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COMMENTARY

Oral Antibiotics in Clinical Development for Community-Acquired Urinary Tract Infections

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ABSTRACT

The treatment of urinary tract infections (UTIs) has been complicated by the emergence of multidrug-resistant, β-lactamase-expressing pathogens. As a result of the limited treatment options, patients often require hospitalization and intravenous therapy. In essence, a strong unmet need for oral antibiotics, active against extended-spectrum β-lactamase (ESBL) uropathogens has emerged. Oral carbapenems (tebipenem and sulopenem) and oral cephalosporin/β-lactamase inhibitor combinations are in various stages of clinical development for the treatment of uncomplicated and complicated UTI. Tebipenem, if approved, will be the first oral treatment for complicated UTI while sulopenem will be for uncomplicated UTI. The β-lactamase inhibitors ETX0282, VNRX7145, ARX1796, and QPX7728 are combined with cefpodoxime proxetil or ceftibuten that achieve favorable exposures in urine compared to other uropathogen-active oral cephalosporins. The combination ceftibuten-QPX7728 has potential broad-spectrum coverage against carbapenemase producers including metallo β-lactamase producers. Other novel combinations, namely cefpodoxime/ETX0282, ceftibuten/VNRX-7145, and ceftibuten/ARX1796, have also demonstrated excellent activity against *Klebsiella pneumoniae* carbapanemase (KPC) and OXA-48-like producers. All these agents, upon their arrival for commercial use, would strengthen the outpatient therapy.

Keywords: Ceftibuten; Cefpodoxime; Tebipenem; Sulopenem; ETX0282; VNRX7145; ARX1796; QPX7728

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Key Summary Points

The treatment of urinary tract infections (UTIs) has been complicated by the emergence of multidrug-resistant and extended-spectrum β-lactamase (ESBL)-expressing Gram-negative pathogens.

Oral carbapenems (tebipenem and sulopenem) and oral cephalosporin/β-lactamase inhibitor combinations are in various stages of clinical development for treating UTIs.

Recently tebipenem and sulopenem have completed phase III trials. Tebipenem, if approved, will be the first oral treatment for complicated UTI while sulopenem will be for uncomplicated UTI.

The combinations cefpodoxime/ETX0282, ceftibuten/VNRX-7145, and ceftibuten/QPX7728 are in phase I development. All these agents, upon their arrival for commercial use, would strengthen the outpatient therapy.

INTRODUCTION

Pharmaceutical organizations that are in antibiotic discovery research prioritize their projects on the basis of evolving antibiotic resistance epidemiology. For instance, the emergence and spread of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and macrolide-resistant *Streptococcus pneumoniae* during 1980s and 1990s compelled these organizations to focus on discovery of novel agents to tackle these Gram-positive pathogens. Emphasis on Gram-negative pathogens that we witness today started when carbapenem-resistant *Klebsiella pneumoniae* through expression of a serine carbapenemase (KPC) was reported in New York during the 2000s [1]. Needless to say, extended-spectrum β-lactamases (ESBLs) and class C β-lactamases in Enterobacterales were a problem even before, but the former are addressed by piperacillin/tazobactam to some extent and carbapenems while the latter are addressed by carbapenems alone [2].

In the last decade, we experienced global spread of KPCs and also other carbapenemases, viz., New Delhi metallo β-lactamases and OXA-β-lactamases [3]. What we have failed to notice is the quiet increase in ESBL pathogens in community-onset urinary tract infection (UTI), a condition usually managed by oral antibiotics such as nitrofurantoin, trimethoprim/sulfamethaxozole, quinolones, and oral cephalosporins. The fact that these uropathogens carrying ESBLs (thus resistant to oral cephalosporins) have acquired resistance to the aforementioned non-β-lactam antibiotics (Table 1) is challenging for treatment [31]. As a result, in today's scenario, in the USA alone, huge numbers of patients with UTIs are hospitalized because of the failure of oral antibiotics and left with intravenous antibiotic options [32, 33]. In these cases, even piperacillin/tazobactam is often not active because of widely prevalent class C and OXA-1 β-lactamases, thus forcing carbapenem use [2]. In essence, a strong unmet need for oral antibiotics that are active against ESBL uropathogens has emerged. Moreover, with an additional activity against carbapenem-resistant uropathogens, these oral drugs can be used as step-down for hospital-treated patients with UTIs, enabling early hospital discharge. In this review, we describe the profile and status of novel oral antibiotics in clinical development. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CARBAPENEMS

Historically, discovering an orally bioavailable carbapenem remained a challenge to medicinal chemists. Initially, the aim was to develop a carbapenem for outpatient treatment of community-origin lower respiratory infections. With this thinking, faropenem was developed and approved in Japan. In the USA, a prodrug of

Table 1 Epidemiology of community-acquired urinary tract infections caused by ESBL-producing bacteria reported across the globe

