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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 bacteremia 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

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with cystic fibrosis (CF). 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 and C. respiraculi LMG 21510 (Laboratory of Microbiology, Ghent University, Ghent, Belgium), were included. Isolates were identified by amplified ribosomal DNA restriction analysis (ARDRA) 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 neocator, 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 × 10⁵ 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.

C. gilardii and C. basilensis by non-Enterobacteriaceae CLSI breakpoints (2019; https://clsi.org) for minocycline and co-trimoxazole. Such discrepancies between meropenem and imipenem activities are possibly due to the overexpression of efflux pumps from the resistance-nodulation-division division. 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, probably due to efflux pumps and aminoglycoside-modifying enzymes. 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. However, Petrou et al. 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. neocator, C. pauculus and C. taiwanensis sequences strains (a query cover >80%, an identity >70% and an E value <1 × 10⁻40 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.

In conclusion, our study showed that minocycline and cephefime 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 ceftazidime/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) |
|-----------------------------|---------------------------------|------------|------------------------------------------|----------------------------------------|
|                             |                                 | MIC₅₀      | MIC₉₀                                     |                                        |
| C. respiraculi (18)         | 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)                               |
|                             | cefotaxime/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)                               |
|                             | 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)                                |
| C. pauculus (5) and C. metallidurans (4) |                         |            |                                          |                                        |
|                             | piperacillin/tazobactam         | 8          | 16                                      | 39 (<4)                                 | 11 (>16)                              |
|                             | temocillin                      | 32         | 32                                      | 50 (<16)                                | 50 (>16)                              |
|                             | tobramycin                      | >256       | >256                                     | 6 (<4)                                 | 94 (>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

| Bacteria (n) | Antibiotic                  | MIC (mg/L) | Percentage susceptible (breakpoint, mg/L) | Percentage resistant (breakpoint, mg/L) |
|--------------|-----------------------------|------------|------------------------------------------|----------------------------------------|
|              |                             | MIC$_{50}$ |                             |                                        |
| 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)                                |
| 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)                                |
| ceftazidine/avibactam |             | 32         | 32                         | 33 (≤8)                                 | 67 (>8)                                |
| ceftolozane/tazobactam |             | 8          | 16                         | 50 (≤4)                                 | 50 (>4)                                |
| ceftriaxone  |                             | 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)                               |
| 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)                                |
| ceftazidine/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)                                |

C. gilardii (6)

C. basilensis (1), C. necator (2), C. taiwanensis (2) and Cupriavidus sp. (1)
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.

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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 (t1/2) 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 t1/2 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/L0/0666) 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

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