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A Selective Culture Medium for Screening Ceftazidime-Avibactam Resistance in *Enterobacterales* and *Pseudomonas aeruginosa*

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ABSTRACT The SuperCAZ/AVI medium was developed for screening ceftazidime-avibactam (CZA) resistance among Gram-negative bacteria (*Enterobacterales* and *Pseudomonas aeruginosa*). It was evaluated using 50 CZA-susceptible and 42 CZA-resistant Gram-negative isolates. Its sensitivity and specificity of detection were 100%. Excellent performance of the medium was also observed by testing spiked stools, with the lower limit of detection ranging from 10^1 to 10^2 CFU/ml. This screening medium provides the opportunity to detect CZA-resistant isolates regardless of their resistance mechanisms.

KEYWORDS ceftazidime, avibactam, screening, *Enterobacterales*, *Pseudomonas aeruginosa*

The emergence and spread of β-lactam resistance, especially resistance to carbapenems, are currently of great concern worldwide, particularly in *Enterobacterales* and *Pseudomonas aeruginosa* (1). Among the recently developed agents active against multidrug-resistant Gram-negative pathogens, a novel drug combination has been launched, namely, ceftazidime-avibactam (CZA) (2). Avibactam (AVI) is a non-β-lactam–β-lactamase inhibitor that inhibits the activities of Ambler class A, class C, and some class D β-lactamases, including carbapenemases (e.g., KPC, OXA-48) (3, 4). However, acquired resistance to CZA is increasingly reported and is mostly related to amino acid substitutions in the active sites of the respective β-lactamases. Many studies have identified KPC variants in *Klebsiella pneumoniae*, such as KPC-31, KPC-35, KPC-41, and KPC-50, all conferring resistance to CZA (5–8). Those KPC variants confer acquired resistance to CZA on the corresponding producers mainly as a consequence of decreased inhibitory activity of AVI against those enzymes, but also due to higher hydrolytic efficiency toward ceftazidime (CAZ). In addition, resistance to CZA in Gram-negative bacteria may be related to the production of Ambler class B enzymes (metallo-β-lactamases [MBL]), such as NDM, VIM, and IMP, or of several non-OXA-48-like class D β-lactamases, such as OXA-28 or OXA-32, whose hydrolytic activity includes CAZ but which are not inhibited by AVI (1). Furthermore, CZA resistance may be related to overproduction of efflux pumps and/or porin defects (9). Taking into account the increasing use of the CZA combination and consequently the increasing isolation of CZA-resistant Gram-negative bacteria, we have developed a selective culture medium for screening CZA-resistant isolates among Gram-negative species (*Enterobacterales*, *P. aeruginosa*).

Citation Sadek M, Poirel L, Tinguely C, Nordmann P. 2020. A selective culture medium for screening ceftazidime-avibactam resistance in *Enterobacterales* and *Pseudomonas aeruginosa*. J Clin Microbiol 58:e00965-20. https://doi.org/10.1128/JCM.00965-20.

Editor Nathan A. Ledeboer, Medical College of Wisconsin

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Received 1 May 2020
Returned for modification 28 May 2020
Accepted 16 June 2020

Accepted manuscript posted online 24 June 2020
Published 24 August 2020

TABLE 1 Preparation of the SuperCAZ/AVI medium

Compound	Stock solution[a]	Quantity or vol to add[b]	Final concn
CHROMagar Orientation medium		13.2 g	3.3%
Distilled water		400 ml	
Ceftazidime pentahydrate	6 mg/ml in PBS (pH 7.2)	400 μl	6 μg/ml
Avibactam sodium hydrate	4 mg/ml in water	400 μl	4 μg/ml
$ZnSO_4 \cdot 7H_2O$	70 mg/ml in water	400 μl	70 μg/ml
Daptomycin	10 mg/ml in water	400 μl	10 μg/ml
Amphotericin B	5 mg/ml in 10% D-(+)-glucose	400 μl	5 μg/ml

[a]PBS, phosphate-buffered saline.
[b]The volume of 400 ml of SuperCAZ/AVI medium was for 20 plates.

