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Original

Activity of oral antibiotics against respiratory tract pathogens in Spain

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SUMMARY

The aim of this study was to carry out a nationwide survey to assess the susceptibility of clinical isolates of four respiratory pathogens against nine antibiotics. Eight Spanish centers participated in the study, collecting a total of 977 isolates of Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae *and* Moraxella catarrhalis. *The susceptibility of* S. pneumoniae *to penicillin was 37.46% susceptible, 30.43% intermediate and 32.11% resistant. MIC_{90} of all antibiotics against this microorganism were 4–8 mg/l, except cefaclor, cefixime and azithromycin. For* S. pyogenes*, all the strains were susceptible to penicillins and cephalosporins, and azithromycin was the least active with a rate of resistance of 11.43%. A total of 95 isolates of* H. influenzae *were betalactamase positive (26.32%). With regard to* M. catarrhalis*, only penicillin and amoxicillin showed $MICs_{90}$ ≥8 mg/l.*

Key words: Susceptibility - Cephalosporins - Cefpodoxime - *S. pneumoniae - S. pyogenes - H. influenzae*

Actividad de los antibióticos orales frente a los microorganismos patógenos de las vías respiratorias en España

RESUMEN

El objetivo de este estudio fue realizar una encuesta de ámbito nacional para evaluar la sensibilidad de las cepas clínicas de cuatro microorganismos patógenos respiratorios a nueve antibióticos. En el estudio participaron ocho centros españoles, recogiendo un total de 977 cepas de Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae *y* Moraxella catarrhalis*. El 37,46% de* S. pneumoniae *fue sensible a la penicilina, el 30,43% mostró resistencia intermedia y el 32,11% fue resistente. Las CMI_{90} de todos los antibióticos frente a este microorganismo fueron de 4-8 mg/l, excepto para cefaclor, cefixima y azitromicina. En el caso de* S. pyogenes*, todas las cepas fueron sensibles a la penicilina y las cefalosporinas, mientras que la azitromicina fue el antibiótico menos activo, con un grado de resistencia que alcanzó el 11,43%. Noventa y cinco cepas de* H. influenzae *fueron betalactamasa positivas (26,32%). En el caso de* M. catarrhalis*, sólo la penicilina y la amoxicilina tuvieron CMI_{90} ≥8 mg/l.*

Palabras clave: Sensibilidad – Cefalosporinas – Cefpodoxima – *S. pneumoniae – S. pyogenes – H. influenzae*

INTRODUCTION

Resistance of pathogens frequently isolated from community-acquired respiratory tract infections to commonly used antimicrobials has increased exorbitantly in the last two decades (1). For *Streptococcus pneumoniae*, a variable geographical distribution of such resistance is observed, with countries such as Taiwan, Hong Kong, Mexico, the United States, the Slovak Republic, France and Spain showing high rates of penicillin intermediate or fully resistant strains (1-3). In Spain, isolates with penicillin MIC ≥0.12 mg/l have increased from 6% in 1979 to over 40% ten years later (4). A recent study reported a 36.5% incidence of fully resistant strains (5).

No less important is the increase in macrolide resistance of this microorganism, which is commonly associated with betalactam resistance (6). Some countries with high rates of penicillin resistance also show high macrolide resistance rates (*i.e.* France, Spain, Hong Kong) (1). However, antimicrobial consumption may also play an important role in this increase, as demonstrated in the case of a region in Italy with high rates of macrolide resistance but low percentages of penicillin resistance (1).

With respect to other microorganisms causing respiratory tract infections, *Haemophilus influenzae* has become important because of the increase in betalactamase-producer strains. Countries such as the United States, Hong Kong, France and Spain again show the highest rates of such isolates, with values around 30% (1). Also of concern is the number of betalactamase-negative and ampicillin-resistant strains, with low rates worldwide (0.3%) though nevertheless indicating the need for caution (1).

In the case of *Streptococcus pyogenes*, which maintains full susceptibility to penicillin, the main problem arises from the increasing rates of macrolide resistance. In Spain, the use of these agents in the treatment of common infections such as pharyngitis has probably led to a 15–25% rate of resistant strains (7-9). This is important because all 14- and 15-membered macrolide agents are affected to the same degree, while miocamycin (a 16-membered ring macrolide) and clindamycin (lincosamide) retain good activity against strains showing the M-phenotype (7).