Location	Duration of the study	Study (age groups)	Organisms (*n*)	ESBL producers (%)	Resistance (%) reported to				References
					Nitrofurantoin	Fosfomycin	Co-trimoxazole	Ciprofloxacin	
USA	2000–2010	Surveillance study (NA)	*E. coli* (12,253,679)	2.1	0.8	NA	6.3	14.1	[4]
USA	2011–2019	Retrospective study (≥ 12 years)	*E. coli* (1,513,882)	6.4	3.8	NA	25.4	21.1	[5]
Egypt	2016–2018	Observational study (≥ 18 years)	*E. coli* (134)	59.7	NA	NA	76	13.7	[6]
Mexico	NA	Observational study (NA)	*E. coli* (240) *K. pneumoniae* (14) *P. aeruginosa* (6) *P. mirabilis* (4) *C. freundii* (3) *S. marcescens* (1)	*E. coli* (26) *K. pneumoniae* (NA)	ESBL *E. coli* (1.3)	ESBL *E. coli* (6.6)	ESBL *E. coli* (53)	ESBL *E. coli* (89)	[7]
India	2012–2018	Retrospective study (≤ 18 years)	ESBL-producing bacteria (240)	*E. coli* (93) *K. pneumoniae* (5.2) *K. oxytoca* (0.8) *P. mirabilis* (0.8)	*E. coli* (1.5) *K. pneumoniae* (0.8)	*E. coli* (1.7) *K. pneumoniae* (1.7)	*E. coli* (68.8) *K. pneumoniae* (3.1)	*E. coli* (47.3) *K. pneumoniae* (2.3)	[8]
Germany	2010	Surveillance study (NA)	*E. coli* (499)	8	NA	1.2	30.9	19.8	[9]
France	2015–2017	Surveillance study	*E. coli* (658) *Klebsiella* spp. (42) *P. mirabilis* (25) *C. koseri* (12) *Enterobacter* spp. (12)	Overall ESBL producers (4.9)	NA	NA	NA	NA	[10]
Romania	2018	Surveillance study (NA)	*E. coli* (787)	9	3	NA	24.3	14.9	[11]
Netherlands	2004–2009 and 2014–2015	Surveillance study (NA)	*E. coli* (446)	2.2	1	0	19	6	[12]

Table 1 continued

Location	Duration of the study	Study (age groups)	Organisms (*n*)	ESBL producers (%)	Resistance (%) reported to				References
					Nitrofurantoin	Fosfomycin	Co-trimoxazole	Ciprofloxacin	
England	2017–2018	Surveillance study	Cefotaxime-resistant *E. coli* (576)	100	7	NA	NA	56.9	[13]
France	2015–2017	Surveillance study	*E. coli* (358,291)	3.3	NA	NA	NA	NA	[14]
Australia	2009–2013	Surveillance study	*E. coli* (4492)	3.7	NA	NA	NA	6.4	[15]
India	2009 and 2014	Retrospective study (< 17 years)	*E. coli* (420) *K. pneumoniae* (66) *K. oxytoca* (24) *P. mirabilis* (30) *P. vulgaris* (26) *C. freundii* (18) *C. koseri* (6) *Morganella* spp. (4) *Pseudomonas* spp. (67) *Acinetobacter* spp. (8) *Serratia* spp. (2)	Overall ESBL producers (33.1)	*E. coli* (43)	NA	*E. coli* (88)	NA	[16]
India	2010–2011	Retrospective study (14–72 years)	*E. coli* (161) *K. pneumoniae* (40) *P. aeruginosa* (13) *P. mirabilis* (12)	*E. coli* (84.5) *K. pneumoniae* (35) *P. aeruginosa* (31.5) *P. mirabilis* (100)	NA	NA	NA	*E. coli* (80.7) *K. pneumoniae* (50) *P. aeruginosa* (23.1) *P. mirabilis* (58.3)	[17]