MATERIALS AND METHODS

The SuperCAZ/AVI medium. In the design of our medium (named the SuperCAZ/AVI medium), the necessity of preventing contamination by Gram-positive bacteria and fungi was considered. Based on our experience in the development of screening media (10), the optimal screening medium was based on the CHROMagar Orientation medium (reference RT412; CHROMagar, Paris, France), which is commonly used as a differential medium for the isolation and differentiation of common urinary tract pathogens. The CZA resistance breakpoint is defined as >8 μg/ml for *Enterobacterales* and *P. aeruginosa* with a fixed concentration of AVI (4 μg/ml) (11). The optimal final concentration of CAZ was 6 μg/ml with a fixed concentration of AVI at 4 μg/ml. Since Gram-positive bacteria, such as *Enterococcus*, *Streptococcus*, and *Staphylococcus* strains, may grow on CHROMagar Orientation medium, daptomycin (code 461375000; Acros Organics) (which can be replaced by vancomycin) was added as an anti-Gram-positive molecule at a final concentration of 10 μg/ml. Amphotericin B (code 45590050; Acros Organics) was also added as an antifungal at a final concentration of 5 μg/ml. In addition, $ZnSO_4$ (70 μg/ml) was added to enhance the activity of MBL producers (10). The stock solutions of CAZ, AVI, daptomycin, and amphotericin B were prepared as shown in Table 1 and may be kept at −20°C for 1 year. For the preparation of the SuperCAZ/AVI medium, the diluted powder of CHROMagar Orientation medium was autoclaved at 121°C for 15 min. After the medium was cooled for 1 h at 56°C, the antibiotic stock solutions were added (Table 1). The SuperCAZ/AVI plates were stored at 4°C and were protected from direct light exposure before use, for as long as 1 week.

Susceptibility testing. The MICs of CZA were determined using Etest strips (bioMérieux, La Balme-les-Grottes, France) on Mueller-Hinton agar plates at 37°C, and the results were interpreted according to the latest EUCAST breakpoints for *Enterobacterales* and *P. aeruginosa* (i.e., susceptibility [S], ≤8 μg/ml; resistance [R], >8 μg/ml) (Table 2) (10).

RESULTS

A total of 92 isolates of worldwide origin were included in this study to evaluate the performance of the SuperCAZ/AVI medium. The β-lactamase contents of all strains were characterized at the molecular level by PCR and sequencing or, for some isolates, by whole-genome sequencing (Table 2). A total of 50 strains were susceptible to CZA (40 *Enterobacterales*, including *Enterobacter cloacae*, *K. pneumoniae*, and *Escherichia coli*, and 10 *P. aeruginosa* strains), and 42 were resistant to CZA (20 *Enterobacterales*, including *E. cloacae*, *K. pneumoniae*, and *E. coli*, and 22 *P. aeruginosa* strains) (Table 2).

Starting with an optical density of a 0.5 McFarland standard (an inoculum of $\sim 1.5 \times 10^8$ CFU/ml), serial 10-fold dilutions were made in 0.85% saline solution, and 100-μl aliquots of each dilution were plated onto the SuperCAZ/AVI medium. To quantify the viable bacteria in each dilution step, tryptic soy agar plates were inoculated concomitantly with 100 μl of each suspension and were incubated overnight at 37°C. Viable colonies were counted the following day. When no growth was observed after 18 h, incubation was extended up to 48 h in order to definitely assess the negativity of the culture. The lower limit of detection for the strains tested was determined using the SuperCAZ/AVI medium.