Finally, *Moraxella catarrhalis* is also an important pathogen, causing infections such as the acute exacerbation of chronic bronchitis and presenting betalactamase production as the only currently known resistance mechanism (1). More than 90% of the strains show this mechanism, though the need for improved knowledge of its susceptibility profile to common antimicrobial agents makes it necessary to include the pathogen in surveillance studies.

Our aim was to carry out a nationwide study in eight centers distributed throughout the country to determine the susceptibility of strains of all these microorganisms to nine antimicrobial agents commonly used in the treatment of community-acquired respiratory tract infections. We included a macrolide (azithromycin), two penicillins (penicillin and amoxicillin), the combination of amoxicillin and clavulanic acid, and five cephalosporins (cefaclor, ceftibuten, cefixime, cefuroxime and cefpodoxime).

MATERIALS AND METHODS

Collaborating centers

Eight Spanish centers were enrolled in the study on the basis of geographical location, as follows: Ciudad Sanitaria y Universitaria de Bellvitge from Barcelona (Dr. R. Martín), Hospital Clínico Universitario from Zaragoza (Dr. R. Gómez-Lus), Hospital Virgen de las Nieves from Granada (Dr. M. De la Rosa), Hospital Universitario "Virgen de la Macarena" from Seville (Dr. E. Perea), Hospital Clínico Universitario from Salamanca (Dr. J.A. García-Rodríguez), Hospital La Fe from Valencia (Dr. M. Gobernado), Hospital Materno Infantil "Teresa Herrera" from A Coruña (Dr. A. Guerrero) and Hospital Clínico San Carlos from Madrid (Dr. J. Prieto). The central laboratory was located (at the Department of Microbiology, School of Medicine, Complutense University in Madrid).

Bacterial isolates

From August 1998 to November 2000 each center was to collect a total of 122 isolates of the following species in the following estimated proportions: *S. pneumoniae* (30–35%), *H. influenzae* (30–35%), *S. pyogenes* (20–25%) and *M. catarrhalis* (10–15%). Depending on the microorganisms, isolates were to be obtained from patients with community-acquired respiratory tract infections, such as pneumonia, acute bronchitis, acute otitis media, tonsillopharyngitis or acute exacerbation of chronic bronchitis. Only sputum, bronchoalveolar lavage, swab or blood culture samples were allowed.

Storage and transport to the central laboratory

After identification, using standard methods to each center, isolates were frozen at –70 ºC. Transport to the central laboratory in Madrid was done in batches, using inoculated swabs maintained in Amies medium or inoculated

agar plates with the appropriate medium for each microorganism. Once in the central laboratory, isolates were grown in medium and 10 samples of each were frozen at –70 ºC in skimmed milk until susceptibility determination.

Antimicrobial agents

The following drugs were used in all susceptibility determinations: penicillin V (Sigma-Aldrich S.A., Madrid, Spain), amoxicillin (Sigma-Aldrich S.A., Madrid, Spain), amoxicillin-clavulanic acid (SmithKline Beecham S.A., Madrid, Spain), cefaclor (Sigma-Aldrich S.A., Madrid, Spain), cefixime (Merck Farma y Química S.A., Barcelona, Spain), cefpodoxime-proxetil (Sankyo Pharma GmbH, Munich, Germany), cefuroxime (Sigma-Aldrich S.A., Madrid, Spain), ceftibuten (Schering-Plough, Madrid, Spain) and azithromycin (Pfizer S.A., Madrid, Spain).

Antimicrobial susceptibility tests

MICs were determined using the broth microdilution technique (10), with a final volume of 100 µl and an inoculum of approximately 10^5 CFU/ml. The medium used was cation-adjusted Mueller-Hinton (Difco, Madrid, Spain) supplemented with 2% v/v lysed horse blood (Biomerieux, Madrid, Spain) for *S. pneumoniae* and *S. pyogenes, Haemophilus* test medium for *H. influenzae* (10), and Mueller-Hinton for *M. catarrhalis*. This process was performed in triplicate.

After overnight incubation at 35 ºC in room air for 20–24 hours, endpoints were read visually, determining the MIC as the mode of the three results. Two strains were also assayed for quality control: *S. pneumoniae* ATCC 49619 for *S. pneumoniae; S. pyogenes* ATCC 19615 for *S. pyogenes*; and *H. influenzae* ATCC 49247 for *H. influenzae.* Only MIC tests where control determinations were within the performance range were accepted.

The antimicrobial concentrations assayed were chosen taking into account the expected susceptibility to each microorganism. Breakpoint concentrations used to calculate resistance rates were based on those published by the National Committee for Clinical Laboratory Standards (10).

