NARA
Nationales Referenzlaboratorium zur Früherkennung
neuer Antibiotikaresistenzen und Resistenzmechanismen

Centre National de Référence des Résistances Emergentes aux Antibiotiques

Characterization of novel or emerging antibiotic resistance mechanisms

The threat of spread of multidrug-resistant Gram-negative bacteria when looking at the epidemiological situation in Switzerland is still dominated by the increasing number of isolates producing carbapenem-hydrolyzing ß-lactamases in Gram negatives. Of particular concern are those producing New Delhi metallo-ß-lactamases (NDM) that have been shown to be commonly identified in our country (Findlay et al. 2021) since those enzymes confer resistance to all commercially-available ß-lactams. Those enzymes are identified among a large variety of Gram-negative species, including *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Citrobacter* spp., *Proteus mirabilis*, *Pseudomonas* spp., and *Acinetobacter baumannii.*

Noteworthy, a novel ß-lactam-ß-lactamase inhibitor (BL/BLI) combination, namely aztreonam-avibactam (ATM-AVI) (Pfizer), is currently under phase 3 development in the USA (https://www.pfizer.com/news/press-release/press-release-detail/phase-3-studies-pfizers-novel-antibiotic-combination-offer). That drug combination may provide an opportunity window to treat infections caused by metallo-ß-lactamase (MBL) producers such as NDM, considering that ATM is the only available ß-lactam being spared by the hydrolytic activity of NDM. In addition, AVI inhibits the activity of most broad-spectrum ß-
We also identified a peculiar NDM variant, namely NDM-35, that confers some cross-resistance or reduced susceptibility to cefiderocol (Poirel et al., 2021; Poirel et al., 2022a). This further suggests that NDM lactamase hydrolyzing ATM and often co-produced by NDM producers. **While awaiting the marketed version of ATM-AVI, it is actually possible to combine the clinically-available ceftazidime-avibactam together with aztreonam.**

However, last year, we reported the emergence of ATM-AVI-resistant *E. coli* isolates in Switzerland and elsewhere in Europe, those isolates being mainly NDM-5 producers exhibiting structural modifications of their penicillin binding protein 3 (main target of ATM) and co-producing plasmid-encoded cephalosporinases, such as CMY-2 or CMY-42 (Sadek et al., 2021).

Although a total of 92 NDM-5-producing *E. coli* isolates had been collected at the NARA during a 5-year period (from 2017 to 2021, 60 months), the exact same number has been recovered in a much shorter period from 2022 to October 2023 (22 months), thanks to the collaboration of the labs of the NARA network, clearly evidencing a dramatic increase of their occurrence. Those isolates belong to several genetic backgrounds / Sequence Types (ST), but the majority belong to ST167 (Sadek et al. 2020). **Such successful epidemic clone being associated with multiresistance traits, it is definitely confirmed that it constitutes a major public health concern, including in Switzerland**.

producers may be a reservoir from which cefiderocol-resistant isolates may be selected upon selective pressure in the future. Similarly cross resistance between ceftazidime-avibactam and cefiderocol has been observed

among *K. pneumoniae* producers (Poirel et al., 2022b).

Although the resistance mechanisms to ceftazidime-avibactam are dominated by the acquisition of specific KPC variants, we showed that specific ESBLs such as VEB-25 may also confer resistance to this combination (Findlay et al., 2023a).

Among the other carbapenemases types, OXA-48 derivatives are continuously identified such as OXA-484 that confers low level resistance to carbapenems (Findlay et al. 2023b). Spread of that gene is associated to a successful plasmid (IncX) different to that commonly associated with the OXA-48 gene. This finding underlines that successful plasmids as well as successful strains may be sources of outbreaks. We have also evidenced the spread of the OXA-48 encoding gene shared among *Enterobacter hormaechi* strains betweeen companion animals and humans. This spread may result from a spread of those strains possibly from humans to animals (Donà et al., 2023).

Another emerging resistance trait corresponds to the acquisition of 16S rRNA methylases (RMTases) encoding high-level resistance to all aminoglycosides such as amikacin, gentamicin, tobramycin, and kanamycin. Those enzymes methylate the target of aminoglycosides, namely the 16S rRNA. The corresponding genes are most often located on plasmids and identified among many different Gram-negative bacteria. By performing a retrospective analysis focusing on carbapenem- and aminoglycoside-resistant clinical isolates recovered in Switzerland during a 3.5-year period between January 2017 and June 2020 (Fournier et al., 2022), we showed an increasing trend overtime, from 7.5%, 10.7%, 11.2% to 13% from 2017 to 2020. **This rate is now at 18% during the 2022-2023 period among isolates recovered in our country**. Such phenomenon is not yet clearly understood, even if one explanation is actually molecular-based, with a frequent association of carbapenemase- and RMTase encoding genes on same plasmids, leading to frequent co-selections.

