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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (KC CLAEYS AND J SMITH, SECTION EDITORS)

Tebipenem and Sulopenem: Dynamic Duo or Double Trouble?

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Abstract

Purpose of Review Antimicrobial resistance is a growing threat to public health, leading to millions of antibiotic-resistant infections and thousands of deaths annually in the USA. One concerning issue is the rise of extended-spectrum beta-lactamase (ESBL)–producing Enterobacterales. Current treatments often involve intravenous carbapenems, leading to prolonged hospital stays and financial burdens.

Recent Findings To address this, new oral penem agents, tebipenem and sulopenem, are being investigated. They are administered as prodrugs, enhancing bioavailability before becoming active in the gastrointestinal tract, potentially treating multidrug-resistant infections in outpatient settings. Despite promise in clinical trials, challenges exist, such as tebipenem's renal excretion, requiring dose adjustments for kidney dysfunction. Additionally, sulopenem failed noninferiority margins in trials, and neither drug has established susceptibility testing standards.

Summary Tebipenem and sulopenem offer potential oral solutions for antimicrobial resistance, especially in urinary tract infections, but further research is needed for optimal dosing and susceptibility testing.

Keywords Tebipenem · Sulopenem · Carbapenem · ESBL

Introduction

Antimicrobial resistance is a growing threat to public health. The CDC's report on antibiotic resistance threats in the USA from 2019 estimated that 2.8 million infections from antibiotic-resistant organisms occur annually, with more than 35,000 deaths occurring from such infections [1]. The report describes the impact of extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae on health systems. When present, ESBL enzymes inactivate numerous antibiotics, including penicillins, cephalosporins, and aztreonam. Unfortunately, data from the CDC demonstrate an increase in annual estimated ESBL cases from 131,900 in 2013 to 197,400 cases in 2019 [1]. Current IDSA guidance suggests that intravenous carbapenems be considered first line for infections outside of the urinary system or for urinary infections with resistance/contraindications to use TMP-SMX, ciprofloxacin, or levofloxacin [2]. While oral fluoroquinolones and TMP-SMX are recommended options for urinary infections caused by ESBL-E, there is a concern for rising resistance rates that could leave these options ineffective. A retrospective analysis at an academic medical center noted high resistance to oral agents in infections caused by ESBL-producing bacteria. In *E. coli* isolates, 69% were resistant to TMP-SMX and 95% were resistant to ciprofloxacin. Among the *K. pneumoniae* isolates, 76% were resistant to nitrofurantoin [3]. The CDC Antibiotic Resistance Portal reports that 35.2% of *E. coli* isolates were resistant to fluoroquinolones [4]. With the resistance rates rising, carbapenems may be the only appropriate agents in some cases. One of the significant drawbacks of using carbapenems is that they are currently only available as intravenous formulations in the USA. To

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receive these antibiotics, patients either remain in the hospital, are transferred to skilled nursing facilities (SNF), or are referred to an outpatient parenteral antimicrobial treatment program for the remainder of their therapy. Each of these options is suboptimal. Continued stay in the hospital or transfer to a SNF places the patient at continued risk for hospital-related complications, and many outpatient infusion programs would require central line placement. With the current estimated cost of inpatient stays for health systems being $2883 per day in the USA, there are financial impacts on the health system as well [5]. Therefore, there is clearly a need for oral therapeutic alternatives for the management of infections due to ESBL-producing Enterobacterales. Encouragingly, some antibiotics are in development or internationally available as oral formulations. Sulopenem and tebipenem are oral agents currently being investigated for approval in the USA to address the need for an oral option for treating multidrug-resistant organisms. This review will focus on the medicinal chemistry, in vitro activity, pharmacokinetics and pharmacodynamics, and clinical data for sulopenem and tebipenem. Finally, their potential place in therapy, if approved, will be discussed.

Medicinal Chemistry

Carbapenems are members of the β-lactam family of antibiotics as they contain a four-membered β-lactam ring. These rings bind to penicillin-binding proteins (PBPs) in susceptible bacteria and confer these compounds with their antibacterial properties. The ability of the β-lactam rings to bind to PBPs is greatly influenced by the nature of the membered rings that are fused to the β-lactam core and one of the characteristics that differentiate different classes within the β-lactam family. These fused rings can be five- or six-membered rings with various atoms at the 1 position. For penicillins and cephalosporins, sulfur occupies the 1 position, while carbapenems contain carbon at that location [6]. The sulfur in the 1 position confers stability against enzymatic dehydropeptidase-1 (DHP-1), while carbapenems (except imipenem) avoid this degradation by having a methyl side chain connected to the 1 position. To avoid this degradation, imipenem must be coadministered with cilastatin. Another distinct feature of the carbapenems' core ring structure is the *trans* orientation of hydrogen atoms at C5 and C6 and a double bond positioned between C2 and C3 [6–9]. A trans-α-1-hydroxyethyl substituent is the last distinctive feature of carbapenem core structure and affords these compounds resistance to degradation by many beta-lactamase enzymes, including ESBLs [7, 8]. In carbapenems, this side chain at the 6 position is in the *trans* orientation versus other classes of β-lactams that have *cis*-oriented side chains in this position.

Tebipenem follows the traditional carbapenem core with a few notable structural differences. As with many β-lactam antibiotics, there is substantial variation in the side chain structure. Tebipenem's side chain is a bicyclic azetidine thiazole moiety located at the 2 position of the core structure and contains a pivoxil ester at the 3 position. The additional ester functional group allows additional tebipenem to act as a prodrug, known as tebipenem pivoxil, which has increased intestinal absorption via organic anion transporting polypides (OATP) 1A2 and 2B1 [10].

Sulopenem's core structure differs from other carbapenems as it retains a sulfur in the 1 position of the five-membered ring, making it a thiopenem rather than a carbapenem. With the retained sulfur in the core structure, sulopenem does not require a methyl group to resist DHP-1 degradation. Sulopenem's side chain is a thioether with a cyclic sulfoxide group in the *(S)* orientation. The resonance created by the sulfoxide in the side chain forms a positive and a negative charge [11]. Additionally, there is a carboxylic acid at the C3 position of the core ring structure [10, 11]. The parent drug of sulopenem is in the S isomeric form and is also available as an oral prodrug, sulopenem etzadroxil. The prodrug is created by adding an etzadroxil to the carboxylic acid at the C3 position. Both of these compounds have similar functional group additions to increase the oral bioavailability of these structures by creating stable prodrug formulations.