Statistical analysis of resistance rates (with *S. pneumoniae* and *S. pyogenes*) and betalactamase production (with *H. influenzae*) in the two-year period of the study was performed by the chi-square test, with Yates correction when necessary (level of significance = 95%).

RESULTS

Number of isolates and geographical distribution

A total of 977 isolates were collected in this study: 299 of *S. pneumoniae* (30.6%), 210 of *S. pyogenes* (21.49%), 361 of *H. influenzae* (36.95%) and 107 of *M. catarrhalis* (10.95%). The percentages of each microorganism were very similar to those expected. Table 1 shows the geographical distribution (number of isolates per center); the largest numbers of isolates were collected from A Coruña and Seville, and the lowest in Granada (107 strains); the mean was approximately 122 strains per center. A total of 37.46% of the strains were isolated in 2000, 55.37% in 1999 and only 7.16% in 1998 or before.

Streptococcus pneumoniae

The susceptibilities of this microorganism to the antimicrobial agents tested are shown in Table 2; isolates were divided according to their susceptibility to penicillin. The overall susceptibility to penicillin was 112 strains sus-

Table 1. Distribution of the isolates in the different centers participating in the study.

Center	*S. pneumoniae*	*S. pyogenes*	*H. influenzae*	*M. catarrhalis*	Total
A Coruña	16	63	46	4	129
Barcelona	41	–	60	20	121
Granada	33	22	43	9	107
Madrid	40	15	32	32	119
Salamanca	53	12	58	2	125
Seville	36	45	47	–	128
Valencia	35	29	30	30	124
Zaragoza	45	24	45	10	124
Total	299	210	361	107	977

Table 2. *In vitro* activities of antimicrobial agents against *S. pneumoniae* (MIC_{90}, range and % of resistant strains). Isolates have been distributed by penicillin susceptibility.

	Penicillin-susceptible n = 112 (37.46%)			Penicillin-intermediate n = 91 (30.43%)			Penicillin-resistant n = 96 (32.11%)			All strains (n = 299)		
Antimicrobial agent	MIC_{90} (mg/l)	Range (mg/l)	Resist. (%)	MIC_{90} (mg/l)	Range (mg/l)	Resist. (%)	MIC_{90} (mg/l)	Range (mg/l)	Resist. (%)	MIC_{90} (mg/l)	Range (mg/l)	Resist. (%)
Penicillin	0.06	0.007–0.06	–	1	0.125–1	–	>8	2–>8	–	4	0.007–>8	32.11
Amoxicillin	0.25	0.007–1	0.00	1	0.03–4	0.00	8	0.5–>8	13.54	4	0.007–>8	4.35
Amoxicillin-clav. acid	0.25	0.007–1	0.00	1	0.03–4	0.00	8	0.5–>8	11.46	4	0.007–>8	3.68
Cefaclor	8	0.25–32	33.04	64	0.06–>128	84.62	>128	2–>128	98.96	128	0.06–>128	69.90
Cefixime	2	0.03–4	NA*	8	0.06–>8	NA*	>8	0.25–>8	NA*	>8	0.03–>8	NA*
Cefpodoxime	0.125	0.015–1	0.00	2	0.03–>8	17.58	8	0.06–>8	84.38	4	0.015–>8	32.44
Cefuroxime	0.25	0.007–8	0.89	4	0.03–8	18.68	8	0.5–>8	87.50	8	0.007–>8	34.11
Ceftibuten	4	0.06–>8	NA*	8	0.06–>8	NA*	>8	0.25–>8	NA*	8	0.06–>8	NA*
Azithromycin	0.25	<0.015–>8	5.36	8	<0.015–>8	15.38	>8	<0.015–>8	55.21	>8	<0.015–>8	24.41

*NA: no breakpoint criteria established by the National Committee for Clinical Laboratory Standards.

ceptible (37.46%), 91 intermediate (30.43%) and 96 resistant (32.11%). By collection dates, in 1999 (n = 166) the penicillin susceptibility was 39.16% susceptible, 24.70% intermediate and 36.14% resistant. In 2000 (n = 110), these rates were 34.55% susceptible, 33.64% intermediate and 31.82% resistant. In 1998 or before, no assessable rates could be calculated owing to the low number of isolates involved (n = 23). No statistically significant differences (p = ns) were found between 1999 and 2000 susceptibility rates.

