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Actinomyces pyogenes: susceptibility of 103 clinical animal isolates to 22 antimicrobial agents

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Summary — *Actinomyces pyogenes* induces suppurative diseases in ruminants and many other animal species. Most of the earlier antimicrobial susceptibility data has been obtained by disk diffusion techniques. Minimal inhibitory concentrations (MIC) of 22 antibiotics for 103 strains of *A pyogenes* of animal origin were determined by agar dilution test (Mueller–Hinton agar supplemented with 5% sheep blood). All the strains were susceptible to penicillin G, amoxicillin, methicillin, cephalothin, cefoperazone, pristinamycin, kanamycin, gentamicin, spectinomycin, chloramphenicol, vancomycin, novobiocin and rifampin. Fifty-nine percent were resistant to streptomycin, 67% to tetracycline, doxycycline and minocycline, 12% to erythromycin, spiramycin and lincomycin. Most of the strains resistant to macrolides and lincosamides exhibited a constitutive MLS(B)-like phenotype. In the cultural conditions used, it was not possible to determine accurate MIC of fucidic acid and pefloxacin.

***Actinomyces pyogenes* / antibiotics / minimal inhibitory concentrations (MIC)**

Résumé — *Actinomyces pyogenes* : sensibilité de 103 souches d'origine animale à 22 antibiotiques. *Les concentrations minimales inhibitrices (CMI) de 22 antibiotiques pour 103 souches d'*Actinomyces pyogenes *d'origine animale ont été déterminées par la technique de dilution en milieu solide (gélose Mueller-Hinton + 5% de sang de mouton). Toutes les souches étaient sensibles à la pénicilline G, l'amoxicilline, la méticilline, la céfalotine, la céfopérazone, la pristinamycine, la kanamycine, la gentamicine, la spectinomycine, le chloramphénicol, la vancomycine, la novobiocine et la rifampicine. Cinquante neuf pour cent étaient résistantes à la streptomycine, 67% à la tétracycline, la doxycycline et la minocycline, 12% à l'érythromycine, la spiramycine et la lincomycine. La plupart*

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des souches résistantes aux macrolides et lincosamides avaient un phénotype semblable au phénotype MLS (B) constitutif. Il n'a pas été possible de mesurer précisément les CMI d'acide fusidique et de péfloxacine dans les conditions de culture utilisées.

Actinomyces pyogenes / *antibiotiques / concentrations minimales inhibitrices / (CMI)*

INTRODUCTION

The species *Actinomyces pyogenes* (formerly *Corynebacterium pyogenes*) was proposed by Reddy *et al* (1982) on the basis of its morphological, physiological and biochemical characteristics. The transfer was further confirmed by Collins and Jones (1982).

This pathogen is commonly isolated from pyogenic processes in cattle, sheep, goats and pigs, and its distribution in these species seems worldwide. It is occasionally found in other species. It seems to thrive best in closed or partly closed cavities and causes bronchopneumonia, endometritis, abortions, abscesses, generalized infections, arthritis and summer mastitis in cattle. *A pyogenes* has been isolated in many cases from clinically normal animals and it is therefore believed that it is an opportunistic pathogen. There are a few records of infections in humans (Kotrajaras *et al,* 1982; Kotrajaras and Togami, 1987).

The *in vitro* susceptibility of *A pyogenes* to antimicrobial compounds is variable. Earlier studies have indicated that all isolates are resistant to nalidixic acid, norfloxacin, and colistin (Mitani *et al,* 1980; Prescott and Yielding, 1990). According to Rhoades (1979), about one-fourth of the strains are susceptible to polymyxin B when using the disk diffusion method but the few minimal inhibitory concentrations (MIC) recorded are about 128 mg/l (Hjerpe and Routen, 1976; Buchholz, 1985). Most of the strains have an intermediate level of susceptibility to novobiocin (Hjerpe and Routen, 1976) but appear susceptible when using disk diffusion test and zone diameter standards for fast-growing bacteria (Rhoades, 1979). *A pyogenes* is moderately susceptible to ciprofloxacin, enrofloxacin, and chloramphenicol (Hjerpe and Routen, 1976; Burrows, 1980; Mitani *et al,* 1980; Gedek *et al,* 1984; Prescott and Yielding, 1990). For this latter drug, only a few resistant strains have been described by Rhoades (1979) and Nattermann and Horsch (1976) whose studies included a large number of isolates; 30% of resistant strains have been reported by Hjerpe and Routen (1976).