While the general structure of each of these molecules is slightly different from one another, they both have vital functional groups that allow both to act prodrugs. The exact moiety added to increase oral absorption differs in the two agents, but the mechanism in which they are converted to active metabolites is similar. Tebipenem pivoxil is converted to the active metabolite by carboxylesterase at the intestinal epithelial cells, and sulopenem etzadroxil is hydrolyzed by intestinal esterases before absorption in the gastrointestinal tract [10, 11].

Microbiological Spectrum

As mentioned in the previous section, carbapenems possess a variety of methods to resist enzymatic degradation by DHP-1 or from β-lactamases. Additionally, these antibiotics have slight variability in target site binding affinity, efflux pump susceptibility, and the ability to pass through porin channels. These factors contribute to slightly different spectrums of activity in relatively similar antibiotics.

Tebipenem has a broad spectrum of activity against gram-negative and gram-positive organisms. Early studies of the prodrug and active metabolite were conducted in Japan in the late 90 s to evaluate in vivo and in vitro activity. These studies found that tebipenem had in vitro activity against methicillin-sensitive *Staphylococcus*

aureus, penicillin-sensitive and resistant *Streptococcus pneumoniae*, and *Streptococcus pyogenes* [12, 13]. For these gram-positive organisms, tebipenem has variable binding affinity for different PBPs. In *S. aureus* isolates, tebipenem will bind to all PBPs but had a lower affinity for PBP2 and PBP3, and little to no activity for PBP2a [14•]. In *S. pneumoniae*, tebipenem has been shown to have binding affinity for PBP1a, PBP1b, PBP2a, PBP2b, and PBP3 [12]. Based on these binding affinities, the MIC_{90} values for MSSA range from 0.025 to 0.125 mg/L, MRSA from 12.5 to 16 mg/L, and *S. pyogenes* between ≤ 0.006 and ≤ 0.125 [12, 14•, 15]. Importantly, these studies also demonstrated a lack of activity against *Enterococcus faecium*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* similar to the activity of ertapenem (Table 1). For other gram-negative organisms, tebipenem has affinity for several PBPs. In *E. coli* and *K. pneumoniae*, tebipenem had high affinity for PBP2 and moderate affinity for PBP1a, PBP1b, and PBP3 [14•]. To compare the spectrum of this new agent to commercially available products, an in vitro analysis was conducted with *E coli*, *K. pneumoniae*, and *P. mirabilis* isolates. For *E. coli*, tebipenem had $MIC_{50/90}$ values of ≤ 0.015/0.03 mg/L which were equivalent to the MICs shown for ertapenem and meropenem and 8 times lower than the MICs seen for imipenem. In *K. pneumoniae* isolates, tebipenem $MIC_{50/90}$ were 0.03/0.06 mg/L which were the same seen in meropenem, 4–8 times lower than the MICs seen for imipenem, and $MIC_{50/90}$ for ertapenem were reported at ≤ 0.015/0.25 mg/L. The last comparative organism was *P. mirabilis* which tebipenem demonstrated $MIC_{50/90}$ of 0.06/0.12 mg/L the same as meropenem, 4–8 times lower than $MIC_{50/90}$ seen for doripenem, but higher than $MIC_{50/90}$ seen for ertapenem (≤ 0.015/ ≤ 0.015). The study went on to compare the activity of tebipenem in ESBL- and AmpC-producing isolates of *E coli*, *K.*

Table 1 MIC_{50} and MIC_{90} ranges noted in studies evaluating activity against microorganism with comparison against meropenem and ertapenem when available [11–13, 15, 18, 19]

	Tebipenem		Sulopenem		Meropenem		Ertapenem	
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
MSSA	0.025 to ≤ 0.125	0.025–0.125	0.06–0.1	0.1–0.12	0.12 to ≤ 0.125	0.25	0.12	0.25
MRSA	6.25–18	12.5–16	12.5–16	64–100	8–16	16–32	4	32
MSSE	≤ 0.03–0.1	0.125–0.5			≤ 0.125	1	0.25	0.25
MRSE	2–8	6.25–8			16	16		
S. pneumonia	0.002 to ≤ 0.006	≤ 0.006–0.032	≤ 0.006–0.008	0.06–0.1	≤ 0.016	0.016	0.016	0.016
S. pyogenes	≤ 0.006 to ≤ 0.125	≤ 0.006 to ≤ 0.125	0.012–0.03	0.025–0.03	≤ 0.125	≤ 0.125	≤ 0.016	≤ 0.016
E. faecalis	0.25–0.5	2–32	3.13–4	6.25–8	2–8	8 to > 128	8	16
E. faecium	64	128			> 128	> 128		
E. coli	≤ 0.025– ≤ 0.125	0.05–1	0.025–0.03	0.03–0.06	0.03 to ≤ 0.125	0.03–1	0.008	0.03
H. influenzae	0.05– ≤ 0.125	0.25–0.39	0.2–0.25	0.2–0.25	0.06 to ≤ 0.125	0.12–0.5	0.06	0.12
K. pneumoniae	≤ 0.025– ≤ 0.125	0.05–0.5	0.025–0.03	0.05–0.12	0.03 to ≤ 0.125	0.03–1	0.008	0.06
M. catarrhalis	0.025 to ≤ 0.063	0.05 to ≤ 0.063	0.03	0.12	0.08	0.08	0.008	0.016
E. cloacae	0.05 to ≤ 0.125	0.2–1	0.12–0.2	0.5–0.78	0.06 to ≤ 0.125	0.12–2	≤ 0.06	0.5
P. mirabilis	≤ 0.125–0.39	≤ 0.125–0.39	0.1–0.25	0.2–0.5	0.06 to ≤ 0.125	0.12–0.5	0.016	0.03
S. marcescens	≤ 0.125–0.39	16–25	0.5–0.78	2–50	0.12 to ≤ 0.125	0.25–32	0.03	0.12
P. aeruginosa	6.25–8	64–100	25–32	> 64–100	0.5–2	4–32	8	8
A. baumannii	16	24	0.5	1	32	64	4	> 8
S. maltophilia	62	64	100–128	> 100 to > 128	62	128	> 8	> 8

