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International Journal of Antimicrobial Agents 21 (2003) 267–273

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.isochem.org

β-lactamase production in Provotella and in vitro susceptibilities to selected β-lactam antibiotics

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Received 21 May 2002; accepted 1 July 2002

Abstract

This study looked for β-lactamase production in 100 Provotella isolates. MICs were determined for amoxycillin, ticarcillin, amoxycillin + clavulanate, cephalothin, cefuroxime, cefixime, cefpodoxime and cefotaxime using the reference agar dilution method (standard M11 A4, NCCLS). Beta-lactamase activity was detected in 58 of the 100 isolates, 24 of 46 black-pigmented Provotella and 34 of 54 non-pigmented Provotella. All β-lactamase-negative strains were susceptible to all β-lactam antibiotics with the exception of cefuroxime and cefixime. Overall, resistance rates of Provotella strains were lower for ticarcillin (8%) and celefotaxime (12%) than for the other cephalosporins. All Provotella isolates were susceptible to amoxyillin and were all inhibited by 2 mg/l or less amoxcillin.

Keywords: *Provotella*; β-lactamase production; Antibiotic resistance

1. Introduction

Anaerobic Gram-negative bacilli other than the *Bacteroides fragilis* group have been shown to be involved in clinical infections, either alone or mixed with other species. Although Fusobacterium and Provotella are the main anaerobic bacilli isolated from human pathological samples, β-lactamase production [1] is more frequent for Provotella (60–70%) than for Fusobacterium (5–10%). These bacteria are involved in pyogenic orofacial and upper respiratory tract infections (chronic sinusitis and otitis). In elderly people, micro-aspiration of saliva may inoculate the lungs and cause pulmonary infections. There have been scattered reports on the antibiotic susceptibility of *Provotella* species, but only rare studies have been based on a large number of Provotella strains [2], apart from strains derived from periodontal isolates. Until the latter half of the 1970s, penicillins and cephalosporins were generally still effective against oral Gram-negative anaerobes. Beta-lactamase production steadily increased during the 1980s. Clinical failures of penicillin treatment for orofacial infections have been documented [3–5] together with reports suggesting that previous penicillin therapy increases the incidence of penicillin-resistant Provotella [6]. Resistance to metronidazole, combinations of penicillins and β-lactamase inhibitors or imipenem is rare and many laboratories now consider identification and susceptibility testing of Provotella to be unnecessary. Oral cephalosporins have a limited anti-anaerobic activity, especially against the *B. fragilis* group, but this activity may vary for other species. Some oral cephalosporins are used to treat community-acquired anaerobic infections, although their anti-anaerobic activities have not been recently reviewed. The activity of β-lactam antibiotics is decreasing due to the increasing incidence of β-lactamase-producing isolates. It is, therefore, important to monitor resistance both to new drugs but also to widely prescribed antibiotics in community-acquired infections in order to guide their empirical use.

In this study, we collected strains of Provotella and tested the susceptibility of a sufficient number of isolates to antimicrobial agents marketed in the community. As

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0924-8579/02/$30
PII: S0924-8579(02)00352-7

Table 1
β-lactamase production in Provotella isolates

Microorganism	Investigated	Number of strains	
		β-lactamase-negative	β-lactamase-positive
Non-pigmented Provotella			
P. buccae	12	5	7
P. oris	9	7	2
P. oralis	9	3	6
P. buccalis	1	0	1
P. bivia	20	5	15
P. spp	3	0	3
All strains	54	20	34 (63%)
Pigmented Provotella			
P. corporis	2	0	2
P. denticola	6	6	0
P. intermedia			
P. nigrescens	11	4	7
P. loescheii	6	5	1
P. melaninogenica	21	7	14
All pigmented strains	46	22	24 (52%)

the β-lactamase of Provotella has been reported to be a cephalosporinase [7,8], ticarcillin was added to this study, although this drug is available only in hospitals.