ß-Lactam /ß-lactamase inhibitor combinations

Recently-developed ß-lactamase inhibitors such as avibactam and relebactam (belonging to the diazabicyclooctane group of molecules), but also vaborbactam (boronic acid derivative) are commercially available, corresponding combinations being ceftazidime-avibactam (CZA), imipenem-relebactam (I/R), and meropenem-vaborbactam (MEB). Avibactam inhibits Ambler class A (KPC) and Ambler class D (OXA-48-like) carbapenemases, while vaborbactam and relebactam class A ß-lactamases only. Currently, none of the clinically-available inhibitors are active against carbapenemases of the metallo-ß-lactamase type. We have performed an evaluation of those new therapeutical options against the NARA collection of **carbapenemase-producing Enterobacterales** recovered from 2018 to 2020 (n=150), including 35% of *Escherichia coli* and 40% of *Klebsiella pneumoniae*, producing KPC-like (32%), OXA-48-like (32%), and NDM-like (24%) enzymes, and showed that **MEB was the most effective combination (77% of susceptibility)**, followed by CZA (63%) and I/R (62%) (Nordmann et al., 2023a).

Importantly, other novel ß-lactamase inhibitors are currently under phase 2 or phase 3 evaluations, including taniborbactam (TAN) which is supposed to be combined with cefepime for therapeutic purposes. Noteworthy, and as opposed to the clinically-available ß-lactamase inhibitors, TAN possesses the ability not only to compromise the hydrolytic activity of class A, C, and D ß-lactamases, but also that of MBLs. Hence, TAN well inhibits the activity of NDM- and VIM-type MBLs, which are the most widespread worldwide, but not that of IMP-type MBLs, which are mainly circulating in Japan and Australia, either among

Enterobacterales or *Pseudomonas aeruginosa* (Karlowsky et al., 2023).

By evaluating the efficacy of TAN against a large diversity of MBL enzymes, including lots of NDM and VIM variants, we identified NDM-9 on one hand and VIM-83 on the other hand that showed resistance to TAN (Le Terrier et al., 2023a). While VIM-83 seems to be so far very rare since identified in a couple of Enterobacterales worldwide, the occurrence of NDM-9 is worrying. Indeed, this variant has been identified in all parts of the world, and in many different bacterial species (*E. coli*, *Klebsiella aerogenes*, *K. pneumoniae*, *K. variicola*, *Cronobacter sakazakii* and *A. baumannii*). In Switzerland, it has so far been identified in clinical *A. baumannii* and *K. pneumoniae* isolates recovered at NARA, as well as in *K. pneumoniae* isolates recovered in wastewater in Basel (collaboration with Pr. R. Stephan, Vetsuisse Faculty, University of Zürich) (Le Terrier et al., 2023b). Nevertheless, no clonal spread of those NDM-9 producers has been identified so far in Switzerland. However, b**oth the clinical and environmental NDM-9-producing *K. pneumoniae* Swiss isolates belonged to Sequence Type ST147 which has been recognized as a high-risk clone due to its global and fast dissemination at the worldwide level**.

Novel rapid diagnostic tests and screening culture media

Rapid detection of resistance to last-resort antibiotic options is crucial in order to optimize the therapeutic choices for clinicians, and recognize at the earliest stage the emergence of isolates being resistant to those newly-developed drugs or drug combinations. Nowadays, there are several tests that allow rapid, accurate and easy-to-implement detection of ESBL-producing or carbapenemase-producing Gram-negative isolates, including biochemical (Rapid ESBL NP [Liofilchem, Italy, distributed by Axon-Lab, Switzerland], Carba NP [bioMérieux, La Balme-les-Grottes, France]) or immuno-chromatographic (NG-CTX-M Multi assay [NG Biotech, Guipry, France, distributed by Euromed, Switzerland), NG-Carba 5 (NG Biotech) and RESIST-Acineto (Coris bioconcept, distributed by AxonLab, Switzerland). However, there are no such tests to evaluate susceptibility/resistance to newly-developed antibiotics or antibiotic combinations. Those latter novel therapeutic options available in Switzerland are the followings; i) cefiderocol as a siderophore cephalosporin with potent activity against carbapenemase and in particular against many MBL producers, ii) meropenem-vaborbactam and imipenem-relebactam that are combinations made of a carbapenem and a newly-developed ß-lactamase inhibitor with activity against KPC-producing isolates), iii) ceftazidime-avibactam that is a combination of a broad-spectrum cephalosporin and the recently-developed ß-lactamase inhibitor avibactam with activity against KPC- and OXA-48-like producers, and iv) aztreonam-avibactam that is not available. (see above). For those therapeutic alternatives, we have developed a rapid and easy to implement and interpret test, that showed excellent specificities and sensitivities. These are the Rapid CAZ-AVI NP test (Nordmann et al., 2023b) for Enterobacterales, Rapid FDC *Acinetobacter baumannii* NP test (Raro et al., 2023) and Rapid Cefiderocol NP test for Enterobacterales (Nordmann et al., 2022), Rapid Aztreonam/Avibactam NP test for Enterobacterales (Viguier et al., 2023), Rapid Meropenem/Vaborbactam for Entero-bacterales (Nordmann et al., 2023c).