pneumoniae, and *P. mirabilis*. When used in presence of these enzymes, tebipenem MIC_{50} remained stable at 0.03 mg/L, while MIC_{90} had a slight increase to 0.25 mg/L [16]. In vitro studies have also evaluated tebipenem as a potential treatment option for *Mycobacterium* infections. One study evaluated the activity of carbapenems alone and in combination with either isoniazid, rifampin, or clavulanic acid against *M. tuberculosis* and *M. abscessus*. When used alone, tebipenem had the highest in vitro potency (MIC_{90} = 1.25–2.5 mg/L) against *M. tuberculosis* compared to faropenem, biapenem, doripenem, peropenem, ertapenem, imipenem, and panipenem. When combined with clavulanic acid, the MIC_{90} of tebipenem was reduced to 0.31–0.62 mg/L. However, tebipenem was much less active against *M. abscessus* isolates with MIC_{90} ranging from 40 to 80 mg/L. The effects of rifampin and isoniazid combination therapy were not evaluated with tebipenem [17].

Sulopenem demonstrates a comparable spectrum of activity to those of tebipenem and ertapenem. Early studies showed that sulopenem binds to PBP2, PBP1a, PBP1b, PBP4, and PBP5 in order from highest to lowest binding affinity and has demonstrated in vitro activity against *S. pneumoniae*, *E. faecalis*, *Listeria monocytogenes*, MSSA, and *Staphylococcus epidermidis* [11]. Similar with tebipenem, sulopenem MIC_{90} against MSSA ranged from 0.10 to 0.12 mg/L, while MRSA values ranged from 64 to 100 mg/L. The elevated MIC values for MRSA isolates can be explained by the fact that sulopenem has a much lower binding affinity for PBP2A that is present in the resistant organism. A more recent study evaluated the activity of sulopenem against 1647 Enterobacterales and 559 anaerobic isolates. This study demonstrated in vitro activity against all isolates tested. Activity was maintained against ESBL-producing Enterobacteriaceae with MIC_{90} values for sulopenem only increasing from 0.06 to 1 in *K. pneumoniae* and from 0.03 to 0.06 in *E. coli* in the presence of ESBL. Unsurprisingly, sulopenem lacks activity against carbapenem-resistant strains, with the MIC_{50} of *K. pneumoniae* increasing from 0.03 to 16 when carbapenem resistance was noted [18]. Similar to ertapenem, sulopenem lacks activity against *Pseudomonas aeruginosa* [19]. This is believed to be due to the poor affinity of sulopenem for PBB5, one of the predominant proteins in *P. aeruginosa*. Compared to currently available carbapenems, sulopenem has a similar in vitro potency. In *E. coli* isolates, sulopenem $MIC_{50/90}$ has been 0.03/0.06 mg/L which was comparable to ertapenem and meropenem, but lower than imipenem values (0.008/0.03 mg/L, 0.03/0.03 mg/L, and 0.25/0.25 mg/L, respectively). Among *Klebsiella* spp., only meropenem had a lower MIC_{90} than sulopenem (0.06 vs 0.12). While sulopenem demonstrates greater activity against *Acinetobacter* spp. than ertapenem, as evident by the decrease in MIC_{50} from 4 to 0.5 mg/L, it is still not as potent as either meropenem or imipenem which both have MIC_{50} values of 0.25 mg/L.

While both new agents have broad spectrums of activity, there are a few notable exclusions. Like other carbapenems, neither of these agents have activity against methicillin-resistant *Staphylococcus aureus* or carbapenem-resistant Enterobacteriaceae. Similar to ertapenem, neither has appreciable coverage against *Pseudomonas* or *Enterococcus*. Unlike tebipenem, sulopenem does have some activity against *Acinetobacter* spp. But considering other available carbapenems are more potent, neither agent is likely to become a first-line option for those infections. For the organisms that these new agents have demonstrated activity against, it is important to note that many of these tests were conducted in vitro or murine models, and there are currently no FDA, CLSI, or EUCAST breakpoints available for either agent.

Pharmacokinetics/Pharmacodynamics

As members of the beta-lactam class, carbapenems are best described as time-dependent killers in which efficacy is related to the amount of time that drug concentrations remain above the MIC. To maximize this target, it is necessary to understand both exposures relative to MIC values with common doses and what T > MIC targets optimize kill with each agent.

Mentioned earlier in this review, tebipenem is a prodrug in the form of tebipenem pivoxil hydrobromide, which is rapidly converted to the active tebipenem moiety by intestinal enzymes. A pooled analysis of three phase 1 studies and one phase 3 study was conducted to develop a population pharmacokinetic model for oral tebipenem. This analysis evaluated 3448 plasma drug concentration from 746 patients. The results of this analysis showed that tebipenem pharmacokinetics can best be described by a two-compartment model with linear elimination following first-order kinetics and two transit compartments for absorption after oral administration. In a patient with normal renal function, tebipenem showed a median maximum plasma concentration of 7.98 µg/mL and a median elimination half-life of 0.708 h. This elimination half-life is similar to that of meropenem and doripenem (1 h) which helps explain the need to dose these medications three times daily. Also noted in this population kinetics study was the increase of drug half-life in the setting of renal dysfunction. When given to patients with creatinine clearances between 30 and 50 mL/min, the half-life increased to 0.967 h. Notably, these patients still received doses of tebipenem every 8 h but at a lower dose [20]. Notably, tebipenem pivoxil, currently available in Japan, does not offer a dose adjustment recommendations

Table 2 PK parameters of median [min–max] [20]

	Tebipenem 300 mg every 8 h (CrCl 30–50)	Tebipenem 600 mg every 8 h (CrCl > 50)
Cmax (μg/mL)	6.68 (1.31–18.2)	7.98 (1.41–51.2)
$AUC_{0\text{-}24}$ (μg*h/mL)	59.2 (11.5 to 273)	60.5 (18.0–669)
Vss (L)	36.7 (26.2–54.5)	41.8 (11.9–104)
$T_{½\alpha}$ (h)	0.967 (3.65–1.46)	0.708 (0.265–1.57)
$T_{½\beta}$ (h)	2.1 (1.40–12.9)	1.77 (1.25–7.88)
CL (L/h)	15.7 (1.77–78.4)	30.7 (2.39–100)

for renal impairment but suggests to consider renal function when using the agent [21]. A summary of the population PK parameters can be found in Table 2.