The MIC_{90} was in the interval of 4–8 mg/l for all agents, with the exception of cefaclor (128 mg/l) and azithromycin (>8 mg/l). Nevertheless, the percentages of resistant strains for each agent according to their NCCLS breakpoints (10) were highly variable: amoxicillin and amoxicillin-clavulanic acid showed the lowest values (4.35 and 3.68% of resistant strains), followed by azithromycin, cefpodoxime and cefuroxime (from 24.41 to 34.11%), and finally cefaclor (69.90%). Both cefixime and ceftibuten lack defined breakpoints.

In the penicillin-susceptible strains, only amoxicillin, amoxicillin-clavulanic acid and cefpodoxime showed 0% resistance, followed by cefuroxime (0.89%). Cefaclor however showed 33.04% resistance. In the penicillin-intermediate strains, only amoxicillin and amoxicillin-clavulanic acid showed 0% resistance; azithromycin, cefpodoxime and cefuroxime showed percentages from 15.38 to 18.68%, while cefaclor reached 84.62%. Finally, in the penicillin-resistant isolates, amoxicillin and amoxicillin-clavulanic acid showed a resistance of 13.54 and 11.46%; the other agents were less active, with percentages of 55.21% for azithromycin, 84.38% for cefpodoxime, 87.50% for cefuroxime and 98.96% for cefaclor. Except for this last agent, the $MICs_{90}$ were nevertheless approximately the same (8 mg/l). Cefixime and ceftibuten were less active than cefpodoxime and cefuroxime, but more active than cefaclor, when taking into account their MIC_{90}.

Streptococcus pyogenes

Isolates were collected as follows: 69 strains (32.86%) in 2000, 116 (55.24%) in 1999, and 25 (11.90%) in 1998 or before. Table 3 shows the results of MIC determinations for this microorganism. The susceptibility to penicillin was 100%, with a MIC_{90} of 0.06 mg/l. This same MIC_{90} was shown by amoxicillin and amoxicillin-clavulanic acid, while cefpodoxime and cefuroxime were one dilution less active (0.125 mg/l). Cefixime MIC_{90} was similar (0.25 mg/l), but cefaclor and ceftibuten showed higher values (2 and 1 mg/l, respectively).

Table 3. *In vitro* activities of antimicrobial agents against *S. pyogenes* (MIC_{50}, MIC_{90}, range and % of susceptible, intermediate and resistant strains).

Antimicrobial agent	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Range (mg/l)	% Susc.	% Inter.	% Resist.
Penicillin	0.06	0.06	0.015–0.125	100	0	0
Amoxicillin	0.03	0.06	0.015–0.125	–*	–*	–*
Amoxicillin-clavulanic acid	0.03	0.06	0.015–0.125	–*	–*	–*
Cefaclor	0.5	2	0.06–2	–*	–*	–*
Cefixime	0.125	0.25	0.03–0.5	NA**	NA**	NA**
Cefpodoxime	0.06	0.125	0.015–0.25	–*	–*	–*
Cefuroxime	0.06	0.125	0.015–0.25	–*	–*	–*
Ceftibuten	0.5	1	0.06–4	–*	–*	–*
Azithromycin	0.125	2	0.015–4	80	8.57	11.43

*All the strains susceptible to penicillin can be susceptible to amoxicillin, amoxicillin-clavulanic acid, cefpodoxime, cefuroxime, ceftibuten and cefaclor (ref. 14).
**NA: no breakpoint criteria established by the National Committee for Clinical Laboratory Standards.

Finally, azithromycin was the least active (MIC_{90} = 2 mg/l), with a rate of intermediate and high resistance of 8.57% and 11.43%, respectively. These rates were not statistically different between the years 1999 and 2000 (p = ns; strains of 1998 or before were not included due to low frequency). The rates were 81.03% and 78.26% of susceptible strains (in 1999 and 2000, respectively), 6.03% and 8.70% of intermediate strains, and 12.93% and 13.04% of resistant strains.

Haemophilus influenzae

The largest number of isolates collected corresponded to this microorganism. In 2000, a total of 153 (42.38%) strains were sent to the central laboratory; in 1999, 192 isolates (53.19%) were collected, and in or before 1998 the number was 13 (3.60%).

In the overall study, a total of 95 isolates were betalactamase positive (26.32%). Comparing the rate of betalactamase-positive strains in 2000 *versus* 1999, no statistical differences were found, though the rates in 1999 were approximately 7% higher than in 2000 (30.21 *versus* 22.88%).

