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Evaluation of SuperCAZ/AVI® Medium for Screening Ceftazidime-avibactam Resistant Gram-negative Isolates

Mustafa Sadek[a,b], Laurent Poirel[a,b,c,*], Manuel Dominguez Pino[a,b], Fernando D'Emidio[d], Stefano Pomponio[d], Patrice Nordmann[a,b,c,e]

[a] Medical and Molecular Microbiology, Faculty of Science and Medicine, University of Fribourg, Fribourg, Switzerland
[b] Swiss National Reference Center for Emerging Antibiotic Resistance (NARA), University of Fribourg, Fribourg
[c] INSERM European Unit (IAME), University of Fribourg, Fribourg
[d] Liofilchem, Roseto degli Abruzzi, Italy
[e] Institute for Microbiology, University of Lausanne and University Hospital Centre, Lausanne, Switzerland

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ABSTRACT

The industrial version of SuperCAZ/AVI® medium developed for screening CAZ/AVI resistant Gram-negative isolates has been evaluated here using a collection of 87 well-characterized clinical isolates of worldwide origin. In addition, testing was performed by spiking stools with a series of resistant and susceptible isolates. In those conditions, the SuperCAZ/AVI® medium exhibited a sensitivity and specificity of 100 %, down to the lower limit of detection of 10^1 to 10^2 CFU/ml. The SuperCAZ/AVI® medium is a sensitive and specific screening medium for detection of CZA-resistant bacteria regardless of their resistance mechanisms.

A novel cephalosporin/β-lactamase inhibitor, ceftazidime-avibactam (CZA), was developed to offer an alternative treatment of serious infections caused by several multidrug-resistant Gram negatives such as extended-spectrum β-lactamase or carbapenemase producing Enterobacterales (CPE) (Wright et al., 2017). This novel combination demonstrates activity against certain CPE such as those producing Ambler class A (e.g. KPC), class C, and some class D β-lactamases (e.g. OXA-48) (Sharma et al., 2016; Zhanel et al., 2013), but not against those producing Ambler class B enzymes (metallo-ß-lactamases) such as NDM, VIM, IMP (van Duin and Bonomo, 2016). Since KPC is one of the most widely spread carbapenemases in clinical isolates from European and worldwide origin, the potent activity of CZA against KPC producers is of critical interest (Kazmierczak et al., 2016; Munoz-Price et al., 2013). However, shortly after the introduction of CZA in clinical use, emergence of resistance to that drug combination has been identified in *Klebsiella pneumoniae*, involving different KPC variants such as KPC-31, KPC-35, KPC-41, KPC-50, and KPC-53 (Barnes et al., 2017; Di Pilato et al., 2020; Hemarajata and Humphries, 2019; Mueller et al., 2019; Poirel et al., 2020). Among the different KPC alleles identified from CZA-resistant isolates, the D179Y amino acid substitution has been the most frequently reported worldwide (Giddins et al., 2017; Haidar et al., 2017; Livermore et al., 2015; Shields et al., 2017; Shields et al., 2018; Venditti et al., 2019; Winkler et al., 2015;). In addition, CZA resistance may be related to overexpressed efflux pumps and/or porin deficiency, mutations, and downregulation (Xu et al., 2021).

The standard method for detection of non-susceptibility to CZA is broth microdilution (EUCAST, 2021). Other methods such as disk diffusion and Etest (bioMérieux, La Balme-les-Grottes, France) are being used (European Centre for Disease Prevention and Control, 2018). Very recently, a selective culture medium, namely the SuperCAZ/AVI medium, was developed for screening CZA resistance among Gram-negative bacteria including Enterobacterales and *Pseudomonas aeruginosa* (Sadek et al., 2020). Here we have evaluated the industrial version of the SuperCAZ/AVI® medium (Liofilchem, Roseto degli Abruzzi, Italy).

This medium was evaluated using a collection of 87 well-characterized isolates from our Unit (Table 1). Isolates were obtained from various clinical sources and countries. A total of 47 strains were susceptible to CZA (38 Enterobacterales and nine *P. aeruginosa*), while 40 were resistant (20 Enterobacterales, including nine isolates producing KPC enzymes with key substitutions conferring resistance to CAZ/AVI, and 20 *P. aeruginosa*). No *Acinetobacter baumannii* strains were included considering that the CZA spectrum of activity does not include that species. All strains were characterized for their resistance determinants by PCR approaches followed by subsequent DNA sequencing (Aires-de-Sousa et al., 2019; Ortiz de la Rosa et al., 2019). E-test strips (bioMérieux, France) were used to determine the minimal inhibitory concentrations (MICs) values of CZA. The MICs results

* Corresponding author.
E-mail address: laurent.poirel@unifr.ch (L. Poirel).