A pyogenes is slightly more susceptible to aminoglycosides than the other *Actinomyces* species. However, according to many studies, most of the strains have acquired resistance to streptomycin (Hjerpe and Routen, 1976; Rhoades, 1979; Burrows, 1980; Mitani *et al,* 1980; Gedek *et al,* 1984, 1988; Buchholz, 1985). Results from Nattermann and Horsch (1976), and Kunter (1975) are contradictory; this could be due either to the origin (milk *versus* respiratory tract) of their isolates or to the date of the study. Resistance to kanamycin or neomycin is unusual (Hjerpe and Routen, 1976; Rhoades, 1979), and exceptional in the case of gentamicin (Burrows, 1980; Gedek *et al,* 1988). The activity of spectinomycin must be confirmed (Bulling, 1954; Kunter, 1975; Nattermann and Horsch, 1976; Hjerpe and Routen, 1976; Rhoades, 1979; Gedek *et al,* 1984; Buchholz, 1985). The percentages of strains resistant to the representatives of the tetracycline family vary between different authors (0% to 80%) (Bulling, 1954; Kunter, 1975; Hjerpe and Routen, 1976; Nattermann and Horsch, 1976; Rhoades, 1979; Gedek *et al,* 1984; Buchholz, 1985).

A pyogenes is highly susceptible to all the ß-lactam antibiotics: penicillins A and cefoperazone are the most effective molecules of this family, followed by cephalothin and oxacillin; MIC reported for penicillin G range from 0.015 to 0.1 mg/l (Bulling, 1954; Hjerpe and Routen, 1976; Burrows, 1980; Mitani *et al,* 1980; Gedek *et al,* 1984, 1988; Buchholz, 1985). A few strains resistant to penicillin G or ampicillin have been described by Rhoades (1979) and Nattermann and Horsch (1976).

Macrolides and lincosamides exhibit a high inhibitory activity. Results show a tendency towards an increasing resistance to macrolides and related antibiotics ranging from 20–80% of the strains without an evident explanation for these dissimilarities (Hjerpe and Routen, 1976; Rhoades, 1979; Burrows, 1980; Gedek *et al,* 1984, 1988). *A pyogenes* is also susceptible to bacitracin and nitrofurantoin (Rhoades, 1979; Mitani *et al,* 1980) and to trimethoprim and the sulfonamides when a suitable medium is used to determine the MIC (Barnett and Bushby, 1970).

The limited available MIC data for *A pyogenes* prompt us to reevaluate the *in vitro* activity of various classes of antibiotics against recent clinical isolates of *A pyogenes.* Apart from antibiotic families used in food animal practice, we included antibiotics of other families essentially from an epidemiological point of view. Sulfonamides and trimethoprim were not tested since only a poor growth was observed for *A pyogenes* on lysed horse blood agar.

MATERIALS AND METHODS

Antimicrobial agents

The antimicrobial compounds tested as laboratory standard powder were kindly supplied as follows: penicillin G, spiramycin, pristinamycin, and the pristinamycin components I and II from Rhône-Poulenc (Vitry, France); pefloxacin from Roger Bellon Laboratory (Neuilly sur Seine, France); cefoperazone from Pfizer France Co (Orsay, France); novobiocin from Upjohn Laboratory (Crawley, UK); lincomycin and spectinomycin from Upjohn Laboratory (La Défense, France); fucidic acid from Leo Pharmaceutical Products (Vernouillet, France); gentamicin, kanamycin, streptomycin, erythromycin, chloramphenicol, and tetracycline from Vétoquinol (Lure, France); cephalothin, and vancomycin from Lilly France (Saint Cloud, France); doxycycline from Rhône-Mérieux (Toulouse, France); amoxicillin from SmithKline Beecham Laboratory (Paris, France); minocycline from Lederle Laboratory (Oullins, France); rifampin from Ciba-Geigy Laboratory (Rueil-Malmaison, France). Methicillin (ref M-1757) was purchased from Sigma Chemical Co (St Louis, USA).