The sensitivity and specificity cutoff values for the detection of CZA-resistant *Enterobacterales* and *P. aeruginosa* were set at 1×10^3 CFU/ml, i.e., the CZA-resistant isolates recovered on SuperCAZ/AVI medium plates at $<1 \times 10^3$ CFU/ml were considered positive, while the CZA-susceptible isolates grown using an inoculum of $\geq 1 \times 10^3$ CFU/ml were considered negative (10). All the CZA-resistant isolates could be recovered within 24 h on SuperCAZ/AVI medium plates by using an inoculum below the cutoff value of 1×10^3 CFU/ml (1×10^1 to 1×10^2 CFU/ml) (Table 2). In contrast, growth of

TABLE 2 MICs of CZA for the strains tested and detection limits of the SuperCAZ/AVI screening medium

Category and strain	Species	Origin	MIC of CZA[a] (mg/liter)	CZA susceptibility or resistance[b]	Resistance determinant(s)	Lower limit of detection (CFU/ml)[c] in:	
						Culture	Stools[c]
Enterobacterales							
R1433	*Enterobacter cloacae*	France	0.19	S	Wild type	$\geq 10^8$	$\geq 10^7$
R254	*Klebsiella pneumoniae*	France	0.064	S	Porin deficiency, SHV, AmpC	10^6	10^6
R1233	*Escherichia coli*	France	0.5	S	ACC-1	$\geq 10^8$	$\geq 10^7$
R1241	*Klebsiella pneumoniae*	USA	1.5	S	ACT-1	10^6	10^6
R2077	*Escherichia coli*	Switzerland	0.5	S	ACC-1	10^7	10^7
R1291	*Escherichia coli*	USA	0.032	S	OXA-1	$\geq 10^8$	$\geq 10^7$
R1335	*Escherichia coli*	France	0.064	S	TEM-1	10^8	$\geq 10^7$
R941	*Enterobacter cloacae*	Switzerland	1.5	S	TEM-1	10^7	10^7
R1906	*Escherichia coli*	France	0.75	S	SHV-12	$\geq 10^8$	$\geq 10^7$
R2180	*Enterobacter cloacae*	France	2	S	GES-5	$\geq 10^8$	$\geq 10^7$
N23	*Escherichia coli*	Switzerland	0.032	S	CTX-M-15	10^8	$\geq 10^7$
N41	*Escherichia coli*	Switzerland	0.064	S	CTX-M-9	10^8	$\geq 10^7$
N44	*Escherichia coli*	France	0.125	S	CTX-M-15	$\geq 10^8$	$\geq 10^7$
N71	*Escherichia coli*	Switzerland	0.032	S	CTX-M-15	$\geq 10^8$	$\geq 10^7$
R1039	*Escherichia coli*	Vietnam	0.25	S	VEB-1, OXA-10, TEM-1	$\geq 10^8$	$\geq 10^7$
R1104	*Klebsiella pneumoniae*	Thailand	0.75	S	VEB-1	$>10^8$	$>10^7$
R1103	*Klebsiella pneumoniae*	Thailand	0.5	S	VEB-1	$>10^7$	$>10^7$
R144	*Escherichia coli*	France	0.75	S	VEB-1	$\geq 10^8$	$\geq 10^7$
R1105	*Klebsiella pneumoniae*	Thailand	0.25	S	VEB-1	$>10^8$	$>10^8$
R2658	*Escherichia coli*	France	0.125	S	VEB-1, TEM-1, OXA-10	$\geq 10^8$	$\geq 10^7$
R3659	*Escherichia coli*	USA	0.5	S	KPC-2 (*E. coli* DH10B/pBR322 bla_{KPC-2})	$\geq 10^8$	$\geq 10^8$