Regarding antimicrobial susceptibility (Table 4), the rate of amoxicillin-resistant strains (27.70%, determined with the ampicillin breakpoints) was approximately the same as the betalactamase-positive rate (26.32%). However, six isolates (1.66%) showed betalactamase-negative activity but were fully resistant to amoxicillin (11); another 1.10% of these isolates were intermediately resistant to amoxicillin. All the strains were completely susceptible to all of the antimicrobial agents tested except cefaclor, which showed a low rate of resistant or intermediate strains (1.94% and 3.32%, respectively).

Table 4. *In vitro* activities of antimicrobial agents against *H. influenzae* (MIC_{50}, MIC_{90}, range and % of susceptible, intermediate and resistant strains).

Antimicrobial agent	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Range (mg/l)	% Susc.	% Inter.	% Resist.
Penicillin	2	>16	0.5–>16	NA*	NA*	NA*
Amoxicillin	0.5	>64	0.125–>64	69.81**	2.49**	27.70**
Amoxicillin-clavulanic acid	0.5	1	0.06–4	100	–	0
Cefaclor	2	8	0.03–64	94.74	3.32	1.94
Cefixime	0.03	0.125	<0.015–0.5	100	–	0
Cefpodoxime	0.06	0.25	0.03–1	100	–	0
Cefuroxime	1	2	0.25–4	100	–	0
Ceftibuten	0.06	0.25	0.03–2	100	–	0
Azithromycin	0.125	0.25	0.03–1	100	–	0

*NA: no breakpoint criteria established by the National Committee for Clinical Laboratory Standards.
**Breakpoint for ampicillin.

Table 5. *In vitro* activities of antimicrobial agents against *M. catarrhalis* (MIC_{50}, MIC_{90} and range).

Antimicrobial agent	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Range (mg/l)
Penicillin	8	>16	0.06–>16
Amoxicillin	4	8	0.03–>8
Amoxicillin-clav. acid	0.125	0.5	0.015–4
Cefaclor	1	4	0.125–8
Cefixime	0.25	0.5	0.06–1
Cefpodoxime	1	2	0.06–2
Cefuroxime	1	4	0.125–4
Ceftibuten	2	4	0.125–8
Azithromycin	0.03	0.06	<0.03–0.125

Moraxella catarrhalis

A total of 107 isolates of this microorganism were collected during the study period. In 2000, 34 strains (31.78%) were isolated *versus* 67 (62.62%) in 2000 and 6 (5.6%) in 1998 or before.

The susceptibility results are shown in Table 5. The most active agent was azithromycin, with a MIC_{90} of 0.06 mg/l, followed by amoxicillin-clavulanic acid and cefixime (0.5 mg/l). Cefpodoxime showed a MIC_{90} of 2 mg/l, lower than cefuroxime (4 mg/l) and other oral cephalosporins (ceftibuten and cefaclor), and lower than the values for amoxicillin and penicillin.

DISCUSSION

Resistance of common respiratory tract pathogens to antimicrobial agents has emerged as one of the most important problems in the field of infectious diseases. Since the first penicillin-resistant strains of *S. pneumoniae* were isolated in the 1960s and 70s, the rate of decreased susceptibility has increased worldwide, though geographical variations have been observed (1-3, 12, 13). In Spain, the rate of penicillin resistance (intermediate and high) has increased in the last two decades from approximately 6% (4) to percentages around 60–65% (5). These same values are observed in our study, as well as in another study performed in the Madrid community in 1999 and 2000 (14), although in this survey full resistance was higher (40.6%); these figures show that only one-third of the isolates are susceptible to penicillin. Amoxicillin (with or without clavulanic acid) shows the lowest resistance rates in our study, mainly due to the recent change in breakpoints by the NCCLS (10), which stipulate that values of ≥8 mg/l represent resistance rather than ≥2 mg/l. Nevertheless, MIC_{90} values of these agents are equal to that of cefpodoxime (4 mg/l) and not very different from other cephalosporins such as cefuroxime or ceftibuten (8 mg/l). The most active cephalosporins in terms of resistance rates are cefpodoxime and cefuroxime, with values around 32 and 43%, respectively. In this way, we could grade the activity of oral betalactams in terms of resistance rates, with agents such as amoxicillin (with or without clavulanic acid) being more active than penicillin; cefpodoxime and cefuroxime (and, to a lesser extent, ceftibuten and cefixime) exhibiting rates equivalent to penicillin; and cefaclor with high rates of resistance (twice the penicillin values).

