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Activity of linezolid against anaerobic bacteria

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Abstract

Minimal inhibition concentrations (MICs) were determined for linezolid (LZD) and compared with those of reference antibiotics against 265 anaerobes. For the *Bacteroides fragilis* group, MIC range for LZD was 2–4 mg/l. Strains resistant to the other antibiotics were detected including one strain of *B. fragilis* showing high level resistance to metronidazole (64 mg/l). LZD MIC_{50} was 4 mg/l for prevotella and 1 mg/l for fusobacteria. LZD MICs were <1 mg/l for porphyromonas and veillonellae and ≤ 4 mg/l for all Gram-positive anaerobes. For all anaerobes, resistance rates were 1, 2.4, 9.8 and 17% for imipenem, amoxycillin–clavulanic acid, metronidazole and clindamycin, respectively. As no strains resistant to LZD were detected, this antibiotic seems a promising candidate to treat infections caused by anaerobes.

Keywords: Linezolid; Oxazolidinones; Anaerobes; MIC determination

1. Introduction

Linezolid (LZD) shows antibacterial activity against Gram-positive pathogens [1–4] and some Gram-negative anaerobic species but not against Gram-negative aerobes [5–8]. Antibiotic resistance of anaerobes has been increasing worldwide and especially in southern Europe [9–13]. As very few studies have been carried out on anaerobes, the aim of this study was to determine LZD antimicrobial activity against a wide range of anaerobic bacteria isolated from human derived specimens. To be representative of the clinical context, the bacteria studied were mostly strains of the *Bacteroides fragilis* group, *Prevotella* spp., *Fusobacterium* spp., *Clostridium* spp. (including *Clostridium perfringens* and *Clostridium difficile*) and Gram-positive anaerobic cocci.

LZD minimal inhibition concentrations (MICs) were compared with those of anti-anaerobic reference drugs, amoxycillin alone or combined with clavulanic acid, imipenem, clindamycin and metronidazole. Cefoxitin, cefotetan and ticarcillin combined with clavulanic-acid were only investigated using the *B. fragilis* group.

2. Materials and methods

2.1. Anaerobes

Anaerobic bacterial strains were isolated from human clinical specimens from October 1999 to December 2000. They were identified according to classical methods, then subcultured in Rosenow medium (Sanofi Pasteur, Marne-la-Coquette, France) and broths were frozen at -20 °C. Before MIC testing, bacterial purity was checked by subculturing the strains on Columbia blood agar (BioMérieux, Marcy l'Etoile, France) and by Gram staining. For quality control and assessment of reproducibility, four reference ATCC control strains were added in each batch of tests. The ATCC control strains, advocated by the M11 A4 Norma of the National Committee for Clinical Laboratory Standards (NCCLS) [14], were *B. fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, *C. perfringens* ATCC 13124 and *Eggerthella lenta* ATCC 43055.

The 265 strains collected were 84 *B. fragilis* group, 21 *Fusobacterium* spp., 6 *Porphyromonas* spp., 44 *Prevotella* spp., 5 *Veillonella* spp., 20 *Clostridium* spp., 4 *Actinomyces* spp., 13 *Propionibacterium* spp., 12 other non sporulating Gram-positive bacilli (NSGPB) and 56 Gram-positive anaerobic cocci.

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2.2. MIC determination

MICs were determined using a reference agar dilution method according to the Norma M11 A4 (1997) [14]. Stock solutions (512 mg/l) of LZD (Pharmacia-Upjohn, Guyancourt, France), amoxycillin (Glaxo-SmithKline, Marly-le-Roi, France), ticarcillin (Glaxo-SmithKline), cefoxitin (Merck, Elkton, UK), cefotetan, imipenem (Merck, Rahway, NJ, USA), clindamycin (Sigma, Saint Quentin-Fallavier, France) and metronidazole (Aventis, Vitry-sur-Seine, France) were prepared. Metronidazole was first dissolved in 2 ml of methanol. Distilled water was then added to the solution. Serial two-fold dilutions were prepared in distilled water according to Ericson and Sherris [15] recommendations. MICs reported here for ticarcillin–clavulanic acid or amoxycillin–clavulanic acid combinations were determined in the presence of a constant concentration of clavulanic acid (Glaxo-SmithKline) of 2 mg/l. To calculate both susceptibility and resistance rates for the amoxycillin–clavulanic acid (Glaxo SmithKline) combination, according to the NCCLS breakpoints, we added four plates containing this combination in a 2/1 ratio: 16/8, 8/4, 4/2 and 2/1 mg/l.