2. Material and methods

2.1. Bacterial isolates

A total of 100 Provotella strains were isolated from human clinical sources (blood culture, pleural fluid, chronic sinusitis and otitis, lung abscess, etc.). and from vaginal samples for *P. bivia* and *P. disiens*. Strains isolated from stools were excluded. The 100 isolates were studied together with appropriate reference and control strains (*B. fragilis* ATCC 25285, *B. thethaiotaomicron* ATCC 29741, *Eggerthella lenta* ATCC 43055 and *C. perfringens* ATCC 13124). All isolates were identified by standard criteria [9]. The *P. intermedia* group includes three phenotypically indistinguishable species: *P. intermedia*, *P. nigrescens* and *P. pallens* [10,11]; this group is referred to as *P. intermedia* in this paper. The numbers and species of isolates tested are shown in Table 1.

2.2. Antimicrobial agents

Standard laboratory powders were obtained from the following sources: amoxycillin, ticarcillin, clavulanic acid, cephalothin, cefuroxime (Glaxo–Smith-Kline, Marly-le-Roi, France), cefotaxime, cefixime, cefpodoxime (Aventis, Paris). Antimicrobials were reconstituted according to each manufacturer's instructions. Serial 2-fold dilutions of antimicrobial agents were prepared on the day of the test and added to the media in various concentrations.

2.3. β-lactamase testing

Beta-lactamase production was tested by using the qualitative chromogenic cephalosporin disk test (Cefinase®, Biomérieux, France). According to Appelbaum's recommendations [12], disks which did not turn from yellow to red within 15 min at room temperature were incubated for 1 h at 37 °C.

2.4. MIC determinations

Susceptibility testing was performed by the reference agar dilution method [13] according to the standards of the National Committee for Clinical and Laboratory Standards (M11-A4). Brucella blood agar (Difco, France) with 5% lysed horse blood (Eurobio, Les Ulis, France) was the basic medium. Amoxycillin and ticarcillin were diluted with clavulanate tested at a constant concentration of 2 μg/ml, as is usual in most European countries. To comply with the interpretative categories of the NCCLS, we added two plates containing 8/4 and 16/8 μg/ml of amoxycillin and clavulanate combinations, respectively. A Mast multipoint inoculator was used to deliver inocula of approximately 10^5 CFU per spot. Plates were incubated in an anaerobic chamber (Don Whitley®, AES, Combourg, France) and MICs were determined after 48 h of incubation at 35 °C and then examined. Resistance rates were calculated at the NCCLS breakpoints. French (CA-SFM) breakpoints

Table 2
Distribution of amoxycillin MICs according to β-lactamase production

Provotella strains	*N*	β-lac*	Distribution of MICs in mg/l												
			0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128
Amoxycillin																
Black pigmented	22	0	4	1	3	10	4									
Non-pigmented	20	0	5	0	2	12	1									
All β-lactamase negative Provotella	42	0	9	1	5	22	5									
Black-pigmented	24	+						2	5	4	5	2	4	2		
Non-pigmented	34	+						1	4	3	3		4	4	1	7
All β-lactamase positive Provotella	58	+						3	9	7	8	9	8	6	1	7
All Provotella	100	0 and +	9	1	5	22	5	3	9	7	8	9	8	6	1	7

were used for some oral cephalosporins, due to the lack of specific breakpoints for anaerobes [14].

3. Results

3.1. β-lactamase production

Beta-lactamase production was detected in 58 of the 100 isolates, including 24 of 46 black-pigmented Provotella (52%) and 34 of 54 non-pigmented Provotella (63%). Beta-lactamase production varied according to the species (Table 1). Beta-lactamase production was more frequent for *P. melaninogenica* (14/21), *P. bivia* (15/20), and *P. intermedia* (7/11). The amoxycillin MIC breakpoint separating β-lactamase-positive and β-lactamase-negative isolates was ≥ 0.5 mg/l (Table 2).