The Rapid Cefiderocol NP test, developed so far for Enterobacterales and *A. baumannii*, is of particular interest since the current solutions for detecting susceptibility and resistance to cefiderocol rely only on determination of MIC according to broth microdilution technique, which is complexified by a specific requirement which is the use of iron-depleted agar media. All those biochemical tests are

based on similar principles, all relying on rapid cultures in presence or absence of the corresponding antibiotic or antibiotic combinations to be tested, which rapid interpretations themselves relying on usage of color markers, either being red phenol turning from red-to-yellow upon bacterial growth (as a consequence of glucose metabolism), or being resazurin turning from blue to purple or pink upon bacterial growth (as a consequence of its property as indicator of redox potential modified upon strain viability status). One of the main advantage of those tests is that they rapidly identify susceptibility/ resistance phenotypes, which is the main criteria required by physicians to accurately define the therapy, regardless the corresponding resistance trait or mechanism. The turn-around-time to get results is actually 3 h to 4 h. They do not require specific equipment, are readable by eye, and are quite inexpensive (price per test being evaluated to be ca. 5 CHF). They can therefore be implemented in all clinical laboratories, corresponding detailed protocols as well as negative and positive controls being providing by NARA upon request.

In addition, similar tests have been developed for antibiotics that have long-term existence but which susceptibility was still not possible to test in a very short timeframe, such as imipenem susceptibility/resistance in *A. baumannii*, as a marker of multidrug-resistant microorganism (Nordmann et al., 2021) and temocillin susceptibility/resistance in Enterobacterales (Findlay et al., 2023). Indeed, temocillin constitutes an interesting alternative for treating urinary tract infections due to ESBL-producing Enterobacterales. This molecule is available in France, Germany, UK, Belgium and its perspective of marketing in Switzerland is currently considered.

Evaluation of immunological based tests for detecting ESBL showed us that several enterobacteral species such as *Citrobacter amanolaticus* and *Citrobacter farmeri* provide false positive reaction since those species produced naturally ESBL of very weak expression (a single chromosomal copy) (Ortiz de la Rosa et al. 2022). We also showed in collaboration with Italian colleagues that the biochemical Rapid ESBL NP test (LiofilChem) and the immunological NG -test CTX-M (NG BioTech) offered comparable result for detecting CTX-M producers in blood, although the Rapid ESBL NP test being less expensive (Boattini et al., 2022). We have also evaluated the Resist Acineto test from Coris Bioconcept (AxonLab, Switzerland), that is a novel immunochromatographic test for detection of the major acquired carbapenemases (OXA-23, OXA-40, OXA-58, and NDM) identified in *Acinetobacter* spp. This rapid and easy-to-perform test showed an excellent specificity and sensitivity, with positive and negatives predictive values of 100% in both cases (Bouvier M et al., 2023).

We have also developed the Rapid Polymyxin Acineto NP test (now marketed by LiofilChem, and distributed by AxonLab in Switzerland) for detecting susceptibility /resistance to polymyxins in *Acinetobacter* spp. in a 3-4 h period of time. This test showed specificity and sensitivity of 96% and 97%, respectively (Bouvier M et al., 2021).

In parallel, a molecular test was developed to rapidly identify plasmid-mediated fosfomycin resistance using a multiplex PCR assay (Freire et al., 2023). This test will provide the opportunity to detect in plasmid-mediated hosfomycin resistance genes circulating among *E. coli* clinical isolates, namely *fosA*-, *fosC*-, and *fosL*-like genes. Such PCR-based test may be interested for epidemiological purposes.

Taking in accournt the growing number of isolations of cefiderocol resistant strains, we have developed a specific screening media for detecting those strains as a source of outbreaks in hospital setttings (Ibrahim et al., 2023).

How to improve the detection of multidrug-resistant bacteria ?