Six antibiotics were used against all anaerobes. Ticarcillin–clavulanic acid combination, cefoxitin and cefotetan were added for the *B. fragilis* group only. Each antibiotic dilution was incorporated in Brucella blood agar (BBL, Becton Dickinson, Le Pont de Claix, France) with sterile defibrinated blood (5%) (Eurobio, Les Ulis, France) added to provide an adequate medium for the growth of anaerobes. Plates contained serial two-fold dilutions of antimicrobial agents (from 256 to 0.125 mg/l for ticarcillin, from 128 to 0.125 mg/l for cefotaxime, cefoxitin and cefotetan, from 128 to 0.06 mg/l for clindamycin, from 128 to 0.03 mg/l for imipenem, and from 64 to 0.06 mg/l for all the other antibiotics. All plates were used within 24 h of preparation. An actively growing culture in Rosenow medium was diluted in Brucella broth (Difco, Becton Dickinson) to reach and match the 0.5 point of a MacFarland standard. The inocula were approximately 7.5×10^7 or 10^8 CFU/ml. For fastidious strains, the following compounds were added to the Brucella broth: haemin (5 μg/l) (Sigma), menadione (0.1 μg/l) (Merck-Eurolab, Fontenay-sous-bois, France), sodium bicarbonate (1 g/l) (Sigma) and 0.1 ml of lysed blood (Eurobio) per 10 ml culture tube. The inocula (2 or 3 μl) were delivered using a Steers replicator (Mast Systems, London, UK) and gave to a final inoculum of 10^5 CFU per spot of inoculation onto the agar plates. At the end of each series of tests, two plates of Brucella blood agar were inoculated without antimicrobial agent. One plate was incubated anaerobically to determine organism viability. It was also used as a control for growth comparison. The other plate was incubated aerobically and showed any aerobic contamination. Incubation of the tested plates containing the antibiotics was performed in an anaerobic chamber (Concept+400, Ruskin, UK) at 35–36 °C. MICs were read on plates after 48 h incubation. The MIC of an antibiotic for an organism was defined as the lowest concentration of an antimicrobial agent yielding no growth. The categorization of the MICs values in clinical categories was done according to the NCCLS breakpoints. Amoxycillin NCCLS breakpoints were used for Gram-negative anaerobes, but as recommended by the NCCLS, all ß-lactamase producing strains were reported as resistant. For Gram-positive anaerobes, as the NCCLS does not recommend any breakpoint for amoxycillin, we used the CA-SFM breakpoint [16,17] (susceptibility corresponds to MIC ≤ 4 mg/l and resistance to MIC ≥ 32 mg/l). LZD breakpoints were set as the following: susceptible: MIC ≤ 4 mg/l, resistant: MIC ≥ 16 mg/l.

3. Results

3.1. MIC determination

Distribution of the MIC values, MIC 50 and MIC 90 values of each antibiotic for each group of bacteria are listed in Table 1 (for the *B. fragilis* group and for the Gram-negative bacteria other than the ones belonging to the *B. fragilis* group), Table 2 for the Gram-positive anaerobes and Table 3 for all anaerobes studied. Resistance rates calculated using NCCLS breakpoints are shown in Fig. 1a, b and c for the *B. fragilis* group, other Gram-negative bacteria including fusobacteria and prevotella and Gram-positive bacteria, respectively.

3.2. Bacteroides fragilis group

The MIC values and the percentage of resistance of the strains to nine antibiotics are shown in Table 1 and Fig. 1a, respectively.

As shown in Table 1, LZD MICs ranged from 0.5 to 4 mg/l (from 2 to 4 mg/l for 83/84 strains). Even if imipenem and metronidazole showed lower MIC_{90} values than LZD $MICs_{90}$, resistant strains to these antibiotics were detected (three for imipenem and one for metronidazole). Simultaneous resistance to imipenem and metronidazole was not detected. There were two strains susceptible to imipenem and resistant to amoxycillin–clavulanic acid. Resistance rates to cefotetan, clindamycin and cefoxitin were 37, 26 and 11%, respectively.