Table 1 continued

Location	Duration of the study	Study (age groups)	Organisms (*n*)	ESBL producers (%)	Resistance (%) reported to				References
					Nitrofurantoin	Fosfomycin	Co-trimoxazole	Ciprofloxacin	
India	2017	Surveillance study (NA)	*E. coli* (131) *K. pneumoniae* (47) *Pseudomonas* spp. (6) *Proteus* spp. (12) *Enterobacter* spp. (2)	*E. coli* (46.6) *K. pneumoniae* (NA0) *Pseudomonas* spp. (NA) *Proteus* spp. (NA) *Enterobacter* spp. (NA)	ESBL *E. coli* (29.5)	NA	ESBL *E. coli* (86.9)	ESBL *E. coli* (88.5)	[18]
Africa	2015–2019	Descriptive cross-sectional study (15–49 years)	*E. coli* (1994) *K. pneumoniae* (193) *P. mirabilis* (179)	*E. coli* (7) *K. pneumoniae* (9) *P. mirabilis* (1)	*E. coli* (5) *K. pneumoniae* (60) *P. mirabilis* (NA)	NA	*E. coli* (62) *K. pneumoniae* (35) *P. mirabilis* (51)	*E. coli* (12) *K. pneumoniae* (4) *P. mirabilis* (1)	[19]
Paris	2014–2015	Prospective study (18–102 years)	*E. coli* (791) *Klebsiella* spp. (95) *Proteus* spp. (70) *Citrobacter* spp. (46)	ESBL-producing Enterobacterales (4.2)	*E. coli* (1.1)	*E. coli* (1.6)	NA	*E. coli* (15.5)	[20]
Iran	2012–2013	Observational study (≥ 18 years)	*E. coli* (154)	40	3.9	NA	57.8	47.4	[21]
Greece	2008–2014	Surveillance study (NA)	*E. coli* (170) *Klebsiella* spp. (15) *Proteus* spp. (17) *P. aeruginosa* (9) *Enterobacter* spp. (2) *M. morgannii* (2) *S. fonticola* (2)	*E. coli* (3) *Klebsiella* spp. (7) *Proteus* spp. (100) *P. aeruginosa* (9) *Enterobacter* spp. (2) *M. morgannii* (2) *S. fonticola* (2)	*E. coli* (3.1) *Klebsiella* spp. (38.5) *Proteus* spp. (NA) *P. aeruginosa* (NA)	NA	*E. coli* (24.7) *Klebsiella* spp. (6.1) *Proteus* spp. (38.5) *P. aeruginosa* (NA)	NA	[22]
Peru	2015	Retrospective study (≥ 18 years)	*E. coli* (172)	40.8	NA	NA	NA	NA	[23]

Table 1 continued

Location	Duration of the study	Study (age groups)	Organisms (*n*)	ESBL producers (%)	Resistance (%) reported to				References
					Nitrofurantoin	Fosfomycin	Co-trimoxazole	Ciprofloxacin	
Spain	2015 and 2016	Retrospective study (≤ 14 years)	*E. coli* (229)	9.2	ESBL *E. coli* (0)	ESBL *E. coli* (9.5)	ESBL *E. coli* (62)	ESBL *E. coli* (71.4)	[24]
Sri Lanka	2016–2017	Descriptive cross-sectional study	*E. coli* (149) *K. pneumoniae* (16) *Enterobacter* spp. (2) *Proteus* spp. (2) *P. aeruginosa* (2)	*E. coli* (46) *K. pneumoniae* (25) *Enterobacter* spp. (NA) *Proteus* spp. (NA) *P. aeruginosa* (NA)	NA	NA	NA	NA	[25]
Japan	2017–2018	Retrospective study	*E.coli* (135) *K. pneumoniae* (22) *P. aeruginosa* (8) *P. mirabilis* (4) *E. cloacae* (3) *P. rettgeri* (3) *S. marcescens* (2) *Citrobacter* spp. (2)	*E. coli* (63)	NA	NA	*E. coli* (90) *K. pneumoniae* (91) *P. aeruginosa* (0) *P. mirabilis* (50) E. cloacae (100) *P. rettgeri* (100) *S. marcescens* (50) *Citrobacter* spp. (100)	*E. coli* (68) *K. pneumoniae* (100) *P. aeruginosa* (88) *P. mirabilis* (100) E. cloacae (100) *P. rettgeri* (100) *S. marcescens* (100) *Citrobacter* spp. (100)	[26]

Table 1 continued

Location	Duration of the study	Study (age groups)	Organisms (*n*)	ESBL producers (%)	Resistance (%) reported to				References
					Nitrofurantoin	Fosfomycin	Co-trimoxazole	Ciprofloxacin	
Korea	2012–2016	Retrospective study	*E. coli* (911) *Klebsiella* spp. (38) *Enterobacter* spp. (27) *Proteus* spp. (11) *Citrobacter* spp. (4) *Pseudomonas* spp. (8) *S. marcescens* (3)	ESBL-producing Enterobacterales (11.3)	NA	NA	NA	NA	[27]
Europe	2013–2014	Surveillance study	*E. coli* (538) *K. pneumoniae* (196) *K. oxytoca* (45) *P. mirabilis* (234)	ESBL-producing Enterobacterales (74)	*E. coli* (0.4) Others (NA)	*E. coli* (1.3) *K. pneumoniae* (33.2) *K. oxytoca* (31) *P. mirabilis* (26.1)	*E. coli* (21.4) *K. pneumoniae* (9.2) *K. oxytoca* (2.2) *P. mirabilis* (30.3)	*E. coli* (23.4) *K. pneumoniae* (6.6) *K. oxytoca* (4.4) *P. mirabilis* (15.8)	[28]
Poland	2013	Surveillance study	*E. coli* (272) *Klebsiella* spp. (37)	*E. coli* (4.8) *Klebsiella* spp. (46.2)	*E. coli* (36)	*E. coli* (33.6)	*E. coli* (35)	*E. coli* (34.2)	[29]
Brazil	2015	Surveillance study	*E. coli* (499)	8	5	NA	30	20	[30]

