

# Antimicrobial Susceptibilities of *Corynebacterium* Species and Other Non-Spore-Forming Gram-Positive Bacilli to 18 Antimicrobial Agents

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**The susceptibilities of 265 strains of *Corynebacterium* species and other non-spore-forming gram-positive bacilli to 18 antimicrobial agents were tested. Most strains were susceptible to vancomycin, doxycycline, and fusidic acid. *Corynebacterium jeikeium* and *Corynebacterium urealyticum* were the most resistant organisms tested. Resistance to  $\beta$ -lactams, clindamycin, erythromycin, azithromycin, ciprofloxacin and gentamicin was common among strains of *Corynebacterium xerosis* and *Corynebacterium minutissimum*. Ampicillin resistance among *Listeria monocytogenes* was more prevalent than previously reported. Optochin, fosfomicin, and nitrofurantoin showed very little activity against most organisms tested, but the use of nitrofurantoin as a selective agent in culture medium may prevent the recovery of some isolates. Except for the unvarying activity of vancomycin against *Corynebacterium* species, the antimicrobial susceptibilities of the latter to other antibiotics are usually unpredictable, such that susceptibility tests are necessary for selecting the best antimicrobial treatment.**

During the last two decades a renewed interest in *Corynebacterium* species and other non-spore-forming gram-positive bacilli has emerged among clinicians and microbiologists alike (2, 8, 9, 32). Infections caused by these organisms are emerging, new species are being recognized (2, 9), and infections by toxigenic and nontoxigenic *Corynebacterium diphtheriae* strains are also being described with increasing frequency, indeed, in countries where diphtheria had been totally or almost eradicated (7, 26). However, this renewed interest has not been followed by an in-depth study to determine the antimicrobial susceptibilities of such organisms. Most available data come from scattered case reports, studies on a particular organism, or very old reports, sometimes published before 1960 (9).

The aim of the study described here was to determine the antimicrobial susceptibilities of a variety of organisms, most of which were isolated from clinical specimens, against 18 antimicrobial agents.

## MATERIALS AND METHODS

**Bacterial strains.** We tested 265 strains of *Corynebacterium* species and other non-spore-forming gram-positive bacilli obtained from the following different sources: clinical samples ( $n = 141$ ), skin ( $n = 25$ ), bacterial collections ( $n = 19$ ), and referrals to our laboratory from other institutions ( $n = 80$ ). Strains from clinical samples were isolated during the period from 1985 to 1993. All strains were identified by conventional methods (2) and also by using the API Coryne system (25), were stored frozen in 10% skim milk, and were maintained at  $-70^{\circ}\text{C}$  until use.

**Antimicrobial agents.** The following antibiotics were kindly provided by the manufacturers as powders for in vitro study: ampicillin and oxacillin (SmithKline Beecham Laboratories, Worthing, United Kingdom), cephalothin and vancomycin (Lilly, S.A., Madrid, Spain), cefuroxime (Glaxo Laboratories, Madrid, Spain), imipenem (Merck Sharp & Dohme, Madrid, Spain), tetracycline, doxycycline, and azithromycin (Pfizer S.A., Madrid, Spain), erythromycin (Abbott Laboratories, Madrid, Spain), clindamycin (Upjohn Co., Madrid, Spain), rifampin (Merrel Dow España, Madrid, Spain), fosfomicin (Cepa, Madrid, Spain), gentamicin (Antibióticos S.A., Madrid, Spain), and ciprofloxacin (Bayer AG, Barcelona, Spain). Optochin, fusidic acid, and nitrofurantoin were obtained from Sigma Chemical Co. (St. Louis, Mo.). Antimicrobial agents were dissolved and diluted

as indicated by the manufacturers or by following the recommendations of the National Committee for Clinical Laboratory Standards (15).