3.2. In vitro susceptibility to β-lactam antibiotics

Most antimicrobial agents were more active against β-lactamase-negative isolates than against β-lactamase-positive isolates (Table 3). All β-lactamase-negative strains were susceptible to all β-lactams, with the exception of one strain of *P. oris* and one strain of *P. bivia* that were resistant to both cefuroxime and cefixime. Beta-lactamase-negative strains were all inhibited by either 0.25 mg/l of amoxycillin+clavulanate, 1 mg/l of ticarcillin or cefpodoxime, or 2 mg/l of cephalothin or cefotaxime.

Amoxycillin-resistant isolates were detected in all species of *Provotella* with the exception of *P. denticola*; the highest resistance rate was observed for *Provotella bivia*. Among β-lactamase-positive strains, amoxycillin MICs were higher for non-pigmented Provotella than for black-pigmented isolates (Table 2). Amoxycillin MIC_{90} for β-lactamase-positive isolates was 9 dilutions higher than that for β-lactamase-negative isolates.

All isolates in this study were susceptible to amoxycillin+clavulanate. Most isolates were susceptible to 64 mg/l of ticarcillin. Although the MICs of cefpodoxime and cefotaxime were generally fairly similar, cefpodoxime, which has lower antibiotic breakpoints, had poor activity against β-lactamase-positive *Provotella* species (Tables 4 and 5). The same was true for cefixime. Among the black-pigmented isolates, only one strain of *P. intermedia* was resistant to cefotaxime; most cefotaxime-resistant strains were, therefore, not pigmented (*P. oralis*, *P. buccae* and *P. bivia*).

On the whole, resistance rates of Provotella strains were lower for ticarcillin (8%) and cefotaxime (12%) than for the other cephalosporins. All Provotella isolates inhibited by 2 mg/l or less of amoxycillin+clavulanate were susceptible to this combination.

Table 3
Activity of three penicillins against 100 strains of *Provotella*: distribution of MICs

Provotella strains	*N*	Distribution of MICs in mg/l														
		0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128
Amoxycillin																
β-lactamase negative Provotella	42	9	1	5	22	5										
β-lactamase positive Provotella	58						3	9	7	8	9	8	6	1	7	
Amoxycillin-clavulanate																
β-lactamase negative Provotella	42	10		31		1										
β-lactamase positive Provotella	58	18	1	17	3	10	3	1	5							
Ticarcillin																
β-lactamase negative Provotella	42	3		18	9	5	5	2								
β-lactamase positive Provotella	58				1	1	1	8	9	7	7	6	7	3	4	4

Table 4
Activity of five cephalosporins against 100 strains of *Provotella*: distribution of MICs

Provotella strains	*N*	Distribution of MICs in mg/l													
		0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin															
β-lactamase negative Provotella	42			10	10	9	7	5	1						
β-lactamase positive Provotella	58						2	4	10	4	8	8	6	5	11
Cefuroxime															
β-lactamase negative Provotella	42		1	12	10	13	2	2					1	1	
β-lactamase positive Provotella	58					1	1	2	12	6	12	2	5	5	12
Cefixime															
β-lactamase negative Provotella	42		2	9	3	17	3	4	2		1	1			
β-lactamase positive Provotella	58			1		2	3	3	15	5		7	4	3	15
Cefpodoxime															
β-lactamase negative Provotella	42		1	11	10	14	4	2							
β-lactamase positive Provotella	58					4	3	8	9	6	10	3	1	6	8
Cefotaxime															
β-lactamase negative Provotella	42		3	15	8	13	2		1						
β-lactamase positive Provotella	58					2	5	9	10	10	1	6	3	7	5

4. Discussion

4.1. β-lactamase production

Most studies of antimicrobial susceptibility of anaerobic bacteria are based on serial isolates from clinical material and, therefore, focus on the more common species and combine the results for less common isolates. Consequently, little information is available about the susceptibility of less commonly isolated *Provotella* species. Beta-lactamase production was low (19–40%) in the 1980s [15,16] and subsequently increased to reach 70% of strains in 1994 [17]. Since then, the frequency of β-lactamase-producing strains has remained in the 60–70% range [1,18]. The prevalence of β-lactamase production of *Provotella* species is in agreement with several previous French studies [1,18]. However, several studies have also reported lower prevalences [19,20]. The various frequencies observed in other reports could be explained by geographical differences and isolate sampling differences [6,19,21].