Escherichia coli E. coli, *Klebsiella pneumoniae K. pneumoniae*, *Klebsiella oxytoca K. oxytoca*, *Enterobacter cloacae E. cloacae*, *Citrobacter freundii C. freundii*, *Citrobacter koseri C. koseri*, *Pseudomonas aeruginosa P. aeruginosa*, *Proteus mirabilis P. mirabilis*, *Proteus vulgaris P. vulgaris*, *Serratia marcescens S. marcescens*, *Serratia fonticola S. fonticola*, *Morganella morgannii M. morgannii*, *Providencia rettgeri P. rettgeri*, *NA* Not available

Table 2 Spectrum of activity of oral antibiotics against Gram-negative pathogens causing community-acquired urinary tract infections

Oral antibiotics	Activity spectrum				
	ESBLs	ampC	CRE		
			KPC	MBL	OXA-48-like
Tebipenem pivoxil hydrobromide	✔	✔	X	X	X
Sulopenem-etzadroxil/probenecid	✔	✔	X	X	X
Cefpodoxime/ETX0282	✔	✔	✔	X	✔
Ceftibuten/VNRX-7145	✔	✔	✔	X	✔
Ceftibuten/ARX1796	✔	✔	✔	X	✔
Ceftibuten/ QPX7728	✔	✔	✔	✔	✔

✔ active, *X* not active, *ESBL* extended-spectrum β-lactamases, *ampC* class C cephalosporinase, *KPC K. pneumoniae* carbapanemases, *MBL* metallo β-lactamases, *OXA-48* oxacillinase, *CRE* carbapenem-resistant Enterobacterales, *CRPA* carbapenem-resistant *P. aeruginosa*, *CRAB* carbapenem-resistant *A. baumannii*

faropenem was developed but ran into regulatory hurdles and was never approved by the US Food and Drug Administration (FDA) [34]. Subsequently, interest in this area waned but returned as resistance to first-line oral antibiotics has increased to a substantial level among community Gram-negative infections. The spectrum of activity of oral carbapenems is given in Table 2. The pharmacokinetic characteristics and in vitro activity of oral carbapenems against urinary isolates of ESBL-producing Enterobacterales are given in Table 3. Two oral carbapenems, tebipenem and sulopenem, have been evaluated in phase 3 studies for the treatment of UTIs (Table 4).

Tebipenem

Tebipenem pivoxil (TBPM-PI) an orally administered prodrug of tebipenem, marketed in Japan by Meiji Seika Pharma Co., Ltd for the treatment of otitis media, sinusitis, and pneumonia in pediatric patients [44]. This oral formulation was not marketed for adult patients. A new formulation for adults consisting of tebipenem pivoxil hydrobromide (TBPM-PI-HBr) salt was designed by Spero Therapeutics to improve the drug substance and drug product properties such as stability [45]. TBPM-PI-HBr is being developed by Spero Therapeutics for the treatment of complicated UTI (cUTI) including acute pyelonephritis (AP). The drug is being promoted as potential treatment option for cUTI caused by Enterobacterales resistant to first-line oral agents, nitrofurantion, sulfamethaxazole/trimethoprim, fluoroquinlones, and oral cephalosporins. It is not active against carbapenem-resistant Enterobacterales.

Tebipenem is highly hydrophilic, which significantly limits its oral absorption. In the past, prodrug strategies have been employed to improve the oral bioavailability of many β-lactam antibiotics. The prodrug TBPM-PI-HBr rapidly gets converted to active tebipenem in the plasma and enterocytes [46]. The pharmacokinetic analysis of single and multiple ascending oral doses of TBPM-PI-HBr indicates that a dose regimen 600 mg q8h provides bioavailability in the range of 50–60% [47]. However, the protein binding of tebipenem (98.7%) is likely higher than ertapenem (90–95%) [48]. Approximately 55–60% of the total tebipenem dose is recovered in the urine as an intact drug, which is 50–100-fold greater than that of free plasma tebipenem concentration [47]. Consequently, such a high urine exposure makes it suitable for the treatment of UTIs.

Table 3 Pharmacokinetic characteristics, MIC_{90} and MIC range of new oral antimicrobials against ESBL- and carbapenemase-producing Enterobacterales

Antibiotics (formulations)	Pharmacokinetic characteristics			Organisms (*n*)	MIC_{90} (mg/L)	MIC range (mg/L)	References
	Plasma binding protein (%)	Oral bioavailability (%)	Urinary concentration (%)				
Tebipenem pivoxil hydrobromide (oral)	60–70%	50–60%	55–60%	ESBL-positive Enterobacterales (118)	0.25	0.03–0.25	[35]
				ESBL-positive *E. coli* (175)	0.03	0.008–0.5	[36]
Sulopenem-etzadroxil/ probenecid (oral and IV)	11%	NA	NA	ESBL-positive *E. coli* (49)	0.06	0.03–0.12	[37]
Cefpodoxime/ETX0282 (oral)	Cefpodoxime (21–29%)	Cefpodoxime (50%)	Cefpodoxime (29–33%)	ESBL-positive Enterobacterales (303)	2	0.06–4	[38]
	ETX1317 (NA)	ETX1317 (NA)	ETX1317 (NA)	ESBL-positive *E. coli* (301)	0.12	≤ 0.015–4	[39]
				ESBL-positive *Klebsiella* spp. (306)	1	0.06–16	
				ESBL-positive *Citrobacter* spp. (120)	0.5	0.03–16	
				ESBL-positive *Enterobacter* spp. (90)	1	0.06–4	
				ESBL-positive *Proteus* spp. (93)	1	≤ 0.015–32	

