Zidovudine: A salvage therapy for mcr-1 plasmid-mediated colistin-resistant bacterial infections?

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Hot Topic

Zidovudine: A salvage therapy for *mcr-1* plasmid-mediated colistin-resistant bacterial infections?

Over the last decade, antibiotic resistance has become a major new threat to human health and a worldwide problem prompting the World Health Organization (WHO) to prioritise the fight against multidrug-resistant (MDR) bacteria. Last year, the WHO positioned Enterobacteriaceae as an antibiotic-resistant priority pathogen [1]. Among all threats, the newly described *mcr-1* plasmid-mediated colistin resistance mechanism [2], which has been described all over the world in Gram-negative bacteria [3], became the most important. We have recently reported that this threat is probably overestimated, since many old antibiotics are still effective and could be re-introduced into the pharmaceutical market to treat such infections [4–6]. The main problem is that these old but useful antibiotics are no longer available in many countries [7]. What could solve both problems of antibiotic resistance and no-longer available drugs in the market is 'drug repurposing', i.e. the use of US Food and Drug Administration (FDA)-approved drugs as new therapeutic agents. Using this approach, by screening a total of 1163 FDA-approved drugs, Ng et al. have recently found that zidovudine, an antiviral drug active against human immunodeficiency virus (HIV), was effective in vitro against 13 carbapenem-resistant and colistin-susceptible Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*) with minimum inhibitory concentrations (MICs) compatible with human use [8]. Zidovudine, a nucleoside reverse transcriptase inhibitor, was the first antiretroviral commercialised for the treatment of HIV infection in 1987 [9]. This nucleotide and synthetic analogue was initially used as an anticancer drug [9] but from 1986 its antibacterial effect was revealed in bacteria [10,11] that possess a thymidine kinase homologue able to activate the drug [12]. Using a similar approach with a different FDA-approved library of 1280 drugs (Prestwick Chemical, Illkirch-Graffenstaden, France), we also identified zidovudine as an effective drug against Enterobacteriaceae. To our knowledge, no study has previously reported the efficacy of zidovudine on colistin-resistant Gram-negative bacteria. In our laboratory, we collected a large number of MDR Enterobacteriaceae, including carbapenem- and colistin-resistant strains, isolated from different geographical areas worldwide for which molecular mechanisms of resistance have been previously characterised. Here we report the efficacy of zidovudine against a series of 40 strains including 16 *E. coli* (12 colistin-resistant isolates, 3 carbapenem-resistant isolates and 1 susceptible isolate) and 22 *K. pneumoniae* (11 colistin-resistant isolates, 9 carbapenem-resistant isolates, 1 colistin- and carbapenem-resistant isolate and 1 susceptible isolate). Molecular mechanisms of resistance to colistin included *mcr-1*, MgrB inactivation and *pmrB* mutation, whereas resistance to carbapenems included bla_{NDM}, bla_{KPC} and bla_{OXA-48} carbapenemase (Table 1). Two strains of *Staphylococcus aureus* that are intrinsically resistant to zidovudine were also used as controls [13] (Table 1).

Zidovudine MICs were determined using the broth microdilution dilution method in Mueller–Hinton II broth with a zidovudine (Sigma-Aldrich, St Louis, MO) concentration ranging from 0.2–100 μM (0.053–26.7 μg/mL). All Enterobacteriaceae strains were susceptible to zidovudine with MICs ranging from 0.2–6.25 μM (0.05–1.67 μg/mL) (Table 1). Interestingly, zidovudine was also highly effective against a clinical isolate that was both carbapenem- and colistin-resistant (*K. pneumoniae* strain 853; Table 1). The two *S. aureus* strains were resistant with MICs > 100 μM (>26.7 μg/mL).