A dose escalation study evaluated absorption in 108 healthy human subjects in fed and fasted states to assess if there was a food effect on absorption. The single ascending dose phase showed that in a fasted state, immediate release (IR) formulations of the prodrug had increased C_{max} and AUC with increased doses, while the tebipenem exposure for the 6- and 12-h extended-release (ER) formulations were lower than the 2- and 4-h ER formulations. The time to maximum concentration ranged from 0.5 to1.3 h and 1.0 to 2.0 h in the IR and ER formulations, respectively. The effects of high fat meals were variable as a fed state increased the C_{max} and AUC with the 6- and 12-h ER formulations but were not seen with 2- and 4-h ER formulations [22]. The population PK study also noted a fed state alters the absorption constant such that absorption was slower compared to an unfed state [20].

When discussing oral dosage forms, it is also important to know if alteration of the formulation leads to altered absorption as some patients may have difficulty swallowing tablets. An open label trail in healthy volunteers evaluated the effects of administering tebipenem via nasogastric tubing (NGT) with and without concomitant feeds compared to the IR oral tablet administration. Using blood samples to measure the plasma concentration of the drug at various timepoints post administration, it was discovered that crushing tebipenem and administering via NGT had virtually no effect on AUC, T_{max}, or elimination half-life [23]. Pivoxil prodrug formulations have been shown to increase absorption leading to bioavailability between 27 and 51% [10]. However, early studies of tebipenem showed that 54–73% of the administered to human subjects were recovered in the urine. This indicated that another mechanism could be leading to increased absorption. A group evaluating the absorption mechanisms of oral tebipenem discovered that, in addition to simple diffusion, tebipenem absorption is also mediated by organic anion transporting polypeptides (OATP) P1A2 and P2B1 [10].

Several studies have evaluated the tissue distribution of tebipenem. The first study reviewed sought to evaluate the drug concentrations in the plasma, epithelial lining fluid (ELF), and alveolar macrophages (AM). Thirty patients were given 600 mg of tebipenem every 8 h for five consecutive doses with blood samples occurring before and after the fifth dose and bronchoscopy occurring after the fifth dose. Based on the drug concentration noted from the bronchoscopies, it was determined that the AUC for the 8-h dosing interval for ELF was 1.65 mg * h/L and 0.41 mg * h/L for AM. Compared to the plasma concentrations noted, this corresponded to an ELF penetration ratio of 0.191 and an AM penetration of 0.047 [24]. Compared to currently available carbapenem agents, tebipenem's penetration into ELF is quite high. Meropenem dosed at 1 g every 8 h has an ELF to plasma concentration ratio ranging between 0.20 and 0.29 depending on the length of infusion time (30 min and 3 h, respectively) [25]. A study evaluating the ability of ertapenem to penetrate into the ELF found an ELF to plasma ratio of 0.34. This study went on to conduct Monte Carlo simulations to determine the likelihood of target attainment of 35% T > MIC in the ELF for various dosing scheems [26]. The results of the simulation showed at > 90% probability of target attainment for MICs between 0.008 and 0.12 mg/L and higher doses could increase the MIC values. To determine the ability of tebipenem to penetrate other tissues, a study in healthy subjects ($n = 6$) and subjects with diabetic foot infections ($n = 6$) used microdialysis to evaluate tissue distribution of tebipenem after receiving 600 mg orally every 8 h for three total doses. The retrodialysis recovery showed that mean AUC tissue concentrations were 5.99 ± 3.07 mg*h/L in healthy subjects and 8.60 ± 2.88 mg*h/L in infected populations. Plasma concentrations between the two cohorts were relatively similar after the third dose with the C_{max} in healthy subjects reaching 3.72 ± 2.35 mg/L and infected patients reaching concentration of 3.40 ± 2.86 mg/L. When tissue concentrations were compared to plasma drug levels, it was determined that tissue penetration was 107.4% ± 42.7% in healthy subjects versus 90.0% ± 16.7% for infected patients [27]. The results of this study are also notable as the previous population PK model noted that infection status also impacted absorption rate constant leading to faster absorption rates compared to patients without active infections [20].

As with other carbapenems, tebipenem is primarily cleared through renal excretion as evident by 300 mg and 600 mg doses where 57% and 67% excreted in the urine on day 1 on administration [22]. To better determine the effects of kidney dysfunction on tebipenem PK, a study of 39 patients was conducted. A single dose of tebipenem 600 mg was administered to patients with eGFR ≥ 90, 60 to < 90, 30 to < 60, and < 30 mL/min, while patients with

Table 3 Effects of renal dysfunction on tebipenem kinetics [28]

	eGFR ≥ 90	eGFR 60 to < 90	eGFR 30 to < 60	eGFR < 30
Cmax (μg/mL)	14.7	14.8	18.4	18.8
$T_{½}$ (h)	1.1 ± 0.23	1.2 ± 0.14	1.3 ± 0.15	3.6 ± 1.8
CL/F (L/h)	21.9	16.1	10.0	4.83
AUC (μg*h/mL)	21.1	28.8	46.0	95.6

Cmax maximum plasma concentration, $T_{1/2}$ elimination half-life, *AUC* area under the curve from hour 0 to last quantifiable concentration, *CL/F* apparent total body clearance

ESRD received a dose after hemodialysis (HD) on day 1 and prior to HD on day 5. As renal function decreased, elimination half-life and AUC increased while clearance of tebipenem decreased (see Table 3). In patients with ESRD, T_{max} was delayed at 4.0 h when given after HD compared to 1.5 h in patients without ESRD. The half-life of tebipenem also dramatically increased from 1.1–3.6 h in patients without ESRD to 7.9 h in patients with ESRD. Even when tebipenem was given prior to HD, levels were still detectable in the serum for up to 48 h [28].

