

Supplementary Table III. Comparative positioning of cefepime–enmetazobactam versus other advanced agents in complicated UTIs: spectrum, advantages, limitations

Agent	β-lactamase/Target coverage	Activity vs key mechanisms	Complicated UTI indication and key efficacy	Safety/ADR highlights	Limitations
(CPM–EMT)	potent vs class A <i>ESBLs</i> ; intrinsic stability vs some <i>AmpC</i> ; not active vs class B <i>MBLs</i> ; variable/limited vs <i>OXA-48/KPC in vitro</i>	<i>ESBL/AmpC</i> : strong; <i>KPC</i> : limited/variable; <i>OXA-48</i> : variable; <i>MBL</i> : none	US/EU approved for cUTI/AP; Phase 3 ALLIUM showed superiority over piperacillin–tazobactam for composite clinical+microbiological cure (79.1% vs 58.9%); <i>ESBL</i> subgroup benefit	Generally well tolerated; common AEs: GI, infusion-site, transaminase elevations; cephalosporin class neurotoxicity risk esp. with renal impairment; requires renal dose adjustment	No activity vs <i>MBLs</i> ; limited clinical evidence in CRE; strong role as carbapenem-sparing option in <i>ESBL</i> -dominant cUTIs
(CZA)	Inhibits class A (incl. <i>KPC</i>) and many class D <i>OXA-48</i> -like; not class B	<i>ESBL/AmpC</i> : strong; <i>KPC</i> : strong; <i>OXA-48</i> : many; <i>MBL</i> : none	Approved for cUTI/AP, HAP/VAP, cIAI; widely used for CRE driven by <i>KPC/OXA-48</i>	GI upset, transaminase elevations, hypersensitivity; cephalosporin-class risks apply	Preferred in confirmed <i>KPC/OXA-48</i> CRE; no MBL coverage; stewardship considerations for carbapenem-sparing may favor CPM–EMT in <i>ESBL</i>
(MVB)	Inhibits class A <i>KPC</i> ; limited vs <i>OXA-48</i> ; not class B	<i>ESBL/AmpC</i> : strong; <i>KPC</i> : strong; <i>OXA-48</i> : limited; <i>MBL</i> : none	Approved for cUTI/AP; strong option for <i>KPC</i> CRE	Carbapenem-class AEs; rare seizures; LFT elevations; C. difficile risk	Excellent for <i>KPC</i> CRE; however, uses a carbapenem—stewardship may prefer non-carbapenem options for <i>ESBL</i>
(IMI–REL)	Restores activity vs some <i>KPC</i> ; improves <i>P. aeruginosa</i> activity; not class B	<i>ESBL/AmpC</i> : strong; <i>KPC</i> : good; <i>OXA-48</i> : limited; <i>MBL</i> : none	Approved for cUTI/AP and HAP/VAP; role in difficult-to-treat <i>Pseudomonas</i>	Imipenem-associated seizure risk (esp. CNS lesions/renal impairment); GI, LFTs (12,26)	Useful for DTR <i>Pseudomonas</i> ; carbapenem exposure a stewardship trade-off in <i>ESBL</i>
Cefiderocol	Siderophore cephalosporin (no BLI); stable to many β-lactamases including <i>MBLs in vitro</i>	<i>ESBL/AmpC</i> : strong; <i>KPC</i> : strong; <i>OXA-48</i> : strong; <i>MBL</i> : strong	Approved for cUTI/AP; used for highly resistant GNs including <i>MBL</i> producers	GI, infusion reactions, LFTs; careful selection recommended by stewardship	Reserved/targeted use for XDR organisms; stewardship prioritises narrow use
CFP–ZID	(PBP2 binder/β-lactam enhancer); broad <i>in vitro</i> potency vs <i>KPC</i> , <i>OXA-48</i> ; not <i>MBL</i>	<i>ESBL/AmpC</i> : strong; <i>KPC</i> : strong; <i>OXA-48</i> : strong; <i>MBL</i> : none	Clinical data limited; not widely approved for cUTI; <i>in vitro</i> MICs often lower than CPM–EMT for selected carbapenemase producers	Limited clinical safety database; cefepime class effects relevant	<i>In vitro</i> potency promising; clinical outcomes evidence still emerging; not a substitute for established, approved options in most settings

CZA, ceftazidime–avibactam; *ESBL*, extended-spectrum β-lactamase; *AmpC*, CFP-ZID, cefepime–zidebactam; MVB, meropenem–vaborbactam; IMI-REL, Imipenem–relebactam; (IMI–REL) class C β-lactamase; *KPC*, *Klebsiella pneumoniae* carbapenemase (class A); *OXA-48*-like, class D carbapenemases; *MBL*, metallo-β-lactamase (class B); cUTI, complicated urinary tract infection; AP, acute pyelonephritis; HAP/VAP, hospital-/ventilator-associated pneumonia; cIAI, complicated intra-abdominal infection; AE, adverse event; LFT, liver function tests; CRE, carbapenem-resistant Enterobacterales; DTR, difficult-to-treat resistant; XDR, extensively drug-resistant.