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Table 1
Detection of CZA susceptibility/resistance using the superCAZ/AVI screening medium.

Strain	Species	Origin	MIC of CZA[a] (mg/L)	CZA Susceptibility/ Resistance[b]	Resistance determinant	Isolate detected at 10^2 and/or 10^1 (CFU/ml)	
						Saline	**Stools**
Enterobacterales							
R1433	*Enterobacter cloacae*	France	0.19	S	Wild type	No	No
R254	*Klebsiella pneumoniae*	France	0.064	S	Porin defiiency + SHV+ AmpC	No	No
R1233	*Escherichia coli*	France	0.5	S	ACC-1	No	No
R1241	*Klebsiella pneumoniae*	USA	1.5	S	ACT-1	No	No
R2077	*Escherichia coli*	Switzerland	0.5	S	ACC-1	No	No
R1291	*Escherichia coli*	USA	0.032	S	OXA-1	No	No
R1335	*Escherichia coli*	France	0.064	S	TEM-1	No	No
R941	*Enterobacter cloacae*	Switzerland	1.5	S	TEM-1	No	No
R1906	*Escherichia coli*	France	0.75	S	SHV-12	No	No
R2180	*Enterobacter cloacae*	France	2	S	GES-5	No	No
N23	*Escherichia coli*	Switzerland	0.032	S	CTX-M-15	No	No
N41	*Escherichia coli*	Switzerland	0.064	S	CTX-M-9	No	No
N44	*Escherichia coli*	France	0.125	S	CTX-M-15	No	No
N71	*Escherichia coli*	Switzerland	0.032	S	CTX-M-15	No	No
R1039	*Escherichia coli*	Vietnam	0.25	S	VEB-1+OXA-10 + TEM-1	No	No
R1104	*Klebsiella pneumoniae*	Thailand	0.75	S	VEB-1	No	No
R1103	*Klebsiella pneumoniae*	Thailand	0.5	S	VEB-1	No	No
R144	*Escherichia coli*	France	0.75	S	VEB-1	No	No
R1105	*Klebsiella pneumoniae*	Thailand	0.25	S	VEB-1	No	No
R2658	*Escherichia coli*	France	0.125	S	VEB-1+TEM-1 + OXA-10	No	No
R3659	*Escherichia coli*	USA	0.5	S	KPC2 (KPC-2 (pBr322) in *E. coli* DH10B	No	No
R99	*Klebsiella pneumoniae*	France	0.5	S	KPC-2	No	No
R3521	*Klebsiella pneumoniae*	Switzerland	1.5	S	KPC-2	No	No
R3668	*Escherichia coli*	USA	0.064	S	KPC-2 (KPC2 in pBcSK in *E. coli* DH10B	No	No
R91	*Klebsiella pneumoniae*	France	0.75	S	KPC-2	No	No
R94	*Klebsiella pneumoniae*	France	2	S	KPC-2	No	No
R3485	*Klebsiella pneumoniae*	Switzerland	1	S	KPC-2	No	No
R3486	*Klebsiella pneumoniae*	Switzerland	1	S	KPC-2	No	No
R3488	*Klebsiella pneumoniae*	Switzerland	1	S	KPC-2	No	No
R3522	*Klebsiella pneumoniae*	Switzerland	1.5	S	KPC-2 +QnrB	No	No
R132	*Klebsiella pneumoniae*	France	1	S	KPC-2	No	No
R297	*Klebsiella pneumoniae*	France	0.25	S	KPC-2+ OXA-1	No	No
R100	*Klebsiella pneumoniae*	France	1.5	S	KPC-11	No	No
R22	*Escherichia coli*	France	0.094	S	OXA-48	No	No
R740	*Escherichia coli*	The Netherlands	1	S	OXA-48	No	No
R19	*Klebsiella pneumoniae*	France	0.5	S	OXA-48	No	No
N59	*Escherichia coli*	Switzerland	0.023	S	OXA-181	No	No
R131	*Klebsiella pneumoniae*	France	1.5	S	OXA-181	No	No
R3338	*Klebsiella pneumoniae*	USA	24	R	CMY-4+VIM-1	Yes	Yes
R169	*Klebsiella pneumoniae*	USA	24	R	VIM-19	Yes	Yes
N284	*Enterobacter cloacae*	Switzerland	48	R	VIM-1	Yes	Yes
R48	*Klebsiella pneumoniae*	France	> 256	R	VIM-1	Yes	Yes
R61	*Escherichia coli*	France	24	R	VIM-1+SHV-12	Yes	Yes
R63	*Klebsiella pneumoniae*	France	24	R	VIM-19		
N6	*Escherichia coli*	Switzerland	> 256	R	NDM-5	Yes	Yes
R464	*Escherichia coli*	France	> 256	R	NDM-4+OXA-1	Yes	Yes
R466	*Escherichia coli*	France	> 256	R	NDM-4+OXA-1+CTX-M-15		
R3778	*Klebsiella pneumoniae*	Spain	48	R	KPC-3 /D179Y	Yes	Yes
R3780	*Klebsiella pneumoniae*	Spain	> 256	R	KPC-3/LN168-169H	Yes	Yes
R3781	*Klebsiella pneumoniae*	Spain	64	R	KPC-3/L169P/A172T	Yes	Yes
R3776	*Klebsiella pneumoniae*	Spain	96	R	KPC-3 /D179Y	Yes	Yes
R3777	*Klebsiella pneumoniae*	Spain	> 256	R	KPC-3/ D179Y/A172T	Yes	Yes
N435	*Klebsiella pneumoniae*	Switzerland	> 256	R	KPC-41	Yes	Yes
N859	*Klebsiella pneumoniae*	Switzerland	> 256	R	KPC-50	Yes	Yes
R3671	*Escherichia coli DH10B + pBR322 KPC2 179Met*	USA	>128	R	KPC-2/D179M	Yes	Yes
R3779	*Klebsiella pneumoniae*	Spain	128	R	KPC-3/D179Y	Yes	Yes
R72	*Escherichia coli*	France	128	R	IMP-1	Yes	Yes
R73	*Klebsiella pneumoniae*	France	> 256	R	IMP-1	Yes	Yes
Pseudomonas aeruginosa							
R1553	*Pseudomonas aeruginosa*	France	1.5	S	None (wild type)	No	No
R2267	*Pseudomonas aeruginosa*	France	0.75	S	None (wild type)	No	No
N382	*Pseudomonas aeruginosa*	Switzerland	0.38	S	None (wild type)	No	No
N339	*Pseudomonas aeruginosa*	Switzerland	0.5	S	None (wild type)	No	No
N146	*Pseudomonas aeruginosa*	Switzerland	4	S	GES-5	No	No
N254	*Pseudomonas aeruginosa*	Switzerland	1	S	None (wild type)	No	No
N214	*Pseudomonas aeruginosa*	Switzerland	0.5	S	None (wild type)	No	No
R1188	*Pseudomonas aeruginosa*	Brazil	2	S	CTX-M-2	No	No
R3451	*Pseudomonas aeruginosa*	France	1	S	GES-6	No	No