Carbapenems are typically described as "time-dependent" antibiotics and *f*T > MIC is the parameter that aligns most with the microbiological activity of the antibiotic. However, this may not hold true for tebipenem. A preclinical trial evaluated the pharmacokinetics and dynamics of tebipenem in a neutropenic murine thigh infection model. This trial noted that none of the standard pharmacodynamic indices for time-dependent agents (e.g., 40% *f*T > MIC) aligned with antibacterial efficacy. When evaluating other standard pharmacodynamic targets, the coefficient of determination (r^2) for AUC/MIC and C_{max}/MIC were also low, 0.73 and 0.33, respectively. The metric that had the highest r^2 value for antibacterial efficacy was the AUC/MIC ratio per length of dosing interval (AUC/MIC-1/tau) [29].

Unlike tebipenem, sulopenem is available in both intravenous and oral formulations. For the purposes of this review, the focus is on the pharmacokinetics of the oral formulation. The availability of data surrounding sulopenem pharmacokinetics is limited, and only one published paper in humans was located in the review of literature. Much of the literature available and subsequently presented herein is from conference abstracts and is subject to change with study completion, peer review, and publication. Similar to tebipenem, studies were performed to assess the impact of fed versus unfed states on the absorption of sulopenem. Additionally, these studies evaluated the impact of probenecid coadministration, in fed and unfed states, on sulopenem exposure in human subjects. In a dose escalation study, sulopenem had a bioavailability ranging from 20.1 to 33.6% in a fasting state, with the percent bioavailable decreasing with larger doses [11]. A study by Dunne et al. compared fed versus fasted states with and without probenecid coadministration. All patients in this study received 500 mg of sulopenem twice daily for 13 doses with or without probenecid 500 mg twice daily for 13 doses. The AUC of sulopenem in a fasted state with no probenecid at steady state was 3.68 ± 0.73 mg*h/L. In a fed state, the AUC increased to 4.55 ± 1.13, an overall increase of 23.6% indicating that a fed state increased oral absorption of the medication. The coadministration of probenecid had variable effects on AUC if administered in a fed or fasting state. When probenecid was given to patients in a fasting state, the AUC of sulopenem increased from 3.68 ± 0.73 to 3.95 ± 0.89 mg*h/L, an increase of 7.3%. However, when probenecid was given to patients in a fed state, the AUC of sulopenem increased by 40.7% (4.55 ± 1.13 to 6.40 ± 1.42 mg*h/L) [11]. The addition of probenecid helps reduce elimination of sulopenem thereby increasing the total drug exposure. Probenecid reduces the renal tubular elimination of sulopenem and other beta lactams by competing for organic anion transports in the kidney that typically help facilitate the antibiotic elimination [30]. The remaining PK parameters of sulopenem were evaluated in a trial of 24 healthy patients to determine the population model of IV and oral sulopenem formulations. Patients were given oral doses of sulopenem ranging from 600 to 1200 mg which were given under fasted condition with and without 1000 mg of probenecid. The results indicated that oral sulopenem obeys a one-compartment model with both absorption and elimination obeying first-order kinetics. The absorption rate constant was determined to be 0.78 1/h; the

Table 4 Pharmacokinetics of oral sulopenem at various doses in a fasted state [11]

Dose	Cmax	AUC	F%	$T_{½}$
400 mg × 1	1.46 ± 0.44	3.45 ± 0.67	33.6 ± 6.5	0.84 ± 0.16
1000 mg × 1	2.86 ± 0.57	6.42 ± 1.21	23.8 ± 4.5	1.00 ± 0.17
2000 mg × 1	4.67 ± 1.18	13.13 ± 2.10	20.1 ± 3.2	1.10 ± 0.62
600 mg × 1	2.21 ± 0.41	5.83 ± 1.0		0.82 ± 0.06
600 mg × 1 with 500 mg of probenecid	2.38 ± 0.41	7.81 ± 3.20		0.99 ± 0.15
600 mg × 1 with 1000 mg of probenecid	3.67 ± 1.61	9.73 ± 2.73		1.41 ± 0.18

clearance per dosing interval divided by the bioavailability (CL_T/F) without probenecid was found to be 122 L/h and 71.4 L/h with probenecid (Table 4) [11].

Unlike tebipenem, sulopenem appears to follow the tradition of other beta-lactam antibiotics in %*f*T > MIC being the best predictor of bacterial activity. A neutropenic murine thigh infection model study compared different pharmacodynamic indices against *S. pneumoniae* and *K. pneumoniae* to determine which best described the underlying mechanism. Compared to *f*AUC/MIC and fC_{max}/AUC, %*f*T > MIC had a much stronger correlation with activity, R^2 of 0.45, 0.45, and 0.84, respectively. To achieve bacteriostasis in *S. pneumoniae*, a %*f*T > MIC of 11.6% is needed while a 3-$\log_{10}$ reduction only requires a slightly higher target of 14.6%. Similar effects against *K. pneumoniae* required higher %*f*T > MIC targets, with bacteriostasis requiring 16.4% and a 2-$\log_{10}$ reduction needing 20.2%.