R99	*Klebsiella pneumoniae*	France	0.5	S	KPC-2	10^7	10^5
R3521	*Klebsiella pneumoniae*	Switzerland	1.5	S	KPC-2	10^5	10^6
R3668	*Escherichia coli*	USA	0.064	S	KPC-2 [*E. coli* DH10B/pBC SK(+) bla_{KPC-2}]	$\geq 10^8$	$\geq 10^8$
R82	*Escherichia coli*	France	0.047	S	KPC-2	$\geq 10^8$	$\geq 10^7$
R91	*Klebsiella pneumoniae*	France	0.75	S	KPC-2	$\geq 10^8$	$\geq 10^7$
R94	*Klebsiella pneumoniae*	France	2	S	KPC-2	$\geq 10^8$	$\geq 10^7$
R3485	*Klebsiella pneumoniae*	Switzerland	1	S	KPC-2	10^6	10^6
R3486	*Klebsiella pneumoniae*	Switzerland	1	S	KPC-2	10^8	$\geq 10^7$
R3488	*Klebsiella pneumoniae*	Switzerland	1	S	KPC-2	10^7	$\geq 10^7$
R3522	*Klebsiella pneumoniae*	Switzerland	1.5	S	KPC-2	$\geq 10^8$	$\geq 10^7$
R132	*Klebsiella pneumoniae*	France	1	S	KPC-2	$\geq 10^8$	$\geq 10^7$
R297	*Klebsiella pneumoniae*	France	0.25	S	KPC-2, OXA-1	$\geq 10^8$	$\geq 10^7$
R100	*Klebsiella pneumoniae*	France	1.5	S	KPC-11	10^8	$\geq 10^7$
R22	*Escherichia coli*	France	0.094	S	OXA-48	$\geq 10^8$	$\geq 10^7$
R740	*Escherichia coli*	The Netherlands	1	S	OXA-48	$\geq 10^8$	$\geq 10^7$
R19	*Klebsiella pneumoniae*	France	0.5	S	OXA-48	10^7	10^6
R23	*Klebsiella pneumoniae*	France	0.5	S	OXA-48	10^7	10^7
N59	*Escherichia coli*	Switzerland	0.023	S	OXA-181	$\geq 10^8$	$\geq 10^7$
R131	*Klebsiella pneumoniae*	France	1.5	S	OXA-181	10^8	$\geq 10^7$
R3338	*Klebsiella pneumoniae*	USA	24	R	CMY-4, VIM-1	10^2	10^1
R169	*Klebsiella pneumoniae*	USA	24	R	VIM-19	10^1	10^1
N284	*Enterobacter cloacae*	Switzerland	48	R	VIM-1	10^1	10^1
R48	*Klebsiella pneumoniae*	France	>256	R	VIM-1	10^1	10^1
R61	*Escherichia coli*	France	24	R	VIM-1, SHV-12	10^2	10^1
R63	*Klebsiella pneumoniae*	France	24	R	VIM-19	10^1	10^1
N6	*Escherichia coli*	Switzerland	>256	R	NDM-5	10^2	10^2
R464	*Escherichia coli*	France	>256	R	NDM-4, OXA-1	10^1	10^1
R466	*Escherichia coli*	France	>256	R	NDM-4, OXA-1, CTX-M-15	10^2	10^1
R3778	*Klebsiella pneumoniae*	Spain	48	R	KPC-3 D179Y	10^1	10^1
R3780	*Klebsiella pneumoniae*	Spain	>256	R	KPC-3 G168N E169H	10^1	10^1
R3781	*Klebsiella pneumoniae*	Spain	64	R	KPC-3 E169P L172T	10^1	10^1
R3776	*Klebsiella pneumoniae*	Spain	96	R	KPC-3 D179Y	10^1	10^1
R3777	*Klebsiella pneumoniae*	Spain	>256	R	KPC-3 D179Y A172T	10^1	10^1
N435	*Klebsiella pneumoniae*	Switzerland	>256	R	KPC-41	10^1	10^1
N859	*Klebsiella pneumoniae*	Switzerland	>256	R	KPC-50	10^1	10^1

(Continued on next page)

TABLE 2 (Continued)