Several procedures are followed by clinical microbiology laboratories and their hygiene departments when the aim is to screen for multidrug-resistant isolates in hospital settings, and, in particular in intensive care units. There are different commercially-available screening media available, for each given resistant microorganism to be targeted (e.g. ESBL-producing Enterobacterales, carbapenem-resistant Gram-negatives, etc… such as the SuperCarba medium etc), polymyxin-resistant Gram negatives (using the different media SuperPolymyxin, CHROMagar COL-APSE, and CHROMID colistin [all distributed by AxonLab in Switzerland]) but also for carbapenem-resistant *Acinetobacter baumannii* or *Pseudomonas aeruginosa* strains (e.g. CHROMagar-Acinetobacter of CHROMagar Pseudomonas, respectively [AxonLab]). The protocol to be followed ahead of the plating of screening samples on those screening media, when using stools or rectal swabs as samples. Indeed, it is questionable whether a pre-enrichment step would be beneficial, though it would require an additional practical step, and slightly increase the overall screening procedure. We have performed an evaluation of different procedures, comparing protocols with non-enrichment, pre-culture enrichment in a broth lacking any antibiotic, or pre-culture-enrichment in a broth supplemented with a subinhibitory concentration of the targeted antibiotic. Our study demonstrated the benefit of enrichment steps in terms of sensitivity of detection of colistin- and carbapenem-resistant non fermenters, ESBL producers and VRE (Nordmann et al., 2021; Sadek et al., 2020). In the context of an outbreak, we therefore propose the following strategy, which has to be to performed in parallel: i) direct plating of the stools on the selective medium and ii) inoculating an enrichment broth (18 h culture) to be further plated on the selective medium, eventually improving the sensitivity of detection of those MDR non-fermenters, if no growth could be observed with direct plating.

Emergence of carbapenemase-producing hypervirulent *Klebsiella pneumoniae* in Switzerland

Hypervirulent *K. pneumoniae* (hvKp) isolates causing invasive infections are increasingly reported worldwide, since their original discovery in 1986 in Taiwan. These strains are mainly associated with community-acquired infections, affecting healthy patients and causing in particular liver abscesses, septicemia, endophthalmitis, or meningitidis. The problem is that an increasing occurrence of *K. pneumoniae* isolates combining multidrug resistance (MDR) and hypervirulence (hv), namely the so-called MDR-hvKp, also called convergent clones, is being observed. Those strains have the potential of causing difficult-to-treat infections in healthy adults with an increased capacity for mortality. It is therefore crucial to track their dissemination to prevent their further spread.

After the idenfication of the first case in Switzerland (Blanc et al., 2021), we have performed a study to investigate the occurrence of carbapenemase-producing hvKp isolates in Switzerland and to determine their genetic profile. A total of 279 MDR carbapenemase-producing *K. pneumoniae* recovered between 2017 and 2020 at the NARA, from different samples (1.5% from urine, 6.1% from respiratory tract, 3.9% from wounds, 3.6% from blood culture, and 6.5% from other biological sites) and from patients hospitalized all over Switzerland (including 10 cantons) was investigated, and a rate of 9.0% *K. pneumoniae* presenting a virulence genotype was identified. Those isolates produced either KPC, NDM, or OXA-48 and many of the corresponding clonal backgrounds identified had been previously reported such as ST23-K1, ST395-K2, and ST147-K20 or

ST147-K64. All the isolates defined as MDR-hvKp (4.7%) possessed the aerobactin and the yersiniabactin clusters. The ST23-K1s were the only isolates presenting the colibactin cluster and achieved higher virulence scores. This study highlights the occurrence and circulation of worrisome MDR-hvKp and MDR non-hypervirulent *K. pneumoniae* (MDR-nhv-Kp) isolates in Switzerland. Our findings raise an alert regarding the need for active surveillance networks to track and monitor the spread of such successful hybrid clones representing a public health threat worldwide (Hallal Ferreira Raro et al., 2023). This monitoring shall primarily rely on surveillance of uncommon clinical cases with infections caused by *K. pneumoniae* since there is not a strict parallelism between presence of those virulence genes and severity of clinical cases.

The emergence of NDM-1-producing *K. pneumoniae* isolates in Switzerland, mirroring the trends observed in Italy, and the NDM-14 peculiar variant

Although the majority of carbapenemase-producing Enterobacterales identified in Switzerland used to be producers of the OXA-48 ß-lactamase (or its derivatives such as OXA-181, OXA-232, OXA-244), recent data collected at the NARA clearly show a rising trend of NDM-like producers, accounting for ca. 40% of the carbapenemase-producing *E. coli* and ca. 30% of the carbapenemase-producing *K. pneumoniae.* This is of major concern, since NDM-like enzymes, unlike OXA-48-like ones, i) does confer higher resistance levels to carbapenems, ii) does confer resistance to broad-spectrum cephalosporins, and iii) are not inhibited by avibactam, relebactam or vaborbactam and therefore corresponding producers exhibit high-level resistance to ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam. Hence, aztreonam-avibactam combination and cefiderocol remain as almost last-chance salvage therapies.