4.2. In vitro susceptibility to β-lactam antibiotics

The amoxycillin MIC distribution clearly distinguished Provotella isolates into two groups according to β-lactamase production (breakpoint ≥ 0.5 mg/l). This value was identical to the penicillin G breakpoint previously proposed by Matto et al. [20]. Beta-lactamase detection is relatively difficult and could be replaced in routine by determination of amoxycillin MICs using the *E*-test and the 0.38 mg/l breakpoint. As recommended by the NCCLS, all Gram-negative anaerobes should be screened for β-lactamase production with nitrocephin

Table 5
Comparative in vitro activity of β-lactam antibiotics against *Provotella* species according to β-lactamase production

Organism (number tested) and antimicrobial agent	MIC (mg/l)			
	β-lactamase O		β-lactamase +	
	Range	Modal MIC	Range	Modal MIC
P. buccae	5 strains	5 strains	7 strains	7 strains
Amoxycillin	0.12	0.12	0.5–32	32
Amoxycillin+clavulanate	≤0.015	≤0.015	≤0.06–2	0.25
Ticarcillin	≤0.06–0.25	0.06	2–64	32
Cephalothin	0.25–1	0.25	2–>64	64
Cefuroxime	≤0.06–0.25	0.125	2–>64	>64
Cefixime	0.25–0.5	0.25	1–>64	2
Cefpodoxime	0.125–0.5	0.5	0.5–>64	2
Cefotaxime	≤0.06–0.25	0.125	0.5–64	1
P. oris	7 strains	7 strains	2 strains	2 strains
Amoxycillin	≤0.015–0.25	0.12	2–8	ND
Amoxycillin+clavulanate	≤0.015–0.25	<0.06	≤0.06–0.25	ND
Ticarcillin	≤0.06–0.25	0.125	2–8	
Cephalothin	0.06–2	0.125	1–2	ND
Cefuroxime	≤0.06–32	0.125	2	ND
Cefixime	≤0.06–8	0.06	2–16	ND
Cefpodoxime	≤0.06–0.25	0.125	1–8	ND
Cefotaxime	≤0.06–0.125	≤0.06	2–4	ND
P. bivia	5 strains	5 strains	15 strains	15 strains
Amoxycillin	≤0.015–0.125	≤0.015	1–>64	8
Amoxycillin+clavulanate	≤0.015	≤0.015	≤0.015–2	≤0.015
Ticarcillin	≤0.06–1	0.125	0.125–64	8
Cephalothin	≤0.06–1	1	1–>64	64
Cefuroxime	≤0.06–64	0.5	0.25–>64	>64
Cefixime	≤0.06–16	2	0.5–>64	>64
Cefpodoxime	≤0.06–0.25	0.25	0.25–8	>64
Cefotaxime	≤0.06–0.25	0.125	0.5–>64	64
P. oralis	3 strains	3 strains	6 strains	6 strains
Amoxycillin	≤0.015–0.12	≤0.06	8–>64	8
Amoxycillin+clavulanate	≤0.015	≤0.015	0.015–0.5	0.5
Ticarcillin	≤0.06–0.5	0.25	4–>128	128
Cephalothin	≤0.06–1	1	2–>64	>64
Cefuroxime	0.125–0.25	0.125	2–>64	>64
Cefixime	0.125–0.25	0.25	0.25–>64	>64
Cefpodoxime	0.125	0.125	4–>64	64
Cefotaxime	≤0.06–0.25	0.125	4–>64	64
P. intermedia	4 strains	4 strains	7 strains	7 strains
Amoxycillin	≤0.015–0.125	≤0.015	1–16	1
Amoxycillin+clavulanate	≤0.015	≤0.015	≤0.015–0.12	≤0.015
Ticarcillin	≤0.06	≤0.06	0.25–128	2
Cephalothin	≤0.06–2	≤0.06	4–64	8
Cefuroxime	≤0.06–0.125	<0.06	1–64	8
Cefixime	≤0.06–1	≤0.06	0.5–>64	8
Cefpodoxime	≤0.06–1	≤0.06	1–64	64
Cefotaxime	≤0.06–0.5	≤0.06	1–64	2
P. melaninogenica	7 strains	7 strains	14 strains	14 strains
Amoxycillin	≤0.015–0.25	0.125	0.5–32	4
Amoxycillin+clavulanate	≤0.015–0.25	≤0.06	≤0.015–0.25	≤0.015
Ticarcillin	≤0.06–1	≤0.06	0.5–32	8
Cephalothin	≤0.06–1	0.5	0.5–32	2
Cefuroxime	≤0.06–1	0.25	2–64	2
Cefixime	≤0.06–1	0.25	0.06–64	2
Cefpodoxime	≤0.06–0.25	0.25	0.25–8	1
Cefotaxime	≤0.06–0.25	0.25	0.25–32	1
All *Provotella* (100)	42 strains	42 strains	58 strains	58 strains
Amoxycillin	≤0.015–0.25	0.125	0.5–128	8
Amoxycillin+clavulanate	≤0.015–0.25	0.06	≤0.015–2	0.06
Ticarcillin	≤0.015–1	0.06	0.125–128	2