Rifampin, fucidic acid, chloramphenicol, spiramycin, erythromycin, pristinamycin, and the pristinamycin components I and II were first dissolved in a small amount of ethanol; tetracycline, and lincomycin in methanol. The volume was then adjusted with distilled water to the final concentration. Further dilutions were made in distilled water. The other drugs were dissolved and diluted in distilled water.

Bacterial strains

A set of 103 strains of *A pyogenes* was used in this study. Ninety-three strains were collected by JL Martel (Laboratoire de Pathologie Bovine, CNEVA, Lyon, France) from clinical isolates and *post-mortem* cases submitted to the Laboratoires Vétérinaires Départementaux, in France between 1984–1990. The other strains were collected by B Poutrel (INRA, Nouzilly, France), E Richard (Laboratoire Vétérinaire Départemental, Lyon, France), J Vidal (Laboratoire Vétérinaire Départemental, Rodez, France) and V Guérin-Faublée (Laboratoire de Microbiologie et Immunologie, ENVL, Lyon, France).

Ninety-seven strains were recovered from cattle, 4 from sheep and 2 from goats; most of them (52 strains) were isolated from the respiratory tract; 20, 6 and 4, respectively, from milk, foetuses and uterine discharges; 11 from various suppurative infections; 10 were of unknown origin.

Organism identification was based on colony morphology, haemolysis, Gram staining and classical biochemical characteristics (Krech and Hollis, 1991). After biotyping, they were stored at −70 °C in brain–heart infusion broth supplemented with 10% glycerol.

Quality controls were run using *Staphylococcus aureus* ATCC25923 and *Escherichia coli* ATCC25922. All the strains were grown aerobically.

Media and supplements

A pyogenes strains were grown on trypto-casein soya agar (ref 64554, Diagnostics Pasteur, Marnes-la-Coquette, France) supplemented with 5% sheep blood (ref 5 582 2, Bio Mérieux, Marcy l'Étoile, France). Liquid media used were brain–heart infusion broth (ref 0037-01-6, Difco, Detroit, USA) supplemented with 5% sterile horse serum (ref 295 990, Boehringer–Mannheim, Mannheim, FRG) and 0.1% (v/v) Tween 80 (ref 822 187, Merck, Darmstadt, FRG).

Agar plates for MIC determination were prepared by adding 2 ml of antibiotic solution and 1 ml of sheep blood to 17 ml of melted Mueller–Hinton agar (ref 64 884, Diagnostics Pasteur). All plates were stored at + 4 °C and used within 24 h. Growth was clearly visible after 24 h of aerobic incubation in these conditions on control plates.

Inoculum preparation

Three to 5 colonies from Trypticase soy blood agar plate were suspended in brain–heart infusion broth supplemented with 0.1% Tween 80 and incubated aerobically for 2 d at 37 °C. Exponential growing inoculum was prepared by inoculating 30 µl of this first liquid medium culture into 10 ml of brain–heart infusion broth supplemented with 0.1% Tween 80 and 5% sterile horse serum. The addition of 0.1% Tween 80 to the liquid media during the growth of the organism prevented the formation of clumps and was necessary to obtain a reproducible inoculum with most of the strains of *A pyogenes*.

After an overnight incubation at 37 °C, optical density was measured at 430 nm on a Shimadzu MPS 2000 spectrophotometer (Shimadzu, Kyoto, Japan). A dilution of the exponential growth culture was made in sterile solution in distilled water with sodium chloride 8 g/l (w/v) according to absorbance such that the final inoculum concentration was approximately 10^7 CFU/ml.