Here we would like to alert about the current epidemiological situation reported in Italy with commonly observed patient transfers, where occurrence of NDM-like-producing and highly cefiderocol-resistant *K. pneumoniae* isolates belonging to ST147 clonal background is on the rise. Nosocomial outbreaks were reported in Toscany (Coppi et al., 2022), and scattered reports observed in Pavia (Bellinzona et al., 2023). Additional resistance to cefiderocol of those carbapenem-resistant *K. pneumoniae* isolates was shown to be related to mutations leading to inactivation of the *cirA* gene encoding a siderophore receptor, therefore corresponding to a chromosomal- and non-transferable resistance determinant, inherent to the strain clonal background. Of note, it was previously shown that some regions of Italy were facing endemic or epidemic situations in relation with NDM-1-producing but cefiderocol-susceptible ST147 *K. pneumoniae*. Therefore, it is likely that the newly-emerging and cefiderocol-resistant isolates identified recently correspond to an evolution of this clonal background toward additional resistance, likely upon selective pressure with cefiderocol (Tascini et al., 2023). Such phenomenon should clearly draw our attention with respect to the current epidemiological situation in Switzerland, with increasing occurrence of NDM-producing *K. pneumoniae* isolates. Timely and continuous monitoring of susceptibility to cefiderocol of such multidrug-resistant isolates will be absolutely required. Likewise, another worrying phenomenon is currently observed in France, another neighboring country, with the emergence and rapid dissemination of highly-resistant *K. pneumoniae* ST147, corresponding to a single clone likely originating from Morocco, which fortunately still shows susceptibility to colistin, aztronam-avibactam, and cefiderocol (Emeraud et al., 2023).

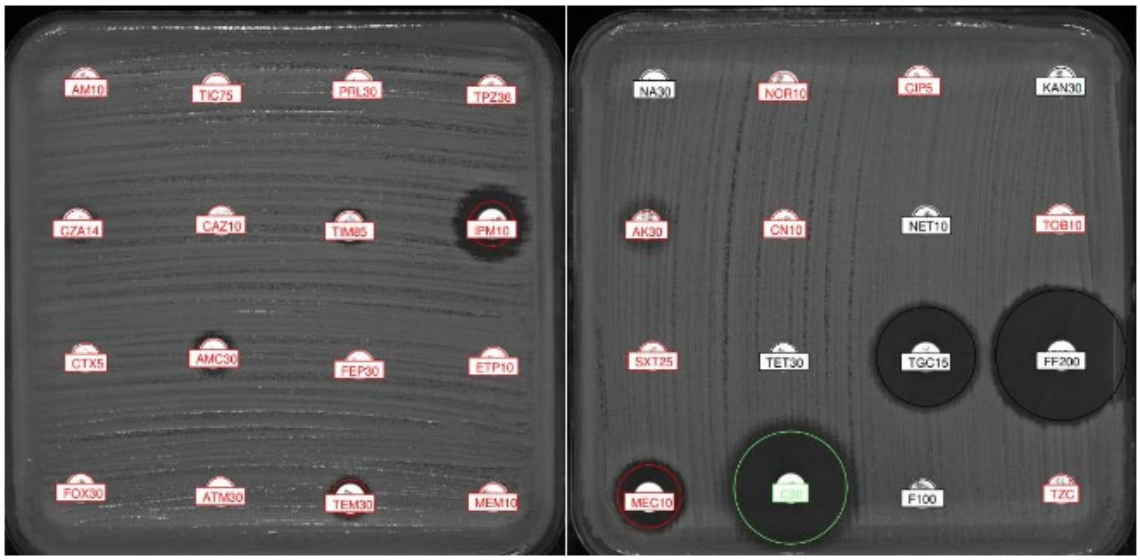
Finally, the occurrence of NDM-1-producing *K. pneumoniae* belonging to ST307 was reported very recently in Germany (Western Pomerania) being responsible for a nosocomial outbreak (Schaufler et al., 2023). Among the

isolates having spread among patients in this hospital, some showed resistance to cefiderocol (here also as a result of a mutation in the *cirA* gene encoding a siderophore receptor), although cefiderocol had not been used in this hospital. This actually questions about the selective pressure that might explain the emergence of such clone, or whether this was just a coincidental feature. On the top of that, those ST307 *K. pneumoniae* isolates possessed a series of virulence genes conferring them a possible degree of hypervirulence.

Antibiograms of clinical interest

K. pneumoniae producing the carbapenemase NDM-1, the extended-spectrum ß-lactamases (ESBL) CTX-M-15, and the ArmA 16S rRNA methylase

High-level resistance to all ß-lactams including to carbapenems is observed. Resistance to ceftazidime-avibactam also observed here since avibactam not inhibiting NDM-1. Resistance to aztreonam due to production of the CTX-M-15 ESBL (co-production of an ESBL observed among 80% of the NDM producers, that explains the resistance observed to aztreonam). Susceptibility to ceftazidime-avibactam + aztreonam when associating those drugs, with avibactam inhibiting the hydrolytic activity of CTX-M-15 and therefore restoring the aztreonam efficacy. Of note, high-level resistance to aminoglycosides observed here, due to the production of the ArmA enzyme. Some phantom zone is observed around the amikacin disk, which is common upon production of 16S rRNA methylases.