**Antimicrobial susceptibility testing.** The activities of the antimicrobial agents were determined by an agar dilution method (15) with Mueller-Hinton agar (Oxoid, Basingstoke, United Kingdom), which was supplemented with 5% sheep blood for some organisms. Inocula of approximately  $10^4$  CFU per spot were applied to the surfaces of plates, which were incubated for 24 to 48 h at  $35^{\circ}\text{C}$  in ambient air. *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* FJD-705 were used as controls. Breakpoints for susceptibility were as follows: erythromycin and clindamycin,  $\leq 0.5$   $\mu\text{g/ml}$ ; ciprofloxacin, nitrofurantoin, and rifampin,  $\leq 1$   $\mu\text{g/ml}$ ; ampicillin, oxacillin, fusidic acid, and azithromycin,  $\leq 2$   $\mu\text{g/ml}$ ; imipenem, vancomycin, gentamicin, tetracycline, and doxycycline,  $\leq 4$   $\mu\text{g/ml}$ ; cephalothin and cefuroxime,  $\leq 8$   $\mu\text{g/ml}$ ; and fosfomicin,  $\leq 32$   $\mu\text{g/ml}$ . No breakpoint for susceptibility to optochin was defined.

## RESULTS

The results of susceptibility studies are given in Table 1. Ampicillin, cephalothin, cefuroxime, and imipenem were active against many isolates. However, resistance to these  $\beta$ -lactam antibiotics was quite common among strains of *Corynebacterium jeikeium*, *Corynebacterium urealyticum*, and to a lesser extent, *Corynebacterium xerosis*, *Corynebacterium minutissimum*, *Corynebacterium striatum*, *Corynebacterium aquaticum*, *Rhodococcus* sp., and *Oerskovia* spp. Of interest were the different activities of cephalothin and cefuroxime against *Listeria monocytogenes*, which was more susceptible to cephalothin than to cefuroxime. Oxacillin had limited activity, although many strains of *Arcanobacterium hemolyticum*, *Actinomyces pyogenes*, *C. diphtheriae*-*Corynebacterium ulcerans*, *Corynebacterium pseudodiphtheriticum*, *Corynebacterium pseudotuberculosis*, *Corynebacterium renale* group, and *Erysipelothrix rhusiopathiae* were inhibited by 2  $\mu\text{g}$  of this antibiotic per ml. The activities of clindamycin, erythromycin, and azithromycin against the organisms tested varied. As a whole, clindamycin was less active than the macrolides, but resistance to erythromycin and azithromycin was very frequent among *C. jeikeium*, *C. urealyticum*, *C. xerosis*, *C. striatum*, and *Oerskovia* spp. Rifampin was active against most strains tested, although *E. rhusiopathiae* was resistant, as were many strains of *C. striatum* and several other species. Ciprofloxacin was active

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TABLE 1. MICs of 18 antimicrobial agents for *Corynebacterium* species and other non-spore-forming gram-positive bacilli<sup>a</sup>