Category and strain	Species	Origin	MIC of CZA[a] (mg/liter)	CZA susceptibility or resistance[b]	Resistance determinant(s)	Lower limit of detection (CFU/ml)[c] in:	
						Culture	Stools[c]
R3671	*Escherichia coli*	USA	>128	R	KPC-2 (*E. coli* DH10B/pBR322 KPC-2 D179M)	10^2	10^2
R3779	*Klebsiella pneumoniae*	Spain	128	R	KPC-3 D179Y	10^2	10^2
R72	*Escherichia coli*	France	128	R	IMP-1	10^1	10^1
R73	*Klebsiella pneumoniae*	France	>256	R	IMP-1	10^1	10^1
Pseudomonas aeruginosa							
R1553	*Pseudomonas aeruginosa*	France	1.5	S	None (wild type)	$\underline{>10^8}$	$\underline{10^7}$
R2267	*Pseudomonas aeruginosa*	France	0.75	S	None (wild type)	$\underline{>10^8}$	$\underline{10^7}$
N382	*Pseudomonas aeruginosa*	Switzerland	0.38	S	None (wild type)	$\underline{10^6}$	$\underline{10^7}$
N339	*Pseudomonas aeruginosa*	Switzerland	0.5	S	None (wild type)	$\underline{>10^8}$	$\underline{10^7}$
N146	*Pseudomonas aeruginosa*	Switzerland	4	S	GES-5	$\underline{10^4}$	$\underline{10^6}$
N254	*Pseudomonas aeruginosa*	Switzerland	1	S	None (wild type)	$\underline{>10^8}$	$\underline{10^8}$
N214	*Pseudomonas aeruginosa*	Switzerland	0.5	S	None (wild type)	$\underline{>10^8}$	$\underline{10^7}$
R1187	*Pseudomonas aeruginosa*	Belgium	4	S	BEL-2	$\underline{10^6}$	$\underline{10^5}$
R1188	*Pseudomonas aeruginosa*	Brazil	2	S	CTX-M-2	$\underline{>10^8}$	$\underline{>10^7}$
R3451	*Pseudomonas aeruginosa*	France	1	S	GES-6	$\underline{10^6}$	$\underline{10^7}$
R3680	*Pseudomonas aeruginosa*	USA	24	R	Unknown mechanism	10^1	10^2
R3681	*Pseudomonas aeruginosa*	USA	32	R	Unknown mechanism	10^1	10^1
R3682	*Pseudomonas aeruginosa*	USA	64	R	Unknown mechanism	10^1	10^1
R3683	*Pseudomonas aeruginosa*	USA	>256	R	Unknown mechanism	10^1	10^1
R1308	*Pseudomonas aeruginosa*	France	>256	R	OXA-28	10^1	10^2
R1311	*Pseudomonas aeruginosa*	France	12	R	OXA-32	10^1	10^1
R609	*Pseudomonas aeruginosa*	Turkey	64	R	VIM-2	10^1	10^1
R50	*Pseudomonas aeruginosa*	France	24	R	VIM-2	10^2	10^1
R51	*Pseudomonas aeruginosa*	France	>256	R	VIM-2	10^1	10^1
R52	*Pseudomonas aeruginosa*	France	16	R	VIM-2	10^1	10^1
R54	*Pseudomonas aeruginosa*	France	>256	R	VIM-2	10^2	10^1
R598	*Pseudomonas aeruginosa*	France	24	R	VIM-2	10^1	10^1
R599	*Pseudomonas aeruginosa*	France	16	R	VIM-2	10^1	10^1
R600	*Pseudomonas aeruginosa*	Japan	16	R	VIM-2	10^2	10^1
R604	*Pseudomonas aeruginosa*	The Netherlands	12	R	VIM-2	10^1	10^1
R608	*Pseudomonas aeruginosa*	France	16	R	VIM-2	10^2	10^2
R610	*Pseudomonas aeruginosa*	France	32	R	VIM-2	10^2	10^2
N885	*Pseudomonas aeruginosa*	Switzerland	>256	R	NDM-1	10^1	10^1
N520	*Pseudomonas aeruginosa*	Switzerland	>256	R	NDM-1	10^1	10^1
N521	*Pseudomonas aeruginosa*	Switzerland	>256	R	NDM-1	10^1	10^1
R186	*Pseudomonas aeruginosa*	France	16	R	NDM-6	10^2	10^2
R2760	*Pseudomonas aeruginosa*	France	>256	R	NDM-1	10^2	10^1

