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2 Sun J, Chen C, Cui CY *et al*. Plasmid-encoded *tet*(X) genes that confer high-level tigecycline resistance in *Escherichia coli*. *Nat Microbiol* 2019; **4**: 1457–64.

3 Chen C, Cui CY, Zhang Y *et al*. Emergence of mobile tigecycline resistance mechanism in *Escherichia coli* strains from migratory birds in China. *Emerg Microbes Infect* 2019; **8**: 1219–22.

4 Wang Y, Wang Y, Wu CM *et al*. Detection of the staphylococcal multiresistance gene *cfr* in *Proteus vulgaris* of food animal origin. *J Antimicrob Chemother* 2011; **66**: 2521–6.

5 Zhang Y, Lei CW, Wang HN. Identification of a novel conjugative plasmid carrying the multiresistance gene *cfr* in *Proteus vulgaris* isolated from swine origin in China. *Plasmid* 2019; **105**: 102440.

6 Chen Y, Lei C, Zuo L *et al*. A novel *cfr*-carrying Tn7 transposon derivative characterized in *Morganella morganii* of swine origin in China. *J Antimicrob Chemother* 2019; **74**: 603–6.

7 Li R, Xie M, Dong N *et al*. Efficient generation of complete sequences of MDR-encoding plasmids by rapid assembly of MinION barcoding sequencing data. *Gigascience* 2018; **7**: 1–9.

8 Bie L, Wu H, Wang XH *et al*. Identification and characterization of new members of the SXT/R391 family of integrative and conjugative elements (ICEs) in *Proteus mirabilis*. *Int J Antimicrob Agents* 2017; **50**: 242–6.

9 Burrus V, Marrero J, Waldor MK. The current ICE age: biology and evolution of SXT-related integrating conjugative elements. *Plasmid* 2006; **55**: 173–83.

10 Burrus V, Waldor MK. Control of SXT integration and excision. *J Bacteriol* 2003; **185**: 5045–54.

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In vitro activity of 20 antibiotics against *Cupriavidus* clinical strains

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Sir,

Cupriavidus are Gram-negative non-lactose-fermenting motile bacilli with peritrichous flagella, a number of which were previously and successively classified in the *Ralstonia* and *Wautersia* genera. Until the recent expansion of MALDI-TOF MS, *Cupriavidus* could be mistaken for *Burkholderia* or *Pseudomonas* species. They are resistant to heavy metals and have been described from environmental (soil and water) samples, as well as from human samples.[1] *Cupriavidus gilardii*, *Cupriavidus pauculus* and *Cupriavidus metallidurans* are involved in invasive human infections, such as bacteraemia and pneumonia, most of which (though not exclusively) occur in immunocompromised patients.[2–4] Additionally, *Cupriavidus* species, *Cupriavidus respiraculi* in particular, are increasingly identified in patients with cystic fibrosis (CF).[5] However, their clinical relevance in CF is not established. Due to the rare occurrence of *Cupriavidus* infections, antibiotic susceptibility data are only available from sparse case reports. Therefore, we determined the MICs of 20 antibiotics for a panel of *Cupriavidus* clinical strains, mainly from respiratory samples of CF patients (82%).

Thirty-seven epidemiologically unrelated clinical isolates of *Cupriavidus* obtained from the collection of the French Observatoire *Burkholderia cepacia* and from 11 French hospitals, as well as two type strains from clinical sources, i.e. *C. pauculus* LMG 3244^T and *C. respiraculi* LMG 21510^T (Laboratory of Microbiology, Ghent University, Ghent, Belgium),[1] were included. Isolates were identified by amplified ribosomal DNA restriction analysis (ARDRA)[6] and MALDI-TOF MS (Maldi Biotyper Microflex®, Bruker Daltonics, Bremen, Germany; IVD 7712). The experimental panel thus comprised 18 *C. respiraculi*, 6 *C. gilardii*, 5 *C. pauculus*, 4 *C. metallidurans*, 2 *Cupriavidus necator*, 2 *Cupriavidus taiwanensis*, 1 *Cupriavidus basilensis* and 1 unidentified *Cupriavidus* sp.