Table 3 continued

Antibiotics (formulations)	Pharmacokinetic characteristics			Organisms (*n*)	MIC_{90} (mg/L)	MIC range (mg/L)	References
	Plasma binding protein (%)	Oral bioavailability (%)	Urinary concentration (%)				
Ceftibuten/VNRX-7145 (oral)	Ceftibuten (65%) VNRX5236 (NA)	Ceftibuten (75–90%) VNRX5236 (NA)	Ceftibuten (57–59%) VNRX5236 (NA)	Enterobacterales (205)	1	≤ 0.015 to > 32	[40]
				ESBL-producing Enterobacterales (50)	0.12	≤ 0.015 to > 32	
				KPC-producing Enterobacterales (50)	0.5	≤ 0.015–8	
				OXA-48-like-producing Enterobacterales (50)	1	≤ 0.015 to > 32	
				Enterobacterales (1066)	2	≤ 0.25 to > 32	[41]
				ESBL-positive Enterobacterales (634)	0.5	≤ 0.25 to > 32	
				KPC-positive Enterobacterales (61)	2	≤ 0.25–32	
Ceftibuten/ARX-1796 (oral)	ARX-1796 (NA)	ARX-1796 (NA)	ARX-1796 (NA)	ESBL-producing Enterobacterales (50)	0.06	≤ 0.03–0.12	[42]
Ceftibuten/QPX7728 (oral and IV)	Ceftibuten (65%) QPX7728 (NA)	Ceftibuten (75–90%) QPX7728 (NA)	Ceftibuten (57–59%) QPX7728 (NA)	*E. coli* (92)	≤ 0.015	NA	[43]

NA Not available

Table 4 New oral antimicrobials and their stage of clinical development

Antibiotics (sponsoring pharmaceutical company)	Potential indications	Clinical phase of development	Doses and duration of new oral antimicrobials	Comparator dose and duration	Healthy volunteers/patients (*n*)	Clinical cure	Findings
Carbapenems							
Tebipenem pivoxil hydrobromide (Spero Therapeutics)	Complicated UTI	Phase I (NCT03395249)	SAD: 100–900 mg q8h for 14 days Multiple ascending doses (300 or 600 mg) q8h for 14 days	None	Healthy subjects (124)	–	Evaluation of SAD and MAD revealed that AUC was more than twofold greater on day 1 (2.7-fold) and day 14 (2.5-fold) for 600 mg q8h than for 300 mg q8h
		Phase I (NCT04178577)	600 mg single dose	None	Patients with renal impairment (39)	–	Completed, awaiting for results
		Phase III ADAPT-PO trial (NCT03788967)	600 mg q8h for 7–10 days	Ertapenem IV: 1 g q24h for 7–10 days	Patients with cUTI or acute pyelonephritis (1372)	Tebipenem (58.8%) Ertapenem (61.6%)	Tebipenem is non-inferior to ertapenem IV

Table 4 continued

Antibiotics (sponsoring pharmaceutical company)	Potential indications	Clinical phase of development	Doses and duration of new oral antimicrobials	Comparator dose and duration	Healthy volunteers/patients (*n*)	Clinical cure	Findings
Sulopenem-etzadroxil/probenecid (Iterum Therapeutics)	Uncomplicated UTI	Phase III SURE-1 trial (NCT03354598)	500 mg twice daily for 5 days	Ciprofloxacin: 250 mg twice daily for 3 days	Patients with uncomplicated UTI (1617)	Sulopenem (65.6%) Ciprofloxacin (67.9%)	Sulopenem is non-inferior to ciprofloxacin
	Complicated UTI	Phase III SURE-2 trial (NCT03357614)	Sulopenem 1 g IV once daily for 5 days followed by sulopenem-etzadroxil/probenecid 500 mg twice daily for 7–10 days	Ertapenem IV: 1 g q24h for 5 days followed by ciprofloxacin 500 mg twice daily for 7–10 days	Patients with complicated UTI (1395)	Sulopenem (67.7%) Ciprofloxacin (86.5%)	Sulopenem is inferior to ertapenem
β-Lactam and β-lactamase inhibitors							
Cefpodoxime/ETX0282 (Entasis Therapeutics)	Complicated UTI	Phase I (NCT03491748)	Single ascending doses (SAD: 100–800 mg)	None	Healthy subjects (99)	–	Completed, awaiting for results
Ceftibuten/VNRX-7145 (Venatorx)	Complicated UTI	Phase I (NCT04243863)	NA	None	Healthy subjects (83)	–	Completed, awaiting for results
Ceftibuten/ARX-1796 (Pfizer)	–	Preclinical		–	–	–	–

