doubling-dilution higher $MIC_{90}$s for ESBL-positive isolates of *Enterobacteriaceae* compared with those of ESBL-negative isolates may be explained by weak sulopenem hydrolytic activity of β-lactamases, including ESBLs, in these isolates. The common cooccurrence of ESBLs in isolates nonsusceptible to ciprofloxacin and in MDR isolates likely explains the correlation between these phenotypes and their one-doubling-dilution higher $MIC_{90}$s for sulopenem compared with susceptible isolate groups. Although a one-doubling-dilution higher $MIC_{90}$ is likely not significant *in vitro*, additional resistance determinants, such as membrane impermeability and hyperproduction of ESBLs or other noncarbapenemase β-lactamases, may potentially lead to clinically relevant increases in MIC.

β-Lactams are widely used in clinical medicine to treat various Gram-positive and Gram-negative bacterial infections because of their proven efficacy and safety. However, resistance to β-lactams does occur and may limit the utility of some or all β-lactams currently marketed for infections caused by specific pathogens. Sulopenem, like other penems, is not expected to have activity against carbapenemase-producing isolates of *E. coli* or other species of *Enterobacteriaceae* carrying class A (e.g., *Klebsiella pneumoniae* carbapenemase [KPC]), class B (metallo-β-lactamases), or class D (e.g., OXA) β-lactamases. However, when indicated, oral sulopenem has the potential to provide reliable therapy similar to that of existing carbapenems; a phase I clinical trial in healthy volunteers who received a single 500-mg dose of oral sulopenem-etzadroxil (with or without 500 mg of probenecid) achieved urine concentrations of sulopenem that remained above the MIC range of *E. coli* tested in the current study (0.015 to 0.12 μg/ml) for ≥12 h after dose administration (12, 29).

In conclusion, sulopenem, given its *in vitro* potency and its oral and parenteral formulations, may represent a valuable new option to treat patients with urinary tract infections caused by pathogens resistant to first- and second-line antimicrobial agents. In the current study, sulopenem demonstrated potent *in vitro* activity (MIC range, 0.015 to 0.12 μg/ml) against current urinary isolates of *E. coli*. Our data support further development of sulopenem for the treatment of urinary tract infections.

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