MIC determination

The agar dilution method was used to determine the MIC of 22 drugs. Inocula were delivered by a Steers replicator apparatus (Denley Multipoint Inoculator A 400, Nattslane, Billingshurst, UK) for a final concentration of approximately 10^4 CFU per spot. After 18–20 h of incubation at 37 °C under atmospheric conditions, the MIC for each strain was recorded as the lowest concentration of antibiotic yielding no growth as determined by the naked eye; 1 to 3 colonies or a barely visible haze were not taken into account.

MIC interpretative standards of the Comité de l'Antibiogramme de la Société Française de Microbiologie (Acar *et al*, 1991) were followed.

RESULTS

The MIC (in mg/l) of the 22 tested antimicrobial agents for the 103 strains of *A pyogenes* are shown in table I and the MIC for the control strains in table II.

In our experimental conditions, MIC of doxycycline, minocycline, pristinamycin component I and pefloxacin for quality control strains were 3-fold higher than those expected. MIC of the component II of pristinamycin and of fucidic acid for *S aureus* ATCC25923 were 16 and 16-32 mg/l respectively, although the reported MIC for susceptible strains of this species are respectively 0.5 and 0.06 mg/l. For these 6 antibiotics the absolute value of the MIC cannot be taken into consideration but the comparison within the *A pyogenes* set of strains remains of value.

All strains were susceptible to ß-lactam antibiotics (penicillin G, amoxicillin, methi-

Table I. MIC of 24 antibiotics for 103 strains of *Actinomyces pyogenes*.

Test agent	*No of isolates with a MIC (mg/l)*														
	<0.03	*0.03*	*0.06*	*0.12*	*0.25*	*0.5*	*1*	*2*	*4*	*8*	*16*	*32*	*64*	*128*	*>128*
Penicillin G	103				*						*				
Amoxicillin	2	72	29						*		*				
Methicillin			30	28	27	17	1	*							
Cephalothin		5	26	62	10					*		*			
Cefoperazone			34	68	1				*			*			
Spiramycin	48	39	3			1		*		*	1		5	4	2
Erythromycin	91						*		*				1		11
Lincomycin	22	51	18					*		*			5	7	
Pristinamycin			5	60	38			*							
Pristinamycin component I								10	64	18	2	3	4	2	
Pristinamycin component II						14	64	20	4	1					
Streptomycin					4	32	0	4	2	*	*	2	5	1	53
Kanamycin							5	39	59	*	*				
Gentamicin					19	65	19		*	*					
Spectinomycin				21	73	5	3	1					*		
Tetracycline							8	25	1*	*			5	52	12
Doxycycline					2	19	12	1	*	*		1			68
Minocycline					7	21	6		*	*		13	22	34	
Chloramphenicol						8	86	8	1	*	*				
Vancomycin					13	67	23		*		*				
Novobiocin					24	72	7	**			**				
Rifampin	103								*		*				
Fucidic acid							1	68*	34		*				
Pefloxacin							*		*			79	24		

* MIC breakpoints according to the Comité de l'Antibiogramme de la Société Française de Microbiologie; ** MIC breakpoints according to the manufacturer.

cillin, cephalothin, and cefoperazone), to pristinamycin, to chloramphenicol, to rifampin, to vancomycin, to novobiocin (2–16, limits given by the manufacturer) and to aminoglycosides (gentamicin, kanamycin, and spectinomycin) except streptomycin.

A bimodal response was observed to streptomycin, the tetracycline family, macrolides and lincosamides.

Of the 103 strains studied, only 42 (41%) were susceptible to streptomycin. The 61 (59%) resistant strains included many different populations and 25 (24%) strains had a high level of resistance.

Most of the strains (69 strains, 67%) were resistant to the tetracycline. For these strains, MIC of doxycycline and minocycline were very much higher than MIC for strains susceptible to tetracycline. The resistance to the tetracycline family was frequently associated with resistance to streptomycin ($\chi^2 = 4.6$, $P < 0.05$).

Table II. MIC (mg/l) of 24 antibiotics for the control strains.