Table 4 continued

Antibiotics (sponsoring pharmaceutical company)	Potential indications	Clinical phase of development	Doses and duration of new oral antimicrobials	Comparator dose and duration	Healthy volunteers/patients (*n*)	Clinical cure	Findings
Ceftibuten/QPX7728 (Qpex Biopharma)	Complicated UTI	Phase I (NCT04380207)	NA	None	Healthy subjects (64)	–	Recruiting participants

AUC area under the curve, *cUTI* complicated urinary tract infection, *MAD* multiple ascending dose, *SAD* single ascending dose, *NA* Not available

Of late 2020, tebipenem HBr completed a phase III trial [ADAPT-PO trial (NCT03788967)] for the treatment of cUTI in adults (Table 4). In the ADAPT-PO trial, orally administered tebipenem HBr (600 mg, q8h; 1.8 g/day) showed non-inferiority to intravenously administered ertapenem (1 g, q24h) both administered for a total of 7–10 days [49]. Tebipenem HBr is well tolerated with a safety profile similar to that of ertapenem. This was the first-ever phase 3 study that evaluated an all-oral treatment for cUTI indication. The company is likely to file the new drug application in the second half of 2021. If approved, tebipenem HBr would be the first oral carbapenem to receive marketing approval for the indication of cUTI in the USA. Tebipenem can be used as a first-line or second-line therapy for those patients who failed with oral antibiotics for community-onset UTIs. However, oral administration of tebipenem HBr may promote the risk of selecting carbapenem resistance and may also have an impact on intestinal flora.

Sulopenem

Sulopenem (formerly CP-70429) is not a classic carbapenem but rather a thiopenem discovered in Pfizer's Japanese laboratories [50]. Sulopenem and its oral prodrug sulopenem etzadroxil (PF-03709270) underwent phase 2 study (NCT00797108; intravenous plus oral step-down) for the indication of community-acquired pneumonia in 2009 but the development was discontinued apparently because of high development costs and market return concerns. In late 2015, Iterum Therapeutics plc (Dublin, Ireland) in-licensed sulopenem and its prodrug from Pfizer and are developing novel therapies for UTI and intra-abdominal infections [51]. Orally administered sulopenem etzadroxil (500 mg) was combined with probenecid (500 mg) as a bilayer tablet to improve the drug half-life and thereby the plasma concentration [52]. Unlike tebipenem, sulopenem shows a low protein binding (11%) [53]. Its antibacterial spectrum is similar to that of ertapenem—it is active against ESBL/class C-expressing Enterobacterales and lacks activity against Gram-negative non-fermenters.

Unsurprisingly, it is not stable to carbapenemases. Iterum undertook three phase 3 studies for sulopenem (Table 4). Sulopenem etzadroxil 500 mg/probenecid 500 mg is the first antibiotic evaluated for the indication of uncomplicated UTI [53]. It should be noted that until recently, there has been no FDA guideline for the conduct of phase 3 study for the indication of uncomplicated UTI. In the all-oral therapy study (SURE-1), sulopenem etzadroxil 500 mg/probenecid 500 mg, q12h for 5 days demonstrated non-inferiority to ciprofloxacin 250 mg, q12h for 3 days [54]. However, in the phase 3 studies for the indication of cUTI (SURE-2) and complicated intra-abdominal infections (SURE-3), a 5-day once-daily 1 g, 2-h infusion, IV sulopenem followed by orally administered sulopenem etzadroxil 500 mg/probenecid 500 mg, q12h step-down failed to meet the non-inferiority margin for the primary endpoint [55]. In both studies, the comparator was ertapenem 1 g, q24h, IV for 5 days followed by an oral step-down therapy.

Iterum submitted the new drug application to the FDA in December 2020 for the approval of sulopenem oral prodrug formulation for the indication of uncomplicated UTI.

NOVEL B-LACTAM AND B-LACTAMASE INHIBITORS

The challenge in discovering orally bioavailable β-lactams is evident from the reality that there is only a single oral β-lactamase inhibitor, clavulanic acid, in clinical use [56]. The combination of amoxicillin and clavulanic acid is generally not preferred for UTI for two reasons: (1) the concentration of intact clavulanic acid eliminated in the urine is low and (2) clavulanic acid is not an inhibitor of class C (and also an inducer) and OXA-1 enzymes commonly associated with ESBL uropathogens [57]. Combining clavulanic acid with an oral cephalosporin was attempted (ceftibuten + clavulanic acid) which is certainly a better combination than amoxicillin + clavulanic acid [58]. Entasis seems to be the first company that ventured into discovering a prodrug of diazabicyclooctane with good oral bioavailability. A few more companies joined the race and one objective that is common among them is to develop an oral β-lactamase inhibitor with an expanded spectrum of activity against ESBLs, class C, and carbapenemases (Tables 2 and 3). These β-lactamase inhibitors are combined with cefpodoxime proxetil or ceftibuten (Table 4), the two oral cephalosporins that achieve favorable exposures in urine compared to other Gram-negative uropathogens–active oral cephalosporins, cefuroxime axetil and cefixime. All these oral β-lactam and β-lactamase inhibitors are undergoing phase I clinical trials (Table 4), except ceftibuten/ARX-1796 which is at the preclinical stage of development.

