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Letters to the Editor

A Promising Target for Treatment of Multidrug-Resistant Bacterial Infections[▽]

Multidrug-resistant infections pose a major quandary for clinicians by complicating therapy choice, compromising patient recovery, and creating a serious threat to public health (1). In Gram-negative bacteria, resistance to almost all β-lactam antibiotics, including the carbapenems, can be conferred by metallo-β-lactamases (MBLs), such as imipenemase (IMP), Verona imipenemase (VIM), German imipenemase (GIM), New Delhi MBL (NDM), and São Paulo MBL (SPM), which are invariably accompanied by additional resistance mechanisms. The ease with which multidrug resistance disseminates among Gram-negative pathogens is illustrated by the rapid global spread of NDM-1 (5). For patients infected with MBL-positive (MBL^+) bacteria, last-resort compounds such as tigecycline and colistin offer the only means of treatment, and, in the case of colistin, often at the cost of serious side effects. Moreover, tigecycline is currently not licensed for treatment of urinary tract infections, the primary infection associated with $NDM\text{-}1^+$ bacteria, and neither agent is 100% effective for all MBL^+ strains. There is thus an urgent need for novel and safe antibiotics that are effective in controlling these "super-bug" infections.

One potential target for new-generation antibiotics are the seven enzymes of the 2-*C*-methyl-D-erythritol 4-phosphate (MEP) or nonmevalonate pathway of isoprenoid biosynthesis, an essential metabolic route in many Gram-negative and Gram-positive bacteria and in malaria parasites (3, 4). The compound 3-(N-formyl-N-hydroxyamino)propyl-phosphonic acid (fosmidomycin), a specific inhibitor of the first step in the MEP pathway, was described in the 1980s as an effective antibacterial agent and has more recently been the subject of clinical trials demonstrating its safety and potency in malaria patients (6). Of note, fosmidomycin not only has a direct antimicrobial effect but may also possess immediate anti-inflammatory properties by inhibiting γδ T-cell-driven immune responses to the MEP pathway intermediate, (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) (2).

Here we report the first evidence of activity of fosmidomycin against multidrug-resistant bacteria with acquired MBL genes. Our data demonstrate that irrespective of MBL type and origin, all isolates of *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* tested were susceptible to fosmidomycin, including laboratory-generated colistin-resistant derivatives (Table 1). Control strains not possessing the MEP pathway, such as *Chryseobacterium indologenes*, were not affected by fosmidomycin. As the MICs defined here are achievable *in vivo* (7), our findings suggest that fosmidomycin and related compounds might be useful in the clinic and help reduce the exposure of patients to the toxic side effects of colistin and the risk of generating colistin-resistant mutants. Taken together, we provide proof of concept that fosmidomycin and other MEP pathway inhibitors represent promising leads for future drugs by targeting an essential metabolic route that is shared by the majority of pathogenic bacteria, including multidrug-resistant clinical isolates, but is absent in humans.

We declare that we have no conflicts of interest.

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TABLE 1. Susceptibility of multidrug-resistant bacteria to fosmidomycin[a]

Species	Gram stain	MEP	Isolate	Origin	MBL	MIC (μg/ml) for:						
						Azt	Amk	Gen	Mer	Imp	Fof	Fos
Enterobacter cloacae	−	+	481234	Brazil	IMP-1	**0.19**	**2**	12	**3**	**3**	>32	**1**
			69–7329	Brazil	IMP-4	**6**	**1.5**	**1.5**	12	**3**	>32	**1**
			IR19	India	NDM-1	>64	>64	>32	>32	32	**16**	**32**
			IR36	India	NDM-1	>64	>64	>32	32	>32	>32	**8**
			IR38	India	NDM-1	>64	>64	>32	>32	>32	**32**	**2**
			IR44	India	NDM-1	>64	>64	>32	16	16	**32**	**4**
			IR59	India	NDM-1	>64	>64	>32	32	>32	**32**	**4**
Escherichia coli	−	+	IR9	India	NDM-1	>64	>64	>32	>32	16	**0.38**	**32**
			IR31	India	NDM-1	>64	>64	>32	>32	16	ND	**64**
			IR60	India	NDM-1	>64	>64	>32	16	16	**32**	**16**
			IR62	India	NDM-1	>64	>64	32	>32	>32	**16**	**64**
Klebsiella pneumoniae	−	+	WCH7	Greece	IMP-4	**0.064**	**2**	**2**	**1**	**0.75**	**32**	**32**
			IR17	India	NDM-1	>64	**6**	>32	>32	>32	**24**	**32**
			IR17-D*	India	NDM-1	ND	ND	ND	ND	ND	ND	**32**
			K1	India	NDM-1	>64	>64	>32	>32	>32	**6**	**8**
			K1-D*	India	NDM-1	>64	>64	>32	24	16	**8**	**32**
			K7	India	NDM-1	>64	>64	>32	>32	>32	>32	**16**
Pseudomonas aeruginosa	−	+	A1	Brazil	SPM-1	**6**	>64	>32	>32	>32	>32	**8**
			A22	Brazil	SPM-1	**12**	>64	>32	>32	>32	**32**	**16**
			A25	Germany	GIM-1	**12**	**4**	12	>32	>32	**12**	**16**
			A31	Greece	VIM-1	48	>64	>32	>32	>32	**12**	**8**
			A37	Italy	VIM-1	**8**	>64	>32	>32	>32	**16**	**4**
			A41	Italy	VIM-1	**8**	>64	>32	>32	>32	>32	**8**
			A57	Italy	VIM-1	**8**	>64	>32	>32	16	**12**	**8**
			A63	France	VIM-2	**4**	>64	>32	>32	>32	>32	**32**
			A67	Poland	VIM-2	**6**	32	>32	>32	>32	**2**	**4**
			A70	Russia	VIM-2	**8**	>64	>32	>32	>32	**16**	**8**
Chryseobacterium indologenes	−	−	S281	UK		ND	ND	ND	ND	ND	ND	>128
Enterococcus faecalis	+	−	IQA	UK		ND	ND	ND	ND	ND	ND	>128
Staphylococcus aureus	+	−	S288	UK		ND	ND	ND	ND	ND	ND	>128

[a] The majority of clinical isolates were resistant (R) to aztreonam (Azt; R > 8 μg/ml; R > 16 for *P. aeruginosa*), amikacin (Amk; R > 16), gentamicin (Gen; R > 4), meropenem (Mer; R > 8), and imipenem (Imp; R > 8), as defined by EUCAST. MICs below breakpoints are bold. Fosfomycin (Fof; R > 32), a specific inhibitor of peptidoglycan biosynthesis, was included in the present study as it shares some pharmacokinetic properties with fosmidomycin (Fos) and targets a similar but not identical spectrum of Gram-positive and Gram-negative species. Fos MICs were determined using the ISO microbroth dilution method accepted by both EUCAST and CLSI. *, laboratory-generated colistin resistant mutants; ND, not done.