Antibiotic	S aureus *ATCC25923*	E coli *ATCC25922*
Penicillin G	0.06	32
Amoxicillin	0.25	8
Methicillin	2	>128
Cephalothin	0.5	8
Cefoperazone	4	0.25
Spiramycin	0.12	64
Erythromycin	0.03	8
Lincomycin	0.12	>128
Pristinamycin	1	128
Pristinamycin component I	16	>128
Pristinamycin component II	16	>128
Streptomycin	0.5	0.5
Kanamycin	1	2
Gentamicin	0.12	0.25
Spectinomycin	>128	2
Tetracycline	2	4
Doxycline	1	4
Minocycline	0.5	2
Chloramphenicol	8	4
Vancomycin	2	>128
Novobiocin	2	>128
Rifampin	0.03	8
Fucidic acid	8	>128
Pefloxacin	2	0.25

The patterns of resistance of *A pyogenes* to macrolides, lincosamides, and streptogramins on the basis of MIC tests are shown in table III. A limited number of strains (12 strains, 12%) showed a cross-resistance between erythromycin, spiramycin and lincomycin; all these strains were susceptible to pristinamycin. Their susceptibility to pristinamycin component II was of the same order of magnitude as that of macrolide- and lincosamide-susceptible strains. Most of these strains (9/12) were resistant to pristinamycin component I as their MIC were 2 to 4-fold superior to MIC of the susceptible strains. This resistance was phenotypically very similar to the constitutive MLS (B) resistance. Three strains were resistant to macrolides and lincosamides, but probably susceptible to pristinamycin components I and II; they may be designated as ML-resistant strains.

DISCUSSION

All the strains of *A pyogenes* are naturally susceptible to numerous antibiotics with narrow or broad spectrum: ß-lactam antibiotics, pristinamycin, gentamicin, kanamycin, chloramphenicol, rifampin, vancomycin and novobiocin. Only few strains are susceptible to streptomycin and the i, tetracycline family but the majority remains susceptible to macrolides and lincosamides.

It was not possible to determine accurately the MIC of fucidic acid, doxycycline, minocycline, pristinamycin components I and II, and pefloxacin as MIC for the control strains were higher than expected. The adjunction of blood to Mueller–Hinton agar, required for the correct growth of *A pyogenes* may explain these problems. Inhibition of fucidic acid by serum is recognised (Barber and Waterworth, 1962) as well as the adverse effect of traces of hemolysis on pristinamycin component II (Videau, 1982). MIC for the tetracycline family are increased by an excess of Ca and Mg ions (Brenner and Sherris, 1972). In the cases of pristinamycin component I and pefloxacin, the discrepancies may be due to the increased growth rate of the control strains in the experimental conditions. A suitable medium for *A pyogenes* susceptibility testing to these antibiotics and to sulfonamides and trimethoprim is under investigation.

MIC interpretative standards are defined for fast growing bacteria; moreover, these values are based only on pharmacokinetic studies in humans and the cut-off criteria

Table III. Patterns of resistance (MIC in mg/l) to macrolides, lincosamides and streptogramins of *Actinomyces pyogenes* strains of animal origin.

Pattern of resistance	*Strain No*	*Macrolides*		*Lincosamides LNC*	*Streptogramins*		
		ERY	*SPI*		*PTN*	*PTN I*	*PTN II*
Resistant strains	1433	256	64	64	0.25	128	1
	1506	256	128	128	0.25	32	1
	1571	>256	256	128	0.25	32	1
	1946	256	128	64	0.25	128	1
	2992	256	64	64	0.25	64	2
	3334	64	128	128	0.25	64	1
	3890	256	256	128	0.12	32	1
	3892	256	64	64	0.12	64	1
	4430	256	128	128	0.12	64	1
	1361	256	16	64	0.25	16	8
	2565	256	64	128	0.25	16	1
	4331	256	64	128	0.12	8	1
Susceptible strains (91)		≤ 0.015	≤ 0.015–0.5	≤ 0.015–0.06	0.06–0.25	2–8	0.5–4

Abbreviations: ERY, erythromycin; SPI, spiramycin; LNC, lincomycin; PTN, pristinamycin; PTN I, pristinamycin component I; PTN II, pristinamycin component II.

does not necessary apply to bacteria pathogenic for animal species.