The MICs of 20 antibiotics, listed in Table 1, were determined using the broth microdilution method, as recommended by EUCAST (www.eucast.org). Briefly, each strain was inoculated on a blood agar plate (bioMérieux, Marcy-l'Étoile, France) for 16 h at 35°C. Bacterial suspensions in Mueller–Hinton broth (Bio-Rad, Marnes-la-Coquette, France) at concentrations of 5×10^5 cfu/mL were dispensed in 96-well microtitre plates (Dutscher, Brumath, France, 160 μL per well). Antimicrobial agents were added at increasing 2-fold concentrations (40 μL per well). The MICs were determined as the lowest antibiotic concentrations that inhibited visible bacterial growth after an 18 ± 2 h incubation at 35°C in an aerobic atmosphere. *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 29213 were used as controls. All MICs were determined in triplicate and replicates never differed by more than 2-fold. For each MIC determination, the median of the replicates was recorded as the MIC. The MICs were interpreted according to *Pseudomonas* EUCAST breakpoints (2019) for colistin, amikacin and tobramycin, according to non-Enterobacteriaceae CLSI breakpoints (2019; https://clsi.org) for minocycline and co-trimoxazole and according to pharmacokinetic/pharmacodynamic (non-species-related) EUCAST breakpoints (2019) for the other antibiotics, except for temocillin, for which the previously proposed breakpoint of 16 mg/L was used.[7] The EUCAST and CLSI breakpoints that could be used to interpret *Cupriavidus* MICs are listed in Table S1 (available as Supplementary data at *JAC* Online).

The susceptibility testing results are summarized in Table 1 and the full MIC distributions of each tested antibiotic are available in Figure S1. Since *C. pauculus* and *C. metallidurans* are phylogenetically close species[1] and exhibited the same susceptibility profiles, they were considered as a group. Our collection comprises very few strains of *C. basilensis, C. necator, C. taiwanensis and Cupriavidus sp*. (maximum $n=2$ for each species). Moreover, these species have similar antibiotic susceptibility profiles, that's why they were also considered as a group. The susceptibility testing results interpreted with CLSI breakpoints are available in Table S2. The only significant change in our study between the EUCAST and CLSI interpretations concerned piperacillin/tazobactam. Eleven strains had an MIC of 8 or 16 mg/L (nine *C. respiraculi*). They were classified as susceptible to piperacillin/tazobactam according to CLSI breakpoints, but intermediate according to EUCAST breakpoints.

Nearly all strains were resistant to amoxicillin, amoxicillin/clavulanate, temocillin and aztreonam. Regarding cephalosporins, only 23% of *Cupriavidus* strains were ceftazidime susceptible, whereas 74% and 82% were susceptible to ceftriaxone or cefotaxime, respectively. The ceftolozane/tazobactam combination also demonstrated good activity, except against *C. gilardii*. For most strains, ceftazidime/avibactam MICs were similar compared with ceftazidime alone. Cefepime was the most active β-lactam, with 95% of strains being susceptible, whereas only a few strains were susceptible to meropenem (8%). Interspecies differences were observed for piperacillin/tazobactam and imipenem, since they were less active against *C. respiraculi* and *C. gilardii* than against the other species. Such discrepancies between meropenem and imipenem activities were previously noticed in case reports.[2,3] Similarly to *P. aeruginosa*, they could be due to the overexpression of efflux pumps from the resistance-nodulation-division family.[8] Indeed, a homologue of the MexAB OprM efflux pump that extrudes meropenem in *P. aeruginosa* has been identified in *C. gilardii*.[9]

Aminoglycosides were poorly active, in agreement with case reports,[2,3] probably due to efflux pumps and aminoglycoside-modifying enzymes.[9] Minocycline was the most active antibiotic, with very low MICs and a 100% susceptibility rate. Fluoroquinolones were frequently active, with over 80% of strains being susceptible, except for *C. pauculus and C. metallidurans*. Interspecies discrepancies were also noticed for co-trimoxazole. It was active against approximatively 80% of *C. gilardii* and *C. respiraculi* strains, whereas more than 50% of the strains belonging to other species were resistant.

Over 90% of *C. respiraculi* and 67% of *C. gilardii* strains were susceptible to colistin, while strains from the other species were mostly colistin-resistant. Colistin susceptibility was one of the characteristics of the *Cupriavidus* genus initially described by Vaneechoutte *et al.*[1] However, Petrou *et al.*[10] showed that the expression of ArnT was particularly strong in a strain of *C. metallidurans*. This enzyme catalyses the attachment of the cationic sugar 4-amino-4-deoxy L-arabinose (L-Ara4N) to lipid A phosphate groups. The subsequent reduction of negative membrane charge is responsible for colistin resistance. We detected homologues of *arnT* (CP000353.2: 1481129–1482725) using BLASTn in *C. basilensis*, *C. necator*, *C. pauculus* and *C. taiwanensis* sequenced strains (a query cover >80%, an identity >70% and an E value $<1\times10^{-40}$ were chosen as cut-off values for significance), which is in accordance with the high rate of colistin resistance in these species observed in our study. Additionally, *C. gilardii* appears to be the origin of the gene *mcr-5*, which is an emerging plasmid-mediated mechanism of colistin resistance in other environmental species such as *Salmonella* and *Pseudomonas*.[11]