Cefpodoxime/ETX0282

Cefpodoxime proxetil is an orally administered prodrug which is absorbed and de-esterified by the intestinal mucosa to release the active metabolite cefpodoxime with 50% systemic bioavailability [59]. Approximately 29–33% of the administered cefpodoxime dose is eliminated unchanged by renal excretion, which makes it as a suitable drug for treating UTIs [60]. Cefpodoxime proxetil has been approved by FDA for multiple indications that include community-origin upper and lower respiratory infections, uncomplicated skin and skin structure infections, and uncomplicated UTI (cystitis). The highest recommended total daily dose is 800 mg of active cefpodoxime (400 mg, q12h) [60].

ETX0282 is a prodrug of ETX1317, a novel diazabicyclooctane-based inhibitor of class A, C, and D β-lactamases [61]. Thus the combination ETX1317 and cefpodoxime is active against ESBL/class C/KPC-expressing Enterobacterales excluding metallo β-lactamases (Table 3). ETX1317 also has some PBP2 binding and therefore shows standalone activity mainly against *E. coli* with MICs in the range of 0.5 to 1 mg/L [62]. Owing to this standalone activity, the MIC of cefpodoxime/ETX 1317 is determined at 1:2 ratio, rather than using a fixed 4 mg/L as in the case of other β-lactam and β-lactamase inhibitor combinations [35]. The originator is Entasis Therapeutics Ltd.,

(Massachusetts, USA) and presently the combination is in phase 1 development.

The current susceptible breakpoint of cefpodoxime for Enterobacterales is 2 mg/L. In a global surveillance study, against 1875 Enterobacterales isolated from patients with UTIs, cefpodoxime/ETX 1317 showed $MIC_{50/90}$ of 0.06/0.12 mg/L [36]. Against ESBL- and ampC-producing Enterobacterales subsets, $MIC_{50/90}$ values of this combination were 0.12/0.25 and 0.25/1 mg/L, respectively [35]. Thus, in sum, the MIC_{90} of cefpodoxime/ETX1317 remained below the current cefpodoxime breakpoint of 2 mg/L for class A, C, and D-expressing β-lactamases.

The preliminary phase I results (Table 4) showed rapid absorption of ETX0282 tested at various doses (100–800 mg), plasma concentrations were reported to be in the expected therapeutic range, and there was no drug–drug interaction between ETX0282 and cefpodoxime proxetil [63]. Generally, ETX0282 is well tolerated either alone or in combination with cefpodoxime proxetil, with no serious adverse events, though mild to moderate emesis has been documented. Additional studies are warranted to further investigate the potential correlation between absorption profile and emesis and to formulate ETX0282 for further clinical development. The bioavailability of ETX0282 observed from the phase 1 studies has not been reported. In preclinical species (rat, dog, and monkey) it showed at least 78% bioavailability [64].

If cefpodoxime proxetil/ETX0282 is developed successfully, we think its main usage would be for the outpatient management of patients with UTIs and suspected or confirmed ESBL pathogen who do not respond to first-line oral agents. The reason is extremely low prevalence of CREs in the community setting.

Ceftibuten/VNRX-7145

Ceftibuten was originally approved by the FDA for the treatment of acute exacerbations of chronic bronchitis, acute otitis media, and pharyngitis caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* in 1995. However, it is not approved in European countries. Ceftibuten is chosen off-label for the treatment of UTI; however, no dosing recommendations exist. Ceftibuten is rapidly absorbed (75–90%) from the gastrointestinal tract in its active form following oral administration, of which 65% binds to plasma proteins [65]. It has a half-life of 2.5 h and eliminated mainly in urine (57–59%) and feces (39%) [66]. Ceftibuten has an excellent systemic exposure following oral doses and adequately achieves its pharmacokinetics (PK) target.

VNRX-7145 is a novel cyclic boronate β-lactamase inhibitor with potent inhibitory activity against class A, C, and D β-lactamases [67]. In vivo, VNRX-7145 undergoes biotransformation to an active inhibitor, VNRX-5236 [68]. It is being developed in combination with ceftibuten as an oral therapy by VenatoRx Pharmaceuticals, Inc. (Pennsylvania, USA). The combination of VNRX-5236 with ceftibuten was tested against a collection of 205 Enterobacterales isolates and showed a $MIC_{50/90}$ of 0.12/1 mg/L [37]. This combination also retained its potent activity against KPC ($MIC_{50/90}$, 0.12/0.5 mg/L) and OXA-48-like producers ($MIC_{50/90}$, 0.25/1 mg/L) [37]. This MIC data suggests that addition of VNRX-5236 maintains twofold lower MICs, compared to ceftibuten susceptibility breakpoint (≤ 2 mg/L).