(*continued*)

Table 1 (*Continued*)

Strain	Species	Origin	MIC of CZA[a] (mg/L)	CZA Susceptibility/ Resistance[b]	Resistance determinant	Isolate detected at 10^2 and/or 10^1 (CFU/ml)	
						Saline	**Stools**
R3680	*Pseudomonas aeruginosa*	USA	24	R	OprD defect and overexpression of efflux pumps	Yes	Yes
R3681	*Pseudomonas aeruginosa*	USA	32	R	OprD defect and overexpression of efflux pumps	Yes	Yes
R3682	*Pseudomonas aeruginosa*	USA	64	R	OprD defect and overexpression of efflux pumps	Yes	Yes
R3683	*Pseudomonas aeruginosa*	USA	> 256	R	OprD defect and overexpression of efflux pumps	Yes	Yes
R1308	*Pseudomonas aeruginosa*	France	> 256	R	OXA-28	Yes	Yes
R1311	*Pseudomonas aeruginosa*	France	12	R	OXA-32	Yes	Yes
R609	*Pseudomonas aeruginosa*	Turkey	64	R	VIM-2	Yes	Yes
R50	*Pseudomonas aeruginosa*	France	24	R	VIM-2	Yes	Yes
R51	*Pseudomonas aeruginosa*	France	> 256	R	VIM-2	Yes	Yes
R52	*Pseudomonas aeruginosa*	France	16	R	VIM-2	Yes	Yes
R54	*Pseudomonas aeruginosa*	France	> 256	R	VIM-2	Yes	Yes
R598	*Pseudomonas aeruginosa*	France	24	R	VIM-2	Yes	Yes
R599	*Pseudomonas aeruginosa*	France	16	R	VIM-2	Yes	Yes
R600	*Pseudomonas aeruginosa*	Japan	16	R	VIM-2	Yes	Yes
R604	*Pseudomonas aeruginosa*	The Netherlands	12	R	VIM-2	Yes	Yes
R608	*Pseudomonas aeruginosa*	France	16	R	VIM-2	Yes	Yes
R610	*Pseudomonas aeruginosa*	France	32	R	VIM-2	Yes	Yes
N885	*Pseudomonas aeruginosa*	Switzerland	> 256	R	NDM-1	Yes	Yes
R186	*Pseudomonas aeruginosa*	France	16	R	NDM-6	Yes	Yes
R2760	*Pseudomonas aeruginosa*	France	> 256	R	NDM-1	Yes	Yes