3.3. Other Gram-negative anaerobes

The activity of six antibiotics against Gram-negative anaerobes is shown in Table 1 and the resistance rates of

Table 1
Activities of nine antibiotics against the strains of the *B. fragilis* group, six antibiotics against the Gram-negative anaerobic strains other than the *B. fragilis* group

Micro-organisms (number of strains)	Antibiotics	MIC distribution (mg/l)														MIC (mg/l)		
		0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	>256	MIC range	MIC 50%	MIC 90%
B. fragilis (52)[a]	Linezolid							8	44								2–4	4	4
	Amoxycillin						1	1		1	17	11	9	12[e]			1–>64	32	>64
	Amoxycillin+clav		3[d]	23	15	2	1	1	2	1	1		1	2[e]			≤0.06–>64	0.125	4
	Ticarcillin+clav			6[d]	18	10	7	3	2	2		1			1	2	≤0.125–>256	0.5	8
	Cefoxitin							1	9	28	7	4	3				2–64	8	32
	Cefotetan							2	13	23	1	3	3	6	1[e]		2–>128	8	128
	Imipenem		5[d]	20	12	11	1					1		2			≤0.06–128	0.25	0.5
	Clindamycin		3[d]	2	6	13	10	3	3	1			1		10[e]		≤0.06–>128	1	>128
	Metronidazole				4	5	32	6	2	1	1		1				0.25–64	1	2
B. fragilis group other than *B. fragilis* (32)	Linezolid					1		12	19								0.5–4	4	4
	Amoxycillin							1		2		14	4	11[e]			2–>64	32	>64
	Amoxycillin+clav			2	6	10	4	6		1	1	1	1				0.125–64	0.5	8
	Ticarcillin+clav			1[d]	6		3	6	6	4	4			1	1		≤0.125–256	2	16
	Cefoxitin								4	3	7	12	6				4–64	32	64
	Cefotetan								4		2	5	10	11			4–128	64	128
	Imipenem		2[d]	2	8	15	5										≤0.06–1	0.5	1
	Clindamycin			1	6		3	6	6	4	4			1	1[e]		0.125–>128	2	16
	Metronidazole				2	13	10	6	1								0.25–4	1	2
Prevotella spp. (44)[b]	Linezolid		1[d]			3	12	8	16	4							≤0.06–8	2	4
	Amoxycillin		10[d]		1	1	3	4	1	1	8	8	1	6[e]			≤0.06–>64	16	>64
	Amoxycillin+clav		24[d]	9	3	3		1		4							≤0.06–8	≤0.06	2
	Imipenem	23[d]	2	3	10	4	2										≤0.03–1	≤0.03	0.5
	Clindamycin		27[d]	2	1	5	1	2		2					4[e]		≤0.06–>128	≤0.06	8
	Metronidazole		6[d]	5	6	15	8	1	2	1							≤0.06–8	0.5	1
Fusobacterium spp. (21)[c]	Linezolid		7[d]		1	7	4	2									≤0.06–2	0.5	1
	Amoxycillin		10[d]		5	1		3	1		1						≤0.06–16	0.25	2
	Amoxycillin+clav		15[d]	2	1	2	1										≤0.06–1	≤0.06	0.5
	Imipenem	11[d]	1	5	1		1	2									≤0.03–2	≤0.03	1
	Clindamycin		15[d]	2	3									1			≤0.06–128	≤0.06	0.25
	Metronidazole		16[d]		2	2		1									≤0.06–2	≤0.06	0.5
Porphyromonas spp. (6)	Linezolid		3[d]		1	1	1										≤0.06–1		
	Amoxycillin		6[d]														≤0.06		
	Amoxycillin+clav		6[d]														≤0.06		
	Imipenem	6[d]															≤0.03		
	Clindamycin		6[d]														≤0.06		
	Metronidazole		6[d]														≤0.06		
Veillonella spp. (5)	Linezolid		3[d]		1	1											≤0.06–0.5		
	Amoxycillin		5[d]														≤0.06		
	Amoxycillin+clav		5[d]														≤0.06		
	Imipenem	3[d]	2														≤0.03–0.06		
	Clindamycin		4[d]	1													≤0.06–0.125		
	Metronidazole		2[d]			1			2								≤0.06–4		