Clinical Efficacy

Tebipenem Clinical Efficacy

The main clinical trial evaluating the efficacy of tebipenem for the treatment of urinary tract infection in humans was the ADAPT-PO trail. This was a phase 3, randomized, double-blind, noninferiority trial that assessed the safety and efficacy of tebipenem compared to ertapenem in hospitalized patients. Study participants had to be at least 18 years of age or older with a diagnosis of either a complicated urinary tract infection (cUTI) or pyelonephritis. Patients with resistant pathogens, septic shock, immunocompromising conditions, and anaphylaxis to beta lactams and those that had received an antibiotic with the preceding 72 h were excluded from the study. Patients were randomized to receive either 600 mg of tebipenem pivoxil oral tablets every 8 h and a placebo infusion every 24 h or 1 g of ertapenem infused every 24 h along with placebo pills every 8 h. While patients with renal dysfunction at baseline were allowed in the study, those with a creatinine clearance of < 30 mL/min were excluded. For patients with creatinine clearance between 30 and 50 m/L, the tebipenem was dose reduced to 300 mg with no dose reduction in patients that were receiving ertapenem. Patients in both groups were treated for a total of 7–10 days of therapy, or in the presence of bacteremia, up to 14 days. The primary endpoint of this trial was overall response which was defined by researchers as a compositive of clinical cure and microbiologic response. A patient was considered to achieve clinical cure if there was a complete resolution or clinically significant improvement of baseline signs and symptoms. Microbiological response was the reduction of pathogens in the urine to less than 10^3 CFU/mL in post treatment urine culture and a clear blood culture if the patient was bacteremic during the treatment. A total of 1372 patients were included in the study with 868 having microbiological data meeting inclusion criteria. The average age of study participants was 58.1 years; 50.8% of patient presented with cUTI and 49.2% presented with pyelonephritis. Causative organisms were balanced between the two groups with *E. coli* being the predominant organism (64.2%), followed by *K. pneumoniae* (14.3%) and *P. mirabilis* (6.7%). Antimicrobial resistance among Enterobacterales was similar between the tebipenem and ertapenem groups with fluoroquinolone resistance noted to be 40.2% and 37.8%, respectively, and TMP-SMX resistance noted to be 42.4% and 43.5%. ESBL-producing organisms accounted for 26.5% of the tebipenem group, and 22% of the ertapenem group. Those treated with tebipenem received an average of 8.7 ± 1.8 days of antimicrobial therapy and those treated with ertapenem received 8.5 ± 1.9 days. The test of cure (TOC) visit occurred on day 19 of the study ± 2 days. At the TOC visit, tebipenem met the noninferiority margin of 12.5% when compared to ertapenem for overall response (58.5% vs 61.6; − 3.3% difference; 95%CI [− 9.7 to 3.2]). A majority of patients achieved clinical cure by TOC, 93.1% of tebipenem group vs 93.6% of the ertapenem group (% difference 0.6; 95%CI [− 4.0 to 2.8]). Interestingly, there was a numerical difference between treatment arms in patients with ESBL-producing organisms. In this subset, clinical cure at TOC was demonstrated in 87.6% of patients treated with tebipenem compared to 95.3% of patients treated with ertapenem. Secondary endpoints of this study compared clinical cure and microbiological cure at the end of treatment and after the test of cure to determine if there was a recurrence of infection. The last follow-up occurred on day 25 of the study ± 2 days. Similar to the test of cure visit, most of the tebipenem (88.6%) and the ertapenem (90.0%) maintained clinical cure at the late follow-up. Rates of microbiological cure were lower than of clinical cure at each of the follow-up visits. The authors attributed the difference to asymptomatic bacteriuria, and no further antimicrobial was prescribed if a patient did not have persistent urinary symptoms. Of note, while this was a multinational study, < 1% of patients included were from North America [31••].

In 2022, the Food and Drug Administration (FDA) issued a complete response letter to the manufacturer of tebipenem stating that the new drug application (NDA) could not be approved in its current state. The FDA stated that the results of the ADAPT-PO trial were insufficient and additional studies were needed prior to approval [32]. The PIVOT-PO trial (NCT06059846) is a currently proposed multinational phase 3 trial that aims to compare IV imipenem-cilastatin to oral tebipenem for the treatment of cUTI or acute pyelonephritis infections. Patients in the experimental arm will receive tebipenem 500 mg orally, and a placebo infusion and the control group will receive imipenem-cilastatin 500 mg

intravenously and placebo tablets. Interestingly, each dose administration will occur every 6 h in both groups, which differs from the ADAPT-PO study that administered doses every 8 h. At the time of this review, the PIVOT-PO trial was not yet recruiting participants.

Sulopenem Clinical Efficacy

SURE-1 was a randomized double-blind, double-dummy study conducted in women diagnosed with uncomplicated urinary tract infections (uUTI). The primary objective of this study was to compare sulopenem etzadroxil in combination with probenecid to ciprofloxacin. To be included in the study, participants had to be at least 18 years of age and have a urinalysis concerning for a UTI and at least two symptoms of a UTI. Patients in the treatment arm received 500 mg of sulopenem etzadroxil with 500 mg of probenecid twice daily for 5 days or ciprofloxacin 250 mg twice daily for 3 days. The primary endpoint of SURE-1 was overall response to treatment on day 12 with clinical success defined as alive at follow-up, resolution of infection symptoms, no new symptom development, and a repeat urine culture that demonstrated < 10 [SPS:refid::bib2][2] CFU/mL of the pathogen isolated in the urine culture at baseline. The modified intention-to-treat (MITT) population in this study included all patients in the safety population that met study definition of uUTI that was then further divided based on the isolation of a urinary pathogens (mMITT). After randomization, there were a total of 1579 patients in the MITT population and 1071 patients in the mMITT population. Of the pathogens isolated in this study, 26.7% of organisms were resistant to ciprofloxacin at baseline. To account for this substantial baseline resistance, the investigators further divided the study population for analysis based on those with ciprofloxacin-resistant infections (mMITT-R) and those with ciprofloxacin-sensitive infections (mMITT-S). As this was a double-blind study, patients in the mMITT-R population were still treated with ciprofloxacin as their treatment medication was unknown. The rates of ciprofloxacin resistance were similar between the two treatment arms with 29% of the sulopenem groups having resistance versus 25.8% of the ciprofloxacin group. The most common organism isolated in this study was *E. coli*, followed by *K. pneumoniae* and *P. mirabilis*. At the test of cure visit, the overall response rate was similar between the two groups with 66.8% of the sulopenem group achieving success and 67.9% of the ciprofloxacin group achieving success (% difference − 2.3; 95% CI (− 7.9 to 3.3)). As one would imagine, these results changed based on the ciprofloxacin sensitivity. At day 12, the rate of overall success in the mMITT-S population was 66.8% for those treated with sulopenem compared to 78.6% of those treated with ciprofloxacin (% difference − 11.8; 95% CI (− 18.0 to − 5.6)). Conversely, the overall success in the mMITT-R population was 62.6% of the sulopenem treatment arm compared to only 36% of those treated with ciprofloxacin who achieved success (% difference 26.6; 95% CI (15.1–37.4). When evaluating only the clinical success and not accounting for repeat urine cultures, the rates of success at day 12 increased. For infections that were sensitive to ciprofloxacin, the clinical response rate was 81.1% for those treated with sulopenem and 84.1% for those treated with ciprofloxacin (− 3.0; 95%CI (− 8.4 to 2.3)). In the mMITT-R population, 83% of those treated with sulopenem had resolution of symptoms, while 62.6% of those treated with ciprofloxacin had resolution of symptoms at day 12 [33••]. It should not be surprising that the success rate of sulopenem was higher than ciprofloxacin in isolates that were ciprofloxacin-resistant. Fluoroquinolones remain an appropriate agent for the treatment of UTIs, but with nearly one-third of *E. coli* being reported as resistant to the class, sulopenem could represent an alternative treatment option [4].