[a]CZA, ceftazidime-avibactam. MICs of CZA were determined using Etest.
[b]R, resistant; S, susceptible.
[c]Underlined CFU counts are considered negative results (cutoff values were set at $>10^3$ CFU/ml).

the CZA-susceptible isolates was possible only when an inoculum of $>10^3$ CFU/ml was used (the lower limit of detection was above the cutoff value of 10^3 CFU/ml), giving rise to 100% sensitivity and specificity.

Spiked stools were also tested with the same representative collection of CZA-resistant and -susceptible Gram-negative bacteria ($n = 92$) using this selective culture medium. Spiked fecal samples were made by adding 100 μl of serial 10-fold bacterial dilutions to 900 μl of a stool suspension. Stool suspensions were obtained by suspending 6 g of freshly pooled feces from healthy volunteers in 60 ml of distilled water as described previously (10). Aliquots (100 μl) of the spiked stool suspension were inoculated onto the SuperCAZ/AVI medium. Aliquots (100 μl) of stool suspensions with no bacteria added were plated onto the SuperCAZ/AVI medium as negative controls. The lower limit of detection was below the cutoff value for all CZA-resistant strains with which stools were spiked, ranging from 10^1 to 10^2 CFU/ml, whereas the lower limit of detection for the CZA-susceptible strains was above the cutoff value, at $\geq 10^6$ CFU/ml (Table 2). Sensitivity and specificity were determined using the same cutoff value, set

at 10^3 CFU/ml (10). Again, the sensitivity and specificity of the SuperCAZ/AVI medium for isolating CZA-resistant isolates were both 100%.

To assess the storage stability of the SuperCAZ/AVI medium, *Candida albicans* and *Staphylococcus aureus* strains, as well as the CZA-susceptible *E. coli* ATCC 25955 reference strain, were subcultured daily onto the SuperCAZ/AVI medium from a single batch of medium stored at 4°C. No growth was observed consistently for at least a 7-day period.

DISCUSSION

The SuperCAZ/AVI medium constitutes an adequate screening medium for the detection of CZA-resistant bacteria regardless of their resistance mechanisms. This SuperCAZ/AVI medium may be used for the screening of patients potentially colonized with CZA-resistant strains in order to rapidly implement infection control measures aimed at limiting their spread. This medium is also adequate for epidemiological surveys aiming to evaluate the prevalence of CZA-resistant Gram-negative bacteria in a given population. Further clinical evaluation of the proposed medium in daily clinical practice is needed. It may be useful for rapid identification of outbreaks of CZA-resistant strains, such as those reported in the United States (12) and Italy (13).

ACKNOWLEDGMENTS

We thank Luis Martinez-Martinez (Spain) and Robert Bonomo (United States) for the gifts of several CZA-resistant strains.

This work was funded by the Swiss National Science Foundation (projects FNS-407240_177381 and FNS-407240_177382).

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AUTHOR CORRECTION

Correction for Sadek et al., "A Selective Culture Medium for Screening Ceftazidime-Avibactam Resistance in *Enterobacterales* and *Pseudomonas aeruginosa*"

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Citation Sadek M, Poirel L, Tinguely C, Nordmann P. 2020. Correction for Sadek et al., "A selective culture medium for screening ceftazidime-avibactam resistance in *Enterobacterales* and *Pseudomonas aeruginosa*." J Clin Microbiol 58:e02539-20. https://doi.org/10.1128/JCM.02539-20.

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Published 18 November 2020