A different issue is the macrolide resistance shown by *S. pneumoniae*. We obtained lower rates with azithromycin (24.41%) than those reported in other studies (1, 5, 14), where rates of 30–35% were observed with both erythromycin and azithromycin in the last four years (1996–2000). It is of interest to point out that in our study, as well as in others (1, 5), macrolide resistance is clearly higher within penicillin-resistant strains: only 5.36% of penicillin-susceptible strains were macrolide resistant, though this rate was 55.21% in the penicillin-resistant isolates. This cross-resistance has been studied and may have an epidemiological justification, since the mechanisms of action of penicillin and the macrolides are different (6, 15).

On the other hand, the rate of resistance of *H. influenzae* to penicillin or aminopenicillins (ampicillin) has also increased during the last two decades (1). In several countries including Spain, the percentage of betalactamase-positive strains is over 30%, though these rates have not changed significantly in the last few years (1, 3). We have found an overall rate of about 26% of these strains, though it is of interest to point out that in 2000 the rate decreased to 22.88% from 30.21% in the previous year. In 1998–1999, Bandak *et al.* (16) showed a 21.80% incidence of betalactamase-positive isolates in Spain. In 1996–1997, other authors in Spain reported rates of 25.7% to 31.7% (1, 17); these figures are not very different from those found in our study in 1999, and are similar to the 30% and 33.3% (Barcelona and Madrid, respectively) reported in a surveillance study in 1992–1993 (18). These results seem to reflect a stagnation in the ampicillin-resistance rate in Spain as well as in other geographical settings.

In terms of antimicrobial activity, cephalosporins are not affected by betalactamases produced by *H. influenzae* and show low MIC_{90} values. Cefixime, cefpodoxime and ceftibuten showed the lowest values (0.125–0.25 mg/l), while the amoxicillin-clavulanic acid and cefuroxime were less active (1–2 mg/l). However, no resistant strains were observed with any antimicrobial agent except penicillin, amo-

xicillin and cefaclor, this drug showing only a small percentage (94.74% of susceptible strains). Azithromycin was at least as active as cefixime, cefpodoxime or ceftibuten, thus representing a possible alternative treatment in infections caused by this pathogen.

The betalactamase-negative and ampicillin-resistant strains require close observation to avoid a new emergence of resistance. The rate of this type of resistance, probably produced by altered PBPs (11, 18), seems to be low in Spain and in other countries (8). In our study the percentage could be only 1.66% (further identification is required, since ampicillin was not tested). This figure is very close to the 1.8% found in 1996 in Barcelona (1), and lower than the presumable 4.6% found in another multicenter study in 1996–1997 (17). All of our isolates maintained good susceptibility to cephalosporins (except cefaclor) and azithromycin.

With *S. pyogenes*, all the betalactam agents showed good activity, and no resistant strains were found to any of them. In terms of MIC values, penicillin and amoxicillin (with or without clavulanic acid) showed the lowest rates. Within the cephalosporins, cefpodoxime and cefuroxime were more active than the rest (cefixime, cefaclor or ceftibuten). This same situation is also observed in recent studies with this pathogen (8), where MIC_{90} values were only significantly higher for cefaclor (≤1 mg/l *versus* 2 mg/l in our study). Macrolides, however, showed a 20% resistance (intermediate and high resistance with azithromycin). Here our percentages of susceptible strains are higher than in other studies reporting rates of 72.9 to 76.5% (7, 8), though the former was *versus* erythromycin (which is a little less active than azithromycin).

Finally, *M. catarrhalis* in our study showed a susceptibility pattern very similar to that obtained in other studies (1, 16). Since the only currently known resistance mechanism shown by this pathogen is the production of betalactamase (almost 100% of isolates in Spain), the most active agents were azithromycin and amoxicillin-clavulanic acid. However, cefixime (and to a lesser extent cefpodoxime) retained acceptable activity against this microorganism, with MIC_{90} ≤2 mg/l.

In conclusion, the issues regarding respiratory pathogens and resistance to antimicrobial agents should be subjected to continuous surveillance. Concerning *S. pneumoniae* resistance to penicillin, the reports from 1996 to 2000 may reflect a stabilization of the rates of non-susceptible strains in Spain at around 30–40%, with obvious geographical variations. There also appears to be a stabilization in the rate of betalactamase-positive *H. influenzae* strains at about 20–30%, though betalactamase-negative and ampicillin-resistant rates should be carefully detected and monitored to identify any rapid increase. This same procedure may be necessary in the case of *S. pyogenes* and macrolide resistance, since the rates of non-susceptibility of this pathogen to agents like azithromycin could increase if parameters such as consumption continue to rise (8).

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