Table 5 (*Continued*)

Organism (number tested) and antimicrobial agent	MIC (mg/l)			
	β-lactamase O		β-lactamase +	
Cephalothin	≤0.06–2	0.125	0.5–>64	2
Cefuroxime	≤0.06–64	0.25	0.25–>64	8
Cefixime	≤0.06–16	0.25	0.06–>64	ND
Cefpodoxime	≤0.06–1	0.25	0.25–64	8
Cefotaxime	<0.06–2	0.06	0.25–64	4

and, if positive, should be reported as resistant to penicillin and ampicillin. No guidelines have been defined for cephalosporins.

In this study, no clear cut-off point was defined for oral cephalosporins between the two populations. However, β-lactamase-negative Provotella were inhibited by either 1 mg/l of cefuroxime and cefpodoxime or 2 mg/l of cephalothin and cefixime. At the 1 mg/l French breakpoint for oral cephalosporins (CA-SFM) 95, 90 and 100% of β-lactamase-negative isolates were susceptible to cefuroxime, cefixime and cefpodoxime, respectively, while, at the same breakpoint, inhibition was observed for only 7, 15 and 25% of β-lactamase-producing isolates, respectively. Valle et al. [7], describing the β-lactamase of a strain of *P. intermedia*, also emphasized the fact that the best substrate for this cephalosporinase was cefuroxime (Vmax rel 600 vs. 100 for cephaloridine). We have, therefore, proposed to the French committee (CA-SFM) that, in the absence of any MIC determination for β-lactams other than amoxycillin, β-lactamase-producing Provotella isolates should be reported as resistant to aminopenicillins, cephalothin, cefuroxime and oral third generation cephalosporins. The poor activity of oral cephalosporins against *Provotella* spp has been well documented for cefuroxime [22], cefixime [23] and cefpodoxime [24]. Cefotaxime was found to be more active than oral cephalosporins, but overall susceptibility never exceeded 90% of strains The greater activity of cefotaxime on pigmented Provotella versus non-pigmented Provotella has also been previously reported by Goldstein et al. [25].

Surveys of antibiotic susceptibility are needed to assess the respective activities of β-lactam antibiotics against anaerobes. As Provotella isolates are involved in many anaerobic or mixed infections (pleuropulmonary, ENT, soft tissue, gynaecological infections and bites), the very good in vitro activity of the amoxycillin–clavulanate combination must be emphasized.

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