In combination with ceftibuten, the $fAUC_{0–24}$/MIC is the PK/pharmacodynamics (PD) index that appeared to drive in vivo efficacy of VNRX-5236 [69]. Furthermore, addition of VNRX-7145 to ceftibuten significantly reduced bacterial burden in a murine UTI model using ESBL- and KPC-2-producing *E. coli* and in a murine thigh infection model using OXA-48- and KPC-producing Enterobacterales. A phase I trial (NCT04243863) is currently enrolled to assess the safety and PK of VNRX-7145 using single and multiple ascending doses (Table 4).

Since VNRX-7145 is not an inhibitor of MBL, the anticipated therapeutic spectrum of ceftibuten/VNRX-7145 combination is comparable to that of cefpodoxime/ETX0282.

Ceftibuten/ARX1796

Avibactam is a potent DBO inhibitor of class A, C, and some D β-lactamases approved for IV dosing in combination with ceftazidime by the FDA in 2015, but the oral bioavailability of avibactam is negligible (ca. 7%) [70]. To expand the clinical utility of avibactam, Arixa Pharmaceuticals (Palo Alto, CA, USA) has discovered a novel orally administered avibactam prodrug (ARX-1796/AV-006) [71]. The prodrug ARX-1796 has been shown to have an oral bioavailability of 60–80% in phase 1 studies [72]. The oral β-lactams ceftibuten, cefixime, amoxicillin, cefpodoxime, sulopenem, and tebipenem were evaluated in combination with ARX-1796 against Enterobacterales expressing ESBL, ampC, KPC, and OXA-48-like [73]. Ceftibuten with ARX-1796 showed lower MICs compared to other combinations. Addition of ARX-1796 to ceftibuten retained its potent activity against KPC and OXA-48-like producers with the low $MIC_{50/90}$ of 0.06/0.5 mg/L and 0.06/0.25 mg/L, respectively [39]. Interestingly, pharma giant Pfizer took over Arixa Pharmaceuticals recently.

Ceftibuten/QPX7728

QPX7728 is an ultrabroad-spectrum boronic acid β-lactamase inhibitor being developed by Qpex Biopharma (San Diego, USA) [74]. Ceftibuten with QPX7728 and meropenem with QPX7728 are in clinical development as an oral and intravenous formulation, respectively [75]. Unlike other orally bioavailable β-lactamase inhibitors (ETX0282, VNRX1745, ARX1796), QPX7728 inhibits serine and metallo β-lactamases of classes A, B, C, and D in Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.

Tebipenem and cefibuten were evaluated in combination with QPX7728 against Enterobacterales with varying resistance mechanisms. Tebipenem-QPX7728 ($MIC_{50/90}$, ≤ 0.06/2 mg/L) is more potent than ceftibuten-QPX7728 combination ($MIC_{50/90}$, 0.25/16 mg/L); however, impermeability decreases the potency of tebipenem-QPX7728 [76].

In preclinical species, QPX7728 has oral bioavailability of 43–53%; however, saturation is likely to be expected with higher doses. QPX7728 is about 89% plasma protein-bound [77]. Approximately 64% of the QPX7728 dose was recovered unchanged in the urine [78]. A phase I study (NCT04380207) is currently underway to assess the safety and PK of QPX7728 alone following single and multiple intravenous doses, and in combination with a β-lactam antibiotic.

CONCLUSION

The ongoing pandemic reiterates the need for best use of hospital resources and to achieve this target, it is necessary to minimize avoidable hospitalization. Since the time Gram-negative pathogens emerged as problematic pathogens because of antibiotic resistance, the focus remained mainly on hospital-treated patients. Meanwhile, first-line oral antibiotics used to treat infections caused by community-onset Gram-negatives, especially the uropathogens, are increasingly non-effective leading to increasing rates of hospitalization. Therefore, there is an unmet need for oral antibiotics active against antibiotic-resistant Gram-negative pathogens encountered in community infections, particularly in UTI. Being safe and having the tendency to achieve higher urinary concentrations, β-lactams have become the preferred choice. As the main challenge to β-lactams is the β-lactamases, novel β-lactamase inhibitors with expanded inhibitory spectrum and good oral bioavailability were discovered and combined with already approved β-lactams. Tebipenem, if approved, will be the first oral treatment for cUTI while sulopenem will be for uncomplicated UTI. Both lack activity against CREs, and CRE-active oral agents are in phase 1 development. All these agents, upon their arrival for commercial use, would strengthen the outpatient therapy.

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