In general, our results were in agreement with those of Bulling (1954), Hjerpe and Routen (1976), Burrows (1980), Mitani *et al* (1980), Gedek *et al* (1984, 1988), and Buchholz (1985). Divergences in terms of effectiveness could be noted. Gedek *et al* (1988) found higher MIC of spiramycin and lincomycin for susceptible strains and Hjerpe and Routen (1976) in the case of novobiocin. *A pyogenes* seems to be more susceptible to lincosamides and novobiocin than the other *Actinomyces* species (Lerner, 1974; Niederau *et al,* 1982). In the same way, we observed lower MIC of penicillin G and cephalothin than the majority of authors (Hjerpe and Routen, 1976; Burrows, 1980; Mitani *et al,* 1980); this could be due to the physiological state of the bacteria: bacteria in exponential growth are more susceptible to ß-lactam antibiotics than those in steady-state growth. MIC of cephalothin were of the same order of magnitude as those reported for other *Actinomyces* species (Lerner, 1974; Schaal *et al,* 1979) but the species *A pyogenes* is especially susceptible to penicillin G and penicillins A (Lerner, 1974; Niederau *et al,* 1982). According to our results, aminosides except streptomycin exhibit a moderate inhibitory activity against *A pyogenes* but better than that described by Hjerpe and Routen (1976), Burrows (1980), and Mitani *et al* (1980). Despite extreme variations in assay technique, the pattern of MIC of aminoglycosides was very different to that of other *Actinomyces* species which are resistant to these compounds (Lerner, 1974; Schaal, 1986). MIC of minocycline,

doxycycline, rifampin, and vancomycin were the same as those of diverse *Actinomyces* species (Lerner, 1974; Schaal, 1986).

A pyogenes was the only species of the genus *Actinomyces* to harbour resistance if we exclude the limited resistance to rifampin developed by *A eriksonii* and *A naeslundii* (Lerner, 1974). Sixty-seven and 59% of the strains were respectively resistant to the tetracycline family and to streptomycin. These high frequencies were similar to those previously reported by Hjerpe and Routen (1976), Gedek *et al* (1984), and Buchholz (1985), but differed from those of Nattermann and Horsch (1976), and Kunter (1975) whose strains were collected earlier. Resistant strains to macrolides and related antibiotics were not as numerous (about 10%), much fewer than reported by Hjerpe and Routen (1976), and Gedek *et al* (1984). Most of the strains resistant to macrolides and lincosamides exhibited a resistance pattern that was phenotypically very similar to the constitutive MLS(B) resistance in staphylococci (Courvalin *et al,* 1985) although the MIC of pristinamycin component I were not as high as those expected in such resistant strains. This phenotype is widely spread among clinical isolates and has been detected in other coryneform bacteria such as *Propionibacterium* species (Eady *et al,* 1989) and *Corynebacterium diphtheriae* strains isolated from cutaneous lesions (Coyle *et al,* 1979; Serwold-Davis and Groman, 1988).

These data are *in vitro* values and as such should guide the clinician in selecting the most appropriate antibiotic to treat animals with *A pyogenes* infections. Since few pharmacokinetic studies are available for ruminants and pigs, it is possible neither to outline comprehensive guidelines for the application of these *in vitro* data nor to judge the relative efficacy of the various molecules. However, the activity of penicillin G, as well as cephalosporins, against *A pyogenes* suggests that these drugs should be useful in the management of animals with *A pyogenes* infections. Penicillins A appear to be an excellent alternative. Some animals failed to respond to therapy without development of resistant strains. Whether or not MIC are attained within a purulent environment could not be ascertained from the available literature. Moreover, *A pyogenes* is practically never the only pathogen present in lesions.

Regular MIC reports by a few laboratories seem to be sufficient to guide the veterinary surgeon. The use of an abbreviated form of the dilution procedure with only 2 concentrations of the antibiotics (the breakpoint concentrations) is under investigation.

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