[a] Including strains of *Bacteroides thethaiotaomicron* (13), *B. ovatus* (6), *B. uniformis* (4), *B. distasonis* (1), *B. caccae* (1), *B. vulgatus* (6), *B. capillosus* (1).
[b] Including *Prevotella buccalis* (1), *P. buccae* (7), *P. oralis* (7), *P. oris* (3), *P. loeschii* (9), *P. corporis* (1), *P. intermedia* (9), *P. melaninogenica* (7).
[c] Including *Fusobacterium nucleatum* (13), *F. mortiferum* (2), *F. necrophorum* (4), *F. varium* (1), *Fusobacterium* spp. (1).
[d] ≤ MIC value indicated.
[e] ≥ 1/2 MIC value indicated.

the strains tested is represented in Fig. 1b. The percentages resistance to amoxycillin reported for the *Prevotella* and *Fusobacterium* species were 73 and 24%, respectively. Most β-lactams had greater efficacy against *Fusobacterium* strains. No resistant strains of *Prevotella* and fusobacteria to LZD, amoxycillin–clavulanic acid, imipenem or metronidazole were found. All strains of *Porphyromonas* and *Veillonella* were susceptible to the β-lactams tested as well as to LZD, clindamycin and metronidazole.

3.4. Gram-positive anaerobes

As shown in Table 2 and Fig. 1c, all strains of clostridia were susceptible to LZD and all β-lactams. *C. perfringens* was susceptible to clindamycin whereas most *C. difficile* strains were resistant to clindamycin, along with one strain each of *Clostridium histolyticum*, *Clostridium innocuum* and *Clostridium ramosum*. One *C. difficile* strain showed decreased susceptibility to metronidazole (MIC: 8 mg/l). All strains of *Actinomyces* and *Propionibacterium* were resistant to metronidazole. Some propionibacteria were resistant to clindamycin but all strains were inhibited at concentrations of the β-lactams tested of 0.25 mg/l or less and at LZD concentrations of 0.5 mg/l or less.

Of the Gram-positive cocci, 12 and 5% of the investigated strains were resistant to clindamycin and metronidazole, respectively. Four strains of *Peptostreptococcus anaerobius* showed higher MICs to all β-lactams including imipenem. No β-lactamase production was detected and MICs to amoxycillin were similar either in absence or presence of clavulanic acid. Against the Gram-positive anaerobes, penicillins, imipenem and LZD proved to have great potential.

3.5. All anaerobes

The activities of six antibiotics against all anaerobes tested are shown in Table 3. The resistance found for these strains are (calculated according the NCCLS): 1.1, 2.4, 9.8 and 17% for imipenem, amoxycillin–clavulanic acid combination, metronidazole and clindamycin, respectively.

4. Discussion

For the *B. fragilis* group the MIC range for LZD was narrow (0.5–4 mg/l) and 4 mg/l of LZD represented MIC_{50} and MIC_{90}. At this low concentration, all strains were inhibited. Ednie et al. [7] compared the activity of a new oxazolidinone AZD2563 with those of eight other antibiotics including LZD. They found MIC ranges of 4–8 mg/l for *B. fragilis* and 2–8 mg/l for the *B. fragilis* group. MIC_{50} and MIC_{90} were similar to our values for *B. fragilis*. Only LZD MIC_{90} was a little higher than our values for the *B. fragilis* group. Wise et al. [18] found similar results to ours for LZD in 1998. In our study, all strains of the *B. fragilis* group were β-lactamase-positive (tested by nitrocephin). They were considered resistant to amoxycillin. The chromosomal enzyme is able to inactivate cefalothin, cefuroxime and third generation cephalosporins. As shown here and demonstrated previously, resistance to cefotetan and clindamycin is high in France whereas cefoxitin, a cefamycin antibiotic, still proves to have good activity. Resistance to metronidazole was seen for the first time in France. This resistance was confirmed using the Etest method (MIC: 48 mg/l). Decreased susceptibility to metronidazole (MIC: 8–16 mg/l) was observed (2.4%) as in previous studies (2–3%) [9,13]. Resistance to imipenem due to carbapenemase production, is still rare (three strains) and is associated with cross-resistance to all β-lactams. The two strains susceptible to imipenem and resistant to amoxycillin–clavulanic acid probably had an increased production of β-lactamase and/or lack of porins [19]. Four of the five strains were also resistant to clindamycin and one strain showed decreased susceptibility to metronidazole. Simultaneous resistance to imipenem and metronidazole was not detected. Imipenem, metronidazole and the combination of clavulanic acid with either amoxycillin or ticarcillin demonstrated good in vitro activity against the *B. fragilis* group involved in many intra-abdominal infections. LZD showed the best antimicrobial activity (all strains were susceptible to this drug).