AM, Ampicillin (10 µg); TIC, Ticarcillin (75 µg); PRL, Piperacillin (30 µg); TPZ, Piperacillin/Tazobactam (30/6 µg); CZA, Ceftazidime/Avibactam (14 µg); CAZ, Ceftazidime (10 µg); TIM, Ticarcillin/Clavulanate (75/10 µg); IPM, Imipenem (10 µg); CTX, Cefotaxime (5 µg); AMC, Amoxicillin/ Clavulanate (20/10 µg); FEP, Cefepime (30 µg); ETP, Ertapenem (10 µg); FOX, Cefoxitin (30 µg); ATM, Aztreonam (30 µg); TEM, Temocillin (30 µg); MEM, Meropenem (10 µg)

NA, Nalidixic acid (30 µg) ; NOR, Norfloxacin (10 µg) ; CIP, Ciprofloxacin (5 µg) ; KAN, Kanamycin (30 µg) ; AK, Amikacin (30 µg) ; CN, Gentamicin (10 µg) ; NET, Netilmicin (10 µg) ; TOB, Tobramycin (10 µg) ; SXT, Triméthoprim/Sulfamethoxazole (1.25/23.75 µg) ; TET, Tetracycline (30 µg) ; TGC, Tigecycline (15 µg) ; FF, Fosfomycine (200 µg); MEC, Mecillinam (10 µg) ; C, Chloramphenicol (30 µg) ; F, Nitrofurantoin (100 µg) ; TZC, Ceftolozane/Tazobactam (30/10 µg)

E. coli producing OXA-244, a derivative of OXA-48

Susceptibility to carbapenems of variable levels depending on the carbapenem molecule. OXA-244 possesses a weaker carbapenemase activity than OXA-48 from which it derivates (associated to weak expression with frequently a single chromosomal insertion of the corresponding gene). This leads to such phenotype with decreased susceptibility to ertapenem and frank susceptibility for imipenem and meropenem.

Susceptibility to the ceftazidime/avibactam combination is preserved.

Resistance to temocillin observed here, which is a common feature of isolates producing OXA-48-like ß-lactamases (although shared by other carbapenemases such as NDM) and can therefore be considered as a key feature to suspect production of such weak carbapenemase. Such isolates are frequently identified among *E. coli* isolates. Their occurrence in Switzerland might be underestimated since such phenotype is not obvious to interpret, and does not systematically lead to suspicion of carbapenemase production.

AM, Ampicillin (10 µg); TIC, Ticarcillin (75 µg); PRL, Piperacillin (30 µg); TPZ, Piperacillin/Tazobactam (30/6 µg); CZA, Ceftazidime/Avibactam (14 µg); CAZ, Ceftazidime (10 µg); TIM, Ticarcillin/Clavulanate (75/10 µg); IPM, Imipenem (10 µg); CTX, Cefotaxime (5 µg); AMC, Amoxicillin/ Clavulanate (20/10 µg); FEP, Cefepime (30 µg); ETP, Ertapenem (10 µg); FOX, Cefoxitin (30 µg); ATM, Aztreonam (30 µg); TEM, Temocillin (30 µg); MEM, Meropenem (10 µg)

NA, Nalidixic acid (30 µg) ; NOR, Norfloxacin (10 µg) ; CIP, Ciprofloxacin (5 µg) ; KAN, Kanamycin (30 µg) ; AK, Amikacin (30 µg) ; CN, Gentamicin (10 µg) ; NET, Netilmicin (10 µg) ; TOB, Tobramycin (10 µg) ; SXT, Triméthoprim/Sulfamethoxazole (1.25/23.75 µg) ; TET, Tetracycline (30 µg) ; TGC, Tigecycline (15 µg) ; FF, Fosfomycine (200 µg); MEC, Mecillinam (10 µg) ; C, Chloramphenicol (30 µg) ; F, Nitrofurantoin (100 µg) ; TZC, Ceftolozane/Tazobactam (30/10 µg)

Future meeting

Symposium "Emerging Antibiotic Resistance 2024" organized by the NARA at Fribourg, September 19th, 2024.