From a clinical point of view, these findings are extremely important for the medical community because of the pharmacokinetic properties of zidovudine. In a study with healthy volunteers, a peak zidovudine serum concentration (C_{max}) of 4 μM (1.07 μg/mL) was obtained 1 h following administration of 200 mg of zidovudine in a single oral administration [14]. Similarly, Wattanagoon et al. have reported in healthy volunteers in Thailand a C_{max} of 17.98 μM (4.8 μg/mL) after a single dose of 300 mg of zidovudine [15]. Zidovudine is used at a dose of 600 mg/day (300 mg twice daily) in HIV treatment, suggesting that a plasma concentration above the MIC could be easily achieved. This dosage could be increased, e.g. to 2400 mg/day (600 mg four times daily) since overdosage of 20 g has previously been reported to be free of side effects in humans [16]. Moreover, zidovudine is currently available either in tablet from or in an intravenous (i.v.) form that could be used as a slow i.v. infusion (zidovudine half-life of 1.1 h) in the case of severe sepsis or meningitis since zidovudine can achieve therapeutic concentrations in the cerebrospinal fluid [17]. Zidovudine could also be used during pregnancy and in children [18]. Finally, side effects, such as haematotoxicity, are well known but are associated with long-term administration of zidovudine, so they could easily be managed as salvage therapy if used for a relatively short period of time.

One question with the use of zidovudine as salvage therapy for MDR bacterial infections is the possibility of resistance development. This has been already reported in *E. coli* in HIV patients treated with zidovudine [19] owing to the loss of thymidine kinase activity [13,20], preventing zidovudine phosphorylation and activation. Thus, it seems reasonable to combine zidovudine with other drugs to circumvent the selection of zidovudine-resistant

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Table 1
Minimum inhibitory concentrations (MICs) of colistin (COL), imipenem (IPM) and zidovudine (AZT) against various colistin- and/or carbapenem-resistant strains.