SURE-2 assessed the role of sulopenem for the treatment of complicated UTI (cUTI) and pyelonephritis in both men and women. This double-blinded randomized control trial was conducted to assess whether sulopenem was non-inferior to other treatments for the management of cUTI. Eligible patients had positive nitrite and pyuria in urine specimens, signs and symptoms of pyelonephritis or cUTI, and a complicating factor to distinguish infection from uUTI. Urine and blood cultures were collected for each patient and urinary organisms present in ≥ 10 [5]. CFU/mL were identified, and susceptibility tests performed. Patients were randomized to receive either IV sulopenem 1000 mg once daily before transitioning to sulopenem etzadroxil 500 mg/probenecid 500 mg twice daily or IV ertapenem 1000 mg once daily followed by oral antibiotics (ciprofloxacin 500 mg twice daily or amoxicillin/clavulanate 875 mg twice daily based on antimicrobial susceptibility of the infecting isolate). Patients had to receive at least 5 days of IV therapy before transitioning to oral options and demonstrate signs of clinical improvement to qualify for the transition. If an appropriate oral agent was not available based on culture sensitivity results, the patient would continue to receive IV treatment. Total treatment duration was set to 7–10 days of therapy but was extended to 14 days in patients that had bacteremia at baseline. The primary endpoint was treatment success defined as clinical and microbiological cure at day 21. Treatment was considered successful if the signs and symptoms present at randomization had resolved, no new signs or symptoms had developed, and the bacteria present in the baseline urine culture had been reduced to $< 10^3$ CFU/mL at day 21. A total of 884 patients were included in the microbiological-modified intention-to-treat population, 444 in the sulopenem arm and 440 treated in the ertapenem arm. Most study participants were female (58.9%), presented with pyelonephritis (58.6%), and had a single pathogen present in baseline urine culture (95.6%).

The most common organisms seen were *E. coli* 76.1% of sulopenem group and 78.6% of the ertapenem group followed by *K. pneumoniae* and *P. mirabilis*. Resistance rates were similar in the sulopenem and ertapenem arms with ESBL noted in 24.7% of the sulopenem arm and 28%% of the ertapenem arm. High rates of resistance were noted in the ertapenem arm with 40% of organisms having fluoroquinolone resistance and 36.6% having TMP-SMX resistance and 17% being resistant to other classes and produce EBSL. The treatment durations were similar between the two arms with the sulopenem arm receiving a median of 5 days of IV therapy and the ertapenem arm receiving 6 days of IV therapy. Both treatment groups received a median of 4 days of oral antibiotics, but more patients were able to transition to oral therapy in the sulopenem arm compared to the ertapenem arm (86.8% vs 66.4%). The inability to transition to an oral agent in the ertapenem arm was driven by the lack of a suitable oral option due to antimicrobial resistance of the causative organism which was not the case in the sulopenem arm. Test of cure that occurred on day 21 of the study demonstrated an overall success rate of 67.8% in the sulopenem group compared to 73.9% in the ertapenem arm (% difference − 6.1; 95% CI (− 12.0 to − 0.1)). Based on these findings, sulopenem did not demonstrate noninferiority to ertapenem based on defined noninferiority margin of 10%. Similar to SURE-1, this study also analyzed the treatment success in ciprofloxacin-sensitive and ciprofloxacin-resistant subpopulations. When ertapenem was stepped down to oral ciprofloxacin (for ciprofloxacin susceptible isolates), the difference in success between sulopenem and ertapenem was much more pronounced (67.7% vs 86.5%; − 18.8; 95% CI (− 26.1 to − 11.0)). However, overall success between the two treatment arms was more comparable when either step down to amoxicillin-clavulanic acid or continued IV therapy was utilized (for ciprofloxacin resistant isolates) (70.4% vs 63.2%; 7.2; 95% CI (− 2.7–16.8)). The inability to demonstrate the noninferiority of sulopenem was primarily due to microbiological failure in the form of asymptomatic bacteriuria. Of patients in the sulopenem arm, 71.2% achieved microbiological success at day 21 compared to 78.0% of the ertapenem arm. This difference in microbiological success was driven by the oral step-down therapy to ciprofloxacin in drug-susceptible isolates. Microbiological failure at day 21 occurred in 21.8% of patients treated with IV and oral sulopenem compared to 4.7% of patients treated with ertapenem and oral ciprofloxacin [34].