For the other Gram-negative anaerobes, the high resistance rates reported for *Prevotella* and *Fusobacterium* species to amoxycillin were due to β-lactamase production detected amongst 32/44 *Prevotella* strains and 5/21 *Fusobacterium* strains. The poor antibiotic activities commonly described for cefalothin, cefuroxime and to a less extent for cefotaxime against prevotella are also related to β-lactamase production. LZD demonstrated excellent activity against prevotella and fusobacteria, similar to those of the amoxycillin–clavulanic acid, imipenem and metronidazole. This is in accordance with previous results reported by Goldstein et al. [8] in 1999 and Ednie et al. [7] in 2002.

For Gram-positive anaerobes, the resistance of *Actinomyces* and propionibacteria to metronidazole is intrinsic. LZD demonstrated good activity against these anaerobes. Identical MIC ranges to ours (0.25–0.5 and 0.5–0.5 mg/l) were previously reported in 2002 by Ednie et al. [7]. Gram-positive cocci are generally known to be susceptible to all β-lactams. In our study, the resistance of the four strains of *P. anaerobius* to the β-lactams tested was not due to β-lactamase production. This resistance might be caused by a mutation in a PBP gene. LZD had also great efficacy against those Gram-positive anaerobes.

Table 2
Activities of six antibiotics against Gram-positive strains

Micro-organisms (number of strains)	Antibiotics	MIC distribution (mg/l)														MIC (mg/l)		
		0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	MIC range	MIC 50%	MIC 90%
Clostridium spp.[a] (20)	Linezolid		1[e]			3	4	5	7							≤0.06–4	2	4
	Amoxycillin		8[e]	1	2	7	2									≤0.06–1	0.25	0.5
	Amoxycillin+clav		9[e]	2	3	6										≤0.06–0.5	0.125	0.5
	Imipenem	2[e]	5	4	1		1	3	4							≤0.03–4	0.125	4
	Clindamycin		8[e]		1		1		3	3					4[f]	≤0.06–>128	1	>128
	Metronidazole		1[e]		4	11	2	1		1						≤0.06–8	0.5	1
Propionibacterium spp.[b] (13)	Linezolid				2	11										0.25–0.5	0.5	0.5
	Amoxycillin		13[e]													≤0.06	≤0.06	≤0.06
	Amoxycillin+clav		13[e]													≤0.06	≤0.06	≤0.06
	Imipenem	12[e]	1													≤0.03–0.06	≤0.03	≤0.03
	Clindamycin		3[e]	1	2		2	3				2				≤0.06–32	1	32
	Metronidazole													13[f]		≥64	>64	>64
NSGPB[c] (16)	Linezolid				1	5	7	1	2							0.25–4	1	2
	Amoxycillin		5[e]	1	2	3	5									≤0.06–1	0.25	1
	Amoxycillin+clav		6[e]		4	4		2								≤0.06–2	0.25	0.5
	Imipenem	6[e]	2	2	1	4	1									≤0.03–1	0.06	0.5
	Clindamycin		11[e]	1	2	2										≤0.06–0.5	≤0.06	0.5
	Metronidazole					4	1			1	1	3		6[f]		0.5–>64	32	>64
Gram-positive anaerobic cocci[d] (56)	Linezolid				2	29	16	9								0.25–2	0.5	2
	Amoxycillin		38[e]	6	4	2		2		2	1	1				≤0.06–16	≤0.06	2
	Amoxycillin+clav		44[e]	5	1	1		1	1	1	1	1				≤0.06–32	≤0.06	0.25
	Imipenem	42[e]	6	2		1	1	3		1						≤0.03–8	≤0.03	0.25
	Clindamycin		19[e]	8	9	5	4	3	1		1	1	2	1	2[f]	≤0.06–>128	0.25	16
	Metronidazole		5[e]	5	32	5	3	3						3[f]		≤0.06–>64	0.25	2
All Gram-positive anaerobes (105)	Linezolid		1[e]		5	48	27	15	9							≤0.06–4	0.5	2
	Amoxycillin		64[e]	8	8	12	7	2		2	1	1				≤0.06–32	≤0.06	1
	Amoxycillin+clav		72[e]	7	8	11		3	1	1	1	1				≤0.06–32	≤0.06	0.5
	Imipenem	62[e]	14	8	2	5	3	6	4	1						≤0.03–8	≤0.03	2
	Clindamycin		41[e]	10	14	7	7	6	4	3	1	3	2	1	6[f]	≤0.06–>128	0.25	32
	Metronidazole		6[e]	5	36	20	6	4		2	1	3		22[f]		≤0.06–>64	0.5	>64