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References

- Bellinzona G, Merla C, Corbella M, Iskandar EN, Seminari E, Di Matteo A, Gaiarsa S, Petazzoni G, Sassera D, Baldanti F, Piazza A, Cambieri P. Concomitant Resistance to Cefiderocol and Ceftazidime/Avibactam in Two Carbapenemase-Producing *Klebsiella pneumoniae* Isolates from Two Lung Transplant Patients. Microb Drug Resist. 2023. In press.
- Boattini M, Bianco G, Comini S, Iannaccone M, Casale R, Cavallo R, Nordmann P, Costa C. Direct detection of extended-spectrum-β-lactamase-producers in Enterobacterales from blood cultures: a comparative analysis. Eur J Clin Microbiol Infect Dis. 2022;41:407-413.
- Bouvier M, Kerbol A, Findlay J, Freire S, Poirel L, Nordmann P. Resist Acineto rapid immunological test for the detection of acquired carbapenemase producers among *Acinetobacter* spp. Diagn Microbiol Infect Dis. 2023;107:116043.
- Bouvier M, Sadek M, Pomponio S, D'Emidio F, Poirel L, Nordmann P. RapidResa Polymyxin *Acinetobacter* NP® Test for Rapid Detection of Polymyxin Resistance in *Acinetobacter baumannii*. Antibiotics (Basel). 2021;10:558.
- Blanc DS, Poirel L, Van Singer M, Greub G, Nordmann P. Hypervirulent *Klebsiella pneumoniae* ST23 producing OXA-48 in Switzerland. Int J Antimicrob Agents. 2021;58:106457.
- Coppi M, Antonelli A, Niccolai C, Bartolini A, Bartolini L, Grazzini M, Mantengoli E, Farese A, Pieralli F, Mechi MT, Di Pilato V, Giani T, Rossolini GM. Nosocomial outbreak by NDM-1-producing *Klebsiella pneumoniae* highly resistant to cefiderocol, Florence, Italy, August 2021 to June 2022. Euro Surveill. 2022;27:2200795.
- Donà V, Nordmann P, Kittl S, Schuller S, Bouvier M, Poirel L, Endimiani A, Perreten V. Emergence of OXA-48-producing Enterobacter hormaechei in a Swiss companion animal clinic and their genetic relationship to clinical human isolates. J Antimicrob Chemother. 2023 dkad337.
- Emeraud C, Mahamat A, Jousset AB, Bernabeu S, Goncalves T, Pommier C, Girlich D, Birer A, Rodriguez C, Pawlotsky JM, Naas T, Bonnin RA, Dortet L. Emergence and rapid dissemination of highly resistant NDM-14-producing *Klebsiella pneumoniae* ST147, France, 2022. Euro Surveill. 2023;28:2300095.
- Findlay J, Duran JB, Poirel L, Nordmann P. Emergence of OXA-484, an OXA-48-type beta-lactamase, in Switzerland. J Glob Antimicrob Resist. 2023b;32:131-133
- Findlay J, Poirel L, Bouvier M, Gaia V, Nordmann P. Resistance to ceftazidime-avibactam in a KPC-2-producing Klebsiella pneumoniae caused by the extended-spectrum beta-lactamase VEB-25. Eur J Clin Microbiol Infect Dis. 2023a;42:639-644.
- Findlay J, Poirel L, Kessler J, Kronenberg A, Nordmann P. New Delhi Metallo-β-Lactamase-Producing Enterobacterales Bacteria, Switzerland, 2019-2020. Emerg Infect Dis. 2021;10:2628-2637.
- Findlay J, Poirel L, Nordmann P. Rapid detection of temocillin resistance in Enterobacterales. J Antimicrob Chemother. 2023c;78:2770-2771.
- Fournier C, Poirel L, Despont S, Kessler J, Nordmann P. Increasing Trends of Association of 16S rRNA Methylases and Carbapenemases in Enterobacterales Clinical Isolates from Switzerland, 2017-2020. Microorganisms. 2022;10:615-620.
- Freire S, Grilo T, Nordmann P, Poirel L, Aires-de-Sousa M. Multiplex PCR for detection of acquired plasmid-borne fosfomycin resistance fos genes in *Escherichia coli*. Diagn Microbiol Infect Dis. 2023;105:115864.