SURE-3 (NCT03358576) is a noninferiority trial investigating sulopenem's efficacy in the treatment of complicated intra-abdominal infections. These data have not been published to date and the results described below are based on an abstract presented at a national conference. Patients were eligible for enrolment if they had an intraoperative or post-operative visualization of infection in the abdominal cavity, preoperative enrolment 24 h in advance of abdominal surgery, and physical findings consistent with intra-abdominal infection, and cultures were available from the surgical intervention for organism identification. Patients were randomized to receive either sulopenem 1000 mg IV once daily followed by sulopenem etzadroxil with probenecid 500 mg orally twice daily or ertapenem 1000 mg IV once daily, followed by ciprofloxacin 500 mg by mouth twice daily along with metronidazole 500 mg four times daily. If patients in the ciprofloxacin arm were found to have an organism resistant to ciprofloxacin, therapy was changed to oral amoxicillin clavulanate 875 mg twice daily. Patients were required to receive at least 5 days of IV therapy before transitioning to oral therapy and would receive a total of 7–10 days of antimicrobial therapy. The main endpoint was clinical success at day 28, which was defined as resolution of initial signs and symptoms of infection, no new symptom development, and no need for additional antibiotics or interventions. A total of 674 participants were enrolled, 338 in the sulopenem arm and 336 in the ertapenem arm. Full microbiological data are not currently available as the results of this trial have not yet been published. Preliminary results in the microbiological-modified intention-to-treat population demonstrate that patients in the sulopenem arm ($n = 249$) were less likely to have clinical success at day 28 than patients in the ertapenem arm ($n = 266$), 85.5% and 90.2%, respectively (% difference − 4.7%; 95% CI (− 10.3% to 1.0)). Based on these results, sulopenem failed to meet the noninferiority margin of 10% in this study. Of note, when evaluating patients between days 11 and 14 after enrollment, there was little difference between clinical success rates of sulopenem and ertapenem, 83.5% and 85.5%, respectively. It is uncertain whether there were any factors driving failure in the sulopenem arm as was seen in the SURE-1 and SURE-2 trials.

Similar to the story of tebipenem, the manufacturers of sulopenem received a complete response letter from the FDA in July of 2021 stating the NDA could not be approved. The rational for the rejection was similar with the FDA requesting additional data before the NDA could be approved. In response, a new phase-3 trail (NCT05584657) is currently underway to compare sulopenem etzadroxil/probenecid against oral amoxicillin/clavulanate for the treatment of uUTIs in women. Participants will receive either sulopenem etzadroxil/probenecid 500 mg/500 mg PO twice daily or amoxicillin/clavulanate PO twice daily each for 5 days. At the time of this review, the study had 2,229 patients enrolled with estimated completion in November of 2023.

Adverse Effects and Tolerability

Tebipenem has been well tolerated in several studies. A study evaluating tissue distribution of tebipenem in healthy participants ($n=6$) and patients with diabetic foot infections ($n=6$) reported no serious adverse events in either group of patients. In the healthy subjects, eight adverse reactions were noted: (1) case of a vasovagal episode associated with nausea and vomiting, (2) subjects had abnormal lab results, and (1) subject had a fever and chills. All of these were reported as isolated incidents and normalized/resolved within 24 h. In the diabetic foot cohort, only three adverse events were noted: one case of transient hypokalemia and two cases of leukocytosis, one of which was attributed to another wound infection [27]. The ADAPT-PO study noted 26% of all study participants experienced an adverse reaction of any severity. In the tebipenem arm, 9.3% of patients experienced an adverse event that was related to the medication, none of which was considered serious. By comparison, 6.1% of patients treated with ertapenem experienced drug-related adverse events. The most commonly noted adverse reactions in those treated with tebipenem were diarrhea (5.7%) and headache (3.8%) which were similar to the rates noted in the ertapenem group (4.4% and 3.8%, respectively) [22].

Studies evaluating the safety and efficacy of sulopenem have demonstrated similar adverse events in participants. In SURE-1, 25% of patients in the sulopenem arm experienced some form of adverse reactions compared to only 14% of the comparator arm. These findings were mainly driven by the higher rates of diarrhea noted in those treated with sulopenem (12.4%). No cases of *Clostridioides difficile* were noted in either treatment arm [33••]. Lower rates of adverse reactions were noted in SURE-2. Adverse reactions of any kind were noted in 15.1% of patients treated with sulopenem and 16.4% of participants in the ertapenem arm. Interestingly, the most common adverse reaction noted in the sulopenem group was headache, 3%, and diarrhea only occurred in 2.7% of sulopenem patients [34]. Between these two studies, only 16 patients experienced an adverse event that led to discontinuation of study drug out of 1528 drug exposures.

Conclusion

The rise of antimicrobial resistance is a growing healthcare concern. One of the more prevalent groups in this landscape of drug resistance are the ESBL-producing Enterobacteriaceae. The current standard of care for infections caused by and ESBL-E is the use of intravenously administered carbapenems, which retain their activity against ESBL enzymes [2]. The main drawback with these medications is that they require a person to either remain in a hospital to receive them or coordinate with an outpatient infusion center for a relatively short treatment duration. Oral carbapenems currently in development, tebipenem and sulopenem, could represent an alternative treatment modality for patients with infections caused by ESBL-E that are otherwise stable for discharge. Studies have demonstrated that these new antibiotics have similar spectrum of activity as previous carbapenems and remain active in the presence of ESBL- and AmpC-producing organisms [11–13, 14•, 15, 16, 18, 19]. Studies evaluating the efficacy of these antibiotics are ongoing and have mixed results. Tebipenem was found to be non-inferior to ertapenem treatment [31••]. Studies evaluating sulopenem efficacy for treatment of UTI against ertapenem are split between non-inferior and failing to demonstrate noninferiority, although the rates of ASB at follow-up greatly impact those findings [33••, 34]. These medications could open the door to allowing patient with urinary tract infections cause by ESBL organism to finish therapy at home as opposed to remaining hospitalized. There are ongoing studies for each agent that will hopefully address the clinical significance of these medications for the treatment of UTIs as the current literature is not sufficient for FDA approval. Even so, there are still many unanswered questions about these medications with a lack of available data or analysis of pharmacokinetics and pharmacodynamics. If these new trials demonstrate a benefit in the management of UTIs, more analysis would still be required before these medications could be applied to treatment of other types of infections.

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Compliance with Ethical Standards

Conflict of Interest BRM owns BioCryst stock. JMP reports grants and personal fees from Merck, GlaxoSmithKline, Shionogi, AbbVie, Entasis, and Melinta outside the submitted work. KEB has no conflicts.

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