In conclusion, our study showed that minocycline and cefepime exhibited the best *in vitro* activities against *Cupriavidus* strains. Meropenem, aminoglycosides and polymyxins, often considered antibiotics of last resort against infections caused by Gram-negative bacilli, do not have reliable activity against *Cupriavidus*. Perhaps resistance to these agents confers a selective advantage to *Cupriavidus* and therefore it may emerge in clinical scenarios where these agents are used, such as in patients with CF. Imipenem was more active than meropenem and cefotaxime/ceftriaxone was more active than ceftazidime. Ceftolozane/tazobactam had reasonable activity against *Cupriavidus*, whereas the novel inhibitor avibactam does not seem to add to the activity of

Table 1. MICs of 20 antibiotics for 39 *Cupriavidus* clinical strains, including two type strains, determined by the broth microdilution method

Bacteria (*n*)	Antibiotic	MIC (mg/L)		Percentage susceptible (breakpoint, mg/L)	Percentage resistant (breakpoint, mg/L)
		MIC_{50}	MIC_{90}		
Cupriavidus spp., all isolates (39)	amikacin	64	512	23 (≤8)	72 (>16)
	amoxicillin	512	>512	5 (≤2)	90 (>8)
	amoxicillin/clavulanate	256	>512	8 (≤2)	87 (>8)
	aztreonam	32	256	0 (≤4)	97 (>8)
	cefepime	1	4	95 (≤4)	0 (>8)
	cefotaxime	1	2	82 (≤1)	8 (>2)
	ceftazidime	16	32	23 (≤4)	54 (>8)
	ceftazidime/avibactam	8	32	69 (≤8)	31 (>8)
	ceftolozane/tazobactam	2	8	90 (≤4)	10 (>4)
	ceftriaxone	1	4	74 (≤1)	10 (>2)
	ciprofloxacin	0.125	1	74 (≤0.25)	18 (>0.5)
	colistin	2	16	56 (≤2)	44 (>2)
	co-trimoxazole	1	128	62 (≤2)	38 (>2)
	imipenem	2	8	69 (≤2)	21 (>4)
	levofloxacin	0.25	2	79 (≤0.5)	18 (>1)
	meropenem	32	64	8 (≤2)	74 (>8)
	minocycline	≤0.06	0.5	100 (≤4)	0 (>8)
	piperacillin/tazobactam	8	128	46 (≤4)	26 (>16)
	temocillin	32	512	31 (≤16)	69 (>16)
	tobramycin	256	>256	21 (≤4)	79 (>4)
C. respiraculi (18)	amikacin	128	512	6 (≤8)	89 (>16)
	amoxicillin	512	>512	0 (≤2)	100 (>8)
	amoxicillin/clavulanate	512	>512	0 (≤2)	100 (>8)
	aztreonam	32	32	0 (≤4)	100 (>8)
	cefepime	2	4	89 (≤4)	0 (>8)
	cefotaxime	1	2	78 (≤1)	11 (>2)
	ceftazidime	16	16	6 (≤4)	61 (>8)
	ceftazidime/avibactam	8	16	72 (≤8)	28 (>8)
	ceftolozane/tazobactam	2	4	94 (≤4)	6 (>4)
	ceftriaxone	1	4	67 (≤1)	17 (>2)
	ciprofloxacin	0.06	>16	83 (≤0.25)	17 (>0.5)
	colistin	1	2	94 (≤2)	6 (>2)
	co-trimoxazole	0.5	128	78 (≤2)	22 (>2)
	imipenem	2	8	61 (≤2)	22 (>4)
	levofloxacin	0.125	16	83 (≤0.5)	17 (>1)
	meropenem	64	64	0 (≤2)	83 (>8)
	minocycline	≤0.06	0.125	100 (≤4)	0 (>8)
	piperacillin/tazobactam	8	16	39 (≤4)	11 (>16)
	temocillin	32	32	50 (≤16)	50 (>16)
	tobramycin	>256	>256	6 (≤4)	94 (>4)
C. pauculus (5) and *C. metallidurans* (4)	amikacin	8	128	56 (≤8)	33 (>16)
	amoxicillin	256	512	0 (≤2)	78 (>8)
	amoxicillin/clavulanate	128	256	11 (≤2)	78 (>8)
	aztreonam	256	512	0 (≤4)	100 (>8)
	cefepime	0.5	1	100 (≤4)	0 (>8)
	cefotaxime	1	2	67 (≤1)	11 (>2)
	ceftazidime	8	16	33 (≤4)	44 (>8)
	ceftazidime/avibactam	8	16	78 (≤8)	22 (>8)
	ceftolozane/tazobactam	2	4	100 (≤4)	0 (>4)
	ceftriaxone	1	2	78 (≤1)	0 (>2)
	ciprofloxacin	0.5	1	44 (≤0.25)	44 (>0.5)