Species	Strain	Origin	Country	Resistance phenotype	Resistance mechanism	MIC (μg/mL) [μM]			Reference
						COL	IPM	AZT	
Escherichia coli	ATCC 25922	Human	USA	None	Susceptible	1	0.19	0.835 [3.125]	ATCC
E. coli	LH1	Human	Laos	Colistin	*mcr-1*	6	0.125	0.104 [0.4]	[22]
E. coli	LH30	Human	Laos	Colistin	*mcr-1*	6	0.19	0.208 [0.8]	[22]
E. coli	LH57	Human	Laos	Colistin	*mcr-1*	6	0.125	0.417 [1.56]	[22]
E. coli	1R4	Human	Saudi Arabia	Colistin	*mcr-1*	4	0.19	0.208 [0.8]	[23]
E. coli	NCTC 13846	Human	England	Colistin	*mcr-1*	4	0.19	0.208 [0.8]	NCTC
E. coli	6R	Human	Saudi Arabia	Colistin	*mcr-1*	4	0.125	0.417 [1.56]	[23]
E. coli	SE65	Human	Algeria	Colistin	*mcr-1*	8	0.19	1.67 [6.25]	[24]
E. coli	LH257	Human	Laos	Colistin	*mcr-1*	12	0.19	0.104 [0.4]	[22]
E. coli	134R	Human	Saudi Arabia	Colistin	*mcr-1*	3	0.19	0.208 [0.8]	[23]
E. coli	44A	Human	Saudi Arabia	Colistin	*mcr-1*	4	0.19	0.104 [0.4]	[23]
E. coli	TH99	Human	Thailand	Colistin	*mcr-1*	4	0.125	0.104 [0.4]	[22]
E. coli	235	Chicken	Algeria	Colistin	*mcr-1*	4	0.125	0.208 [0.8]	[22]
E. coli	CMUL64	Human	Lebanon	Carbapenems	bla_{OXA-48}	0.38	0.023	0.052 [0.2]	[25]
E. coli	CSURP5142	Human	Marseille, France	Carbapenems	bla_{OXA-48}	1	32	0.208 [0.8]	Unpublished data
E. coli	CSURP1954	Human	Algeria	Carbapenems	bla_{NDM-5}	0.25	>32	0.052 [0.2]	[26]
Klebsiella pneumoniae	ATCC 13883	Human	Unknown	None	Susceptible	1	0.38	0.052 [0.2]	ATCC
K. pneumoniae	LH70	Human	Laos	Colistin	Unknown	12	0.19	0.052 [0.2]	[27]
K. pneumoniae	LH12	Human	Laos	Colistin	*mgrB*	32	0.19	0.104 [0.4]	[27]
K. pneumoniae	FHM169	Human	France	Colistin	*mgrB*	8	0.19	0.208 [0.8]	[27]
K. pneumoniae	TH20	Human	Thailand	Colistin	*mgrB*	32	0.19	0.417 [1.56]	[27]
K. pneumoniae	TH28	Human	Thailand	Colistin	*mgrB*	8	0.19	0.208 [0.8]	[27]
K. pneumoniae	TH176	Human	Thailand	Colistin	*mgrB*	12	0.19	<0.052 [<0.2]	[27]
K. pneumoniae	LH17	Human	Laos	Colistin	*mcr-1* + *pmrB*(T157P)	12	0.125	0.835 [3.125]	[27]
K. pneumoniae	LH92	Human	Laos	Colistin	*mcr-1*	12	0.19	0.104 [0.4]	[27]
K. pneumoniae	FHA60	Human	France	Colistin	*mcr-1*	8	0.19	0.104 [0.4]	[27]
K. pneumoniae	FHM128	Human	France	Colistin	*mcr-1*	4	0.19	0.417 [1.56]	[27]
K. pneumoniae	TH68	Human	Thailand	Colistin	*mcr-1*	8	0.19	0.104 [0.4]	[27]
K. pneumoniae	CSURP5123	Human	France	Carbapenems	bla_{OXA-48}	1	6	0.104 [0.4]	Unpublished data
K. pneumoniae	CSURP5233	Human	France	Carbapenems	bla_{OXA-48}	0.25	2	0.835 [3.125]	Unpublished data
K. pneumoniae	NCTC 13443	Human	Unknown	Carbapenems	bla_{NDM-1}	1	>32	0.208 [0.8]	Unpublished data
K. pneumoniae	CSURP5141	Human	France	Carbapenems	bla_{NDM-1}	0.25	4	0.835 [3.125]	Unpublished data
K. pneumoniae	CSUR5135	Human	France	Carbapenems	bla_{NDM-1}	1	0.38	0.417 [1.56]	Unpublished data
K. pneumoniae	CSURP1572	Human	Algeria	Carbapenems	bla_{KPC-3}	0.125	8	0.104 [0.4]	[28]
K. pneumoniae	853	Human	Israel	Carbapenems, colistin	bla_{KPC}, *mgrB*	48	>32	0.104 [0.4]	Unpublished data
K. pneumoniae	1348	Human	Israel	Carbapenems	bla_{KPC}	<2	8	0.835 [3.125]	Unpublished data
K. pneumoniae	695	Human	Israel	Carbapenems	bla_{KPC}	<2	8	0.417 [1.56]	Unpublished data
K. pneumoniae	473	Human	Israel	Carbapenems	bla_{KPC}	<2	6	0.417 [1.56]	Unpublished data
Staphylococcus aureus	CSURP1943	Human	France	MRSA	*mecA*	–	–	26.7 [>100]	[29]
S. aureus	ATCC 25923	Unknown	Unknown	None	Susceptible	–	–	26.7 [>100]	ATCC

MRSA, methicillin-resistant *Staphylococcus aureus.*

strains, e.g. fosfomycin or minocycline that are known to be effective against such strains [5,6] or tigecycline as recently reported by Ng et al. [8].

To conclude, our in vitro study demonstrated that drug repurposing is an effective way to (re)discover existing drugs that may be able to solve some of the current problems of worldwide antibiotic resistance. Indeed, the antibacterial activity of zidovudine was previously described in mice [11] and was suspected in vivo in humans [21]. Revival of old antibiotics can be useful to fight bacteria resistant to multiple current antibacterial drugs, both by screening of large libraries of approved drug as well as screening of the literature for old data on antibacterial activities. Here, zidovudine is identified as a leader in the context of the worldwide emergence of colistin resistance. Case reports and clinical trials with zidovudine in combination with other drugs to treat patients infected with carbapenem- and/or colistin-resistant bacteria definitely prompt us to add this drug to our therapeutic arsenal against MDR bacteria. As patents on zidovudine expired in 2005, several generics exist and as this drug is less used as an antiretroviral therapeutic, its use as an antibacterial drug could be an affordable alternative.

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Competing interests

None declared.

Ethical approval

Not required.

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