- Hallal Ferreira Raro O, Nordmann P, Dominguez Pino M, Findlay J, Poirel L. Emergence of Carbapenemase-Producing Hypervirulent *Klebsiella pneumoniae* in Switzerland. Antimicrob Agents Chemother. 2023;67:e0142422.
- Ibrahim A, Bouvier M, Sadek M, Decousser JW, Poirel L, Nordmann P. A Selective Culture Medium for Screening Cefiderocol Resistance in Enterobacterales, Pseudomonas aeruginosa, and *Acinetobacter baumannii*. J Clin Microbiol. 2023;61:e0188322.
- Karlowsky JA, Hackel MA, Wise MG, Six DA, Uehara T, Daigle DM, Cusick SM, Pevear DC, Moeck G, Sahm DF. *In Vitro* Activity of Cefepime-Taniborbactam and Comparators against Clinical Isolates of Gram-Negative Bacilli from 2018 to 2020: Results from the Global Evaluation of Antimicrobial Resistance via Surveillance (GEARS) Program. Antimicrob Agents Chemother. 2023;67:e0128122.
- Le Terrier C, Gruenig V, Fournier C, Nordmann P, Poirel L. NDM-9 resistance to taniborbactam. Lancet Infect Dis. 2023;23:401-402.
- Le Terrier C, Nordmann P, Buchs C, Di DYW, Rossolini GM, Stephan R, Castanheira M, Poirel L. Wide dissemination of Gram-negative bacteria producing the taniborbactam-resistant NDM-9 variant: a One Health concern. J Antimicrob Chemother. 2023;78:2382-2384.
- Nordmann P, Bouvier M, Delaval A, Tinguely C, Poirel L, Sakek, M. Rapid detection of ceftazidime-avibactam susceptibility / resistance in Enterobacterales. Emerg Infect Dis 2023b. In press.
- Nordmann P, Bouvier M, Poirel L. Efficacy of ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam combinations against carbapenemase-producing Enterobacterales in Switzerland. Eur J Clin Microbiol Infect Dis. 2023a;42:1145-1152.
- Nordmann P, Bouvier M, Poirel L, Sadek M. Rapid cefiderocol NP test for detection of cefiderocol susceptibility/resistance in Enterobacterales. J Antimicrob Chemother. 2022 28;77:3456-3461.
- Nordmann P, Fournier C, Poirel L. A Selective Culture Medium for Screening Carbapenem Resistance in *Pseudomonas* spp. Microb Drug Resist. 2021;27:1355-1359. doi: 10.1089/mdr.2020.0461. APMID: 33877916.
- Nordmann P, Kerbol A, Bouvier M, Sadek M, Poirel L, Raro OHF. Rapid meropenem/vaborbactam NP test for detecting susceptibility/resistance in Enterobacterales. J Antimicrob Chemother. 2023c;78:2428-2434.
- Nordmann P, Sadek M, Tinguely C, Poirel L. Rapid ResaImipenem/Acinetobacter NP Test for Detection of Carbapenem Susceptibility/Resistance in *Acinetobacter baumannii*. J Clin Microbiol. 2021;59:e03025-20.
- Ortiz de la Rosa JM, Bouvier M, Poirel L, Greub G, Blanc D, Nordmann P. Cross-reaction of naturally-produced β-lactamases from *Citrobacter farmeri* and *Citrobacter amalonaticus* with immunological detection of CTX-M enzymes. Diagn Microbiol Infect Dis. 2022;104;115760.
- Poirel L, Ortiz de la Rosa JM, Sakaoglu Z, Kusaksizoglu A, Sadek M, Nordmann P. NDM-35-Producing ST167 *Escherichia coli* Highly Resistant to β-Lactams Including Cefiderocol. Antimicrob Agents Chemother. 2022a;66:e0031122.
- Poirel L, Sadek M, Kusaksizoglu A, Nordmann P. Co-resistance to ceftazidime-avibactam and cefiderocol in clinical isolates producing KPC variants. Eur J Clin Microbiol Infect Dis. 2022b;41:677-680.
- Poirel L, Sadek M, Nordmann P. Contribution of PER-Type and NDM-Type β-Lactamases to Cefiderocol Resistance in *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2021;65:e0087721.

- Raro OHF, Bouvier M, Kerbol A, Decousser JW, Poirel L, Nordmann P. Rapid detection of cefiderocol susceptibility/resistance in *Acinetobacter baumannii*. Eur J Clin Microbiol Infect Dis. 2023;42:1511-1518.
- Sadek M, Juhas M, Poirel L, Nordmann P. Genetic Features Leading to Reduced Susceptibility to Aztreonam-Avibactam among Metallo-β-Lactamase-Producing *Escherichia coli* Isolates. Antimicrob Agents Chemother. 2020;64:e01659-20.
- Sadek M, Poirel L, Nordmann P. Optimal detection of extended-spectrum β-lactamase producers, carbapenemase producers, polymyxin-resistant Enterobacterales, and vancomycin-resistant enterococci from stools. Diagn Microbiol Infect Dis. 2020;96:114919
- Sadek M, Ruppé E, Habib A, Zahra R, Poirel L, Nordmann P. International circulation of aztreonam/avibactam resistant NDM-5 producing *Escherichia coli* isolates; successful epidemic clones. J Glob Antimicrob Resist. 2021;27:326-328.
- Schaufler K, Echelmeyer T, Schwabe M, Guenther S, Bohnert JA, Becker K, Fickenscher H, Bueter A, Maschkowitz G, Krumbholz A, Nurjadi D, Heiden SE, Eger E. Convergent *Klebsiella pneumoniae* strains belonging to a sequence type 307 outbreak clone combine cefiderocol and carbapenem resistance with hypervirulence. Emerg Microbes Infect. 2023;12:2271096.
- Tascini C, Coppi M, Antonelli A, Niccolai C, Bartolini A, Pecori D, Sartor A, Giani T, Rossolini GM. In vivo evolution to high-level cefiderocol resistance of NDM-1-producing *Klebsiella pneumoniae*, followed by intra-hospital cross-transmission. Clin Microbiol Infect. 2023:S1198-743X(23)00563-3.
- Viguier C, Bouvier M, Sadek M, Kerbol A, Poirel L, Nordmann P. Rapid Aztreonam/Avibactam NP test for detection of aztreonam/avibactam susceptibility/resistance in Enterobacterales. J Clin Microbiol. 2023;61:e0058823.

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