Continued

Table 1. *Continued*

		MIC (mg/L)			
Bacteria (*n*)	Antibiotic	MIC$_{50}$	MIC$_{90}$	Percentage susceptible (breakpoint, mg/L)	Percentage resistant (breakpoint, mg/L)
	colistin	16	32	0 (≤2)	100 (>2)
	co-trimoxazole	16	256	22 (≤2)	78 (>2)
	imipenem	0.25	2	100 (≤2)	0 (>4)
	levofloxacin	1	2	44 (≤0.5)	44 (>1)
	meropenem	16	64	11 (≤2)	67 (>8)
	minocycline	0.25	0.5	100 (≤4)	0 (>8)
	piperacillin/tazobactam	2	32	67 (≤4)	22 (>16)
	temocillin	256	512	0 (≤16)	100 (>16)
	tobramycin	64	128	44 (≤4)	56 (>4)
C. gilardii (6)	amikacin	64	128	0 (≤8)	100 (>16)
	amoxicillin	>512	>512	0 (≤2)	100 (>8)
	amoxicillin/clavulanate	>512	>512	0 (≤2)	100 (>8)
	aztreonam	128	128	0 (≤4)	100 (>8)
	cefepime	4	4	100 (≤4)	0 (>8)
	cefotaxime	1	1	100 (≤1)	0 (>2)
	ceftazidime	32	32	17 (≤4)	83 (>8)
	ceftazidime/avibactam	32	32	33 (≤8)	67 (>8)
	ceftolozane/tazobactam	8	16	50 (≤4)	50 (>4)
	ceftriaxone	1	2	67 (≤1)	17 (>2)
	ciprofloxacin	0.25	0.25	83 (≤0.25)	0 (>0.5)
	colistin	1	4	67 (≤2)	33 (>2)
	co-trimoxazole	1	1	83 (≤2)	17 (>2)
	imipenem	8	8	17 (≤2)	67 (>4)
	levofloxacin	0.25	0.25	100 (≤0.5)	0 (>1)
	meropenem	64	64	0 (≤2)	100 (>8)
	minocycline	0.125	0.125	100 (≤4)	0 (>8)
	piperacillin/tazobactam	128	128	0 (≤4)	83 (>16)
	temocillin	512	>512	0 (≤16)	100 (>16)
	tobramycin	256	>256	0 (≤4)	100 (>4)
C. basilensis (1), *C. necator* (2), *C. taiwanensis* (2) and *Cupriavidus* sp. (1)	amikacin	32	64	50 (≤8)	50 (>16)
	amoxicillin	32	256	33 (≤2)	67 (>8)
	amoxicillin/clavulanate	16	64	33 (≤2)	50 (>8)
	aztreonam	64	128	0 (≤4)	83 (>8)
	cefepime	≤0.25	≤0.25	100 (≤4)	0 (>8)
	cefotaxime	0.5	1	100 (≤1)	0 (>2)
	ceftazidime	4	8	67 (≤4)	17 (>8)
	ceftazidime/avibactam	4	8	83 (≤8)	17 (>8)
	ceftolozane/tazobactam	1	1	100 (≤4)	0 (>4)
	ceftriaxone	0.25	1	100 (≤1)	0 (>2)
	ciprofloxacin	0.125	0.25	83 (≤0.25)	0 (>0.5)
	colistin	16	16	17 (≤2)	83 (>2)
	co-trimoxazole	16	64	50 (≤2)	50 (>2)
	imipenem	0.25	2	100 (≤2)	0 (>4)
	levofloxacin	0.125	0.25	100 (≤0.5)	0 (>1)
	meropenem	8	16	33 (≤2)	33 (>8)
	minocycline	≤0.06	0.5	100 (≤4)	0 (>8)
	piperacillin/tazobactam	1	4	83 (≤4)	17 (>16)
	temocillin	128	512	50 (≤16)	50 (>16)
	tobramycin	64	64	50 (≤4)	50 (>4)

ceftazidime. Interspecies variations were observed, especially concerning colistin, co-trimoxazole, fluoroquinolones and piperacillin/tazobactam. Clinical data is now required to establish the optimal treatment of *Cupriavidus* infections.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 and Figure S1 are available as Supplementary data at *JAC* Online.