[a] CZA, ceftazidime-avibactam, MICs of CZA were determined using E-test.
[b] R, resistant; S, susceptible.

were interpreted according to the latest EUCAST breakpoints for Enterobacterales and *P. aeruginosa* (i.e. S, ≤8 μg/ml; R, >8 μg/ml) (EUCAST, 2021).

Serial 10-fold dilutions were made in 0.85% saline solution with bacterial suspensions with an optical density of 0.5 McFarland standard (inoculum of ~1.5 × 10^8 CFU/ml). Then, aliquots of 100 μl of each dilution were inoculated onto the SuperCAZ/AVI® medium. For the quantification of the viable bacteria in each dilution step, tryptic soy agar plates were inoculated with 100 μl of each suspension and incubated overnight at 37 °C. The number of colonies was counted the next day. When no growth was observed after 18 h, incubation was extended up to 48 h. The sensitivity and specificity cut-off values were set at 1 × 10^3 CFU/ml. All the CZA-resistant isolates grew on the SuperCAZ/AVI® medium within 24 h and the lowest limit of detection was below the cut-off value, ranging from 10^1 to 10^2 CFU/ml. By contrast, all the CZA-susceptible isolates did not grow under those conditions, showing an excellent specificity. The sensitivity and specificity of the SuperCAZ/AVI® medium for selecting CZA-resistant isolates were both at 100%. Spiked stools were also tested with the same representative collection of CZA-resistant and susceptible isolates using the SuperCAZ/AVI® medium. Spiking experiments were performed as previously described using human stools of different healthy donors (Nordmann et al., 2012; Sadek et al., 2020). All CZA-resistant strains spiked in stools were well detected below the cut-off value, ranging from 10^1 to 10^2 CFU/ml. Again, the sensitivity and specificity values were found at 100%.

In conclusion, the SuperCAZ/AVI® medium showed a sensitivity and specificity of 100%, down to the lower limit of detection of 10^1 to 10^2 CFU/ml. The SuperCAZ/AVI® medium is therefore a sensitive and specific screening medium for detection of CZA-resistant bacteria regardless of their resistance mechanisms. The use of culture media that do not include carbapenems as selective agents, such as SuperCAZ/AVI, could represent a valuable option to screen for the carriage of CZA-resistant KPC-producing *K. pneumoniae* strains, particularly in geographical areas where KPC-producing *K. pneumoniae* strains are endemic and where subsequently KPC variants are more likely to be selected. Indeed, most of the KPC-producing and CZA-resistant isolates described so far showed susceptibility to carbapenems as a consequence of a reduced carbapenemase activity of those enzyme variants (Di Pilato et al., 2020). Due to its low limit of detection, such selective medium may be used for prospective screening and epidemiological surveys of CZA-resistant isolates. Also, it may contribute to a rapid implementation of infection control measures in order to limit their further spread.

Author contributions

L.P., P.N., F.E., S.P. conceptualization-supervision and funding acquisition; M.S., L.P., P.N., methodology and design of the study; M. S., M.D.P., investigation; all authors, analysis and interpretation of data; M.S., P.N., L.P., writing - original draft; all authors, writing-review- editing and final approval of the version to be submitted.

Disclosure statement

S.P. and F.E. are employees of the Liofilchem company.

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Declaration of Competing Interest

All authors have nothing to declare.

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