[a] Including *C. difficile* (5), *C. perfringens* (5), *C. butyricum* (2), *C. fallax* (1), *C. histolyticum* (1), *C. innocuum* (3), *C. ramosum* (2), *C. tertium* (1).
[b] *Propionibacterium acnes* (13).
[c] Non-sporulating Gram-positive bacilli including *Actinomyces* spp. (4), *Bifidobacterium* spp. (7), *E. lenta* (7).
[d] Including *P. anaerobius* (9), *P. asaccharolyticus* (19), *P. prevotii* (7), *P. tetradius* (1), *Peptostreptococcus* spp. (10), *Finegoldia magna* (6), *Micromonas micros* (4).
[e] ≤MIC value indicated.
[f] ≥1/2 MIC value indicated.

Table 3
Activities of six antibiotics against 265 anaerobic bacteria

Micro-organisms (number of strains)	Antibiotics	MIC distribution (mg/l)													MIC (mg/l)		
		0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	MIC range	MIC 50%	MIC 90%
Anaerobes (265)	Linezolid		15[a]		8	61	44	45	88	4						≤ 0.06–8	2	4
	Amoxycillin		95[a]	8	14	14	11	11	2	6	27	34	14	29[b]		≤ 0.06– > 64	1	> 64
	Amoxycillin + clav		125[a]	43	33	28	6	11	3	7	3	2	2	2[b]		≤ 0.06– > 64	0.125	2
	Imipenem	105[a]	26	38	33	35	12	8	4	1		1		2		≤ 0.03–128	0.125	1
	Clindamycin		96[a]	18	30	25	21	17	13	10	5	3	3	3	21[b]	≤ 0.06– > 128	0.25	64
	Metronidazole		36[a]	10	50	56	56	18	7	4	2	3	1	22[b]		≤ 0.06– > 64	0.5	16

[a] ≤ MIC value indicated.
[b] ≥ 1/2 MIC value indicated.

Fig. 1. (a) Resistance percentages of the *B. fragilis* group ($n = 84$). (b) Resistance percentages of the other Gram-negative bacteria including fusobacteria and prevotella ($n = 76$). (c) Resistance percentage of the Gram-positive bacteria ($n = 105$).

To conclude, only LZD was able to inhibit all 265 anaerobes investigated in this study at concentrations of 8 mg/l or less. Resistance rates lower than 10% were only observed for the amoxycillin or ticarcillin–clavulanic

acid combination, metronidazole and imipenem. All strains were susceptible to LZD. Metronidazole resistance occurred amongst strains of actinomyces and *Propionibacteria* (intrinsic resistance) but also amongst some strains of peptostreptococci (acquired resistance). Clindamycin resistance was found in many species (17%). Independently of β-lactamase production, LZD was very potent against all strains of fusobacteria, prevotella and porphyromonas. As no resistant strains to LZD were detected in vitro, this antibiotic is a new candidate to treat infections caused by anaerobes. Further clinical trials would be useful.

5. Abbreviations (and NCCLS breakpoints in mg/l)

AMOX, amoxicillin (≥ 2); AMOX/CA, co-amoxiclav ($\geq 16/8$); LZD, linezolid (≥ 16); CFOT, cefotetan (≥ 64); CLI, clindamycin (≥ 8); FOX, cefoxitin (≥ 64); IMIP, imipenem (≥ 16); MTR, metronidazole (≥ 32); TICC/CA, ticarcillin + clavulanic acid ($\geq 128/2$).

6. Comments

A strain tested β-lactamase positive by nitrocephin was reported as resistant to AMOX when: $0.5 \leq$ MIC value < 2 (for the *B. fragilis* group, prevotella and fusobacteria).

As there are no NCCLS breakpoints for Gram-positive anaerobic bacteria, French values were used: here, AMOX (> 16 mg/l).

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