References

1 Vaneechoutte M, Kämpfer P, De Baere T *et al*. *Wautersia* gen. nov., a novel genus accommodating the phylogenetic lineage including *Ralstonia eutropha* and related species, and proposal of *Ralstonia* [*Pseudomonas*] *syzygii* (Roberts *et al*. 1990) comb. nov. *Int J Syst Evol Microbiol* 2004; **54**: 317–27.

2 Bianco G, Boattini M, Audisio E *et al*. Septic shock due to meropenem- and colistin-resistant *Cupriavidus pauculus*. *J Hosp Infect* 2018; **99**: 364–5.

3 Kobayashi T, Nakamura I, Fujita H *et al*. First case report of infection due to *Cupriavidus gilardii* in a patient without immunodeficiency: a case report. *BMC Infect Dis* 2016; **16**: 493.

4 D'Inzeo T, Santangelo R, Fiori B *et al*. Catheter-related bacteremia by *Cupriavidus metallidurans*. *Diagn Microbiol Infect Dis* 2015; **81**: 9–12.

5 Coenye T, Spilker T, Reik R *et al*. Use of PCR analyses to define the distribution of *Ralstonia* species recovered from patients with cystic fibrosis. *J Clin Microbiol* 2005; **43**: 3463–6.

6 Segonds C, Paute S, Chabanon G. Use of amplified ribosomal DNA restriction analysis for identification of *Ralstonia* and *Pandoraea* species: interest in determination of the respiratory bacterial flora in patients with cystic fibrosis. *J Clin Microbiol* 2003; **41**: 3415–8.

7 Fuchs PC, Barry AL, Thornsberry C *et al*. Interpretive criteria for temocillin disk diffusion susceptibility testing. *Eur J Clin Microbiol* 1985; **4**: 30–3.

8 Pragasam AK, Raghanivedha M, Anandan S *et al*. Characterization of *Pseudomonas aeruginosa* with discrepant carbapenem susceptibility profile. *Ann Clin Microbiol Antimicrob* 2016; **15**: 12.

9 Ruiz C, McCarley A, Espejo ML *et al*. Comparative genomics reveals a well-conserved intrinsic resistome in the emerging multidrug-resistant pathogen *Cupriavidus gilardii*. *mSphere* 2019; **4**: e00631-19.

10 Petrou VI, Herrera CM, Schultz KM *et al*. Structures of aminoarabinose transferase ArnT suggest a molecular basis for lipid A glycosylation. *Science* 2016; **351**: 608–12.

11 Zhang H, Zong Z, Lei S *et al*. A genomic, evolutionary, and mechanistic study of MCR-5 action suggests functional unification across the MCR family of colistin resistance. *Adv Sci (Weinh)* 2019; **6**: 1900034.

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Pharmacokinetics of once-daily doravirine over 72 h following drug cessation

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Sir,

Successful combination ART (cART) relies on daily adherence to cART.[1,2] The 'optimal' adherence pattern may be difficult to adopt as cART is for life and doses can be forgotten or delayed, making antiretrovirals with long half-lives ($t_{1/2}$s) desirable. Such drugs may allow for missed or delayed doses when drug concentrations are maintained at therapeutic levels until the next dose is administered.

Data on drug persistence and terminal $t_{1/2}$ are available for different cARTs and have been useful to advise clinicians and patients on delayed or missed doses.[3] Herein, we investigated the pharmacokinetic (PK) 'forgiveness' of the new NNRTI doravirine. Doravirine was recently approved to treat HIV infection as a single entity (Pifeltro®) and as a fixed-dose combination with tenofovir disoproxil fumarate and lamivudine (Delstrigo®).[4] Since the PK forgiveness of tenofovir disoproxil fumarate and lamivudine has been extensively studied,[5,6] in the present study we characterized the persistence of doravirine in the absence of other agents.

Regulatory and ethical approvals (London Westminster Research Ethics Committee 19/LO/0666) were obtained before initiating the study. Written informed consent was obtained from participants prior to study enrolment. In this Phase I, open-label, PK study, the participants received 100 mg of doravirine once daily for 7 days to