| Organism<br>(no. of isolates)       | Antimicrobial<br>agent | MIC ( $\mu\text{g/ml}$ ) <sup>b</sup> |              |              |
|-------------------------------------|------------------------|---------------------------------------|--------------|--------------|
|                                     |                        | Range                                 | 50%          | 90%          |
| <i>C. jeikeium</i> (43)             | Ampicillin             | $\leq 0.015$ ->256                    | 256          | >256         |
|                                     | Oxacillin              | $\leq 0.015$ ->256                    | >256         | >256         |
|                                     | Cephalothin            | 0.060->256                            | >256         | >256         |
|                                     | Cefuroxime             | 0.060->256                            | >256         | >256         |
|                                     | Imipenem               | $\leq 0.003$ ->256                    | >256         | >256         |
|                                     | Tetracycline           | 0.5->256                              | 2            | 64           |
|                                     | Doxycycline            | 0.250-8                               | 1            | 4            |
|                                     | Erythromycin           | 0.030->256                            | >256         | >256         |
|                                     | Azithromycin           | 0.125->256                            | >256         | >256         |
|                                     | Clindamycin            | 0.125->256                            | >256         | >256         |
|                                     | Rifampin               | $\leq 0.003$ ->256                    | $\leq 0.003$ | 64           |
|                                     | Fusidic acid           | 0.5-32                                | 2            | 32           |
|                                     | Ciprofloxacin          | 0.030-128                             | 2            | 64           |
|                                     | Gentamicin             | 0.060->256                            | >256         | >256         |
|                                     | Vancomycin             | 0.250-0.5                             | 0.250        | 0.5          |
|                                     | Optochin               | 256->256                              | 256          | >256         |
|                                     | Fosfomycin             | >256                                  | >256         | >256         |
|                                     | Nitrofurantoin         | 4->256                                | 16           | 256          |
| <i>C. minutissimum</i> (20)         | Ampicillin             | 0.030-32                              | 0.250        | 32           |
|                                     | Oxacillin              | 0.250->256                            | 2            | >256         |
|                                     | Cephalothin            | 0.060-128                             | 0.250        | 128          |
|                                     | Cefuroxime             | 0.125-64                              | 2            | >256         |
|                                     | Imipenem               | $\leq 0.003$ -4                       | 0.030        | 4            |
|                                     | Tetracycline           | 0.125-64                              | 4            | 64           |
|                                     | Doxycycline            | 0.060-1                               | 0.250        | 1            |
|                                     | Erythromycin           | 0.030->256                            | 0.5          | >256         |
|                                     | Azithromycin           | 0.125->256                            | 0.5          | >256         |
|                                     | Clindamycin            | 0.250->256                            | 4            | >256         |
|                                     | Rifampin               | $\leq 0.003$ -256                     | $\leq 0.003$ | 256          |
|                                     | Fusidic acid           | $\leq 0.015$ -0.250                   | 0.030        | 0.060        |
|                                     | Ciprofloxacin          | 0.030-256                             | 0.060        | 16           |
|                                     | Gentamicin             | 0.030->256                            | 0.060        | >256         |
|                                     | Vancomycin             | 0.250-0.5                             | 0.250        | 0.5          |
|                                     | Optochin               | 1-256                                 | 128          | 256          |
|                                     | Fosfomycin             | >256                                  | >256         | >256         |
|                                     | Nitrofurantoin         | 0.5-256                               | 16           | 256          |
| <i>C. pseudodiphtheriticum</i> (12) | Ampicillin             | $\leq 0.015$ -0.250                   | 0.030        | 0.060        |
|                                     | Oxacillin              | $\leq 0.015$ -2                       | 0.250        | 0.5          |
|                                     | Cephalothin            | $\leq 0.015$ -0.125                   | $\leq 0.015$ | $\leq 0.015$ |
|                                     | Cefuroxime             | $\leq 0.015$ -1                       | 0.060        | 0.060        |
|                                     | Imipenem               | $\leq 0.003$ -0.120                   | $\leq 0.003$ | 0.015        |
|                                     | Tetracycline           | 1-2                                   | 1            | 2            |
|                                     | Doxycycline            | 0.250-0.5                             | 0.250        | 0.250        |
|                                     | Erythromycin           | $\leq 0.015$ -128                     | 0.030        | 128          |
|                                     | Azithromycin           | $\leq 0.015$ ->256                    | 0.125        | >256         |
|                                     | Clindamycin            | 0.030->256                            | 0.125        | >256         |
|                                     | Rifampin               | $\leq 0.003$                          | $\leq 0.003$ | $\leq 0.003$ |
|                                     | Fusidic acid           | $\leq 0.015$ -0.060                   | $\leq 0.015$ | 0.030        |
|                                     | Ciprofloxacin          | $\leq 0.015$ -0.5                     | 0.250        | 0.5          |
|                                     | Gentamicin             | 0.030-1                               | 0.060        | 0.125        |
|                                     | Vancomycin             | 0.250-1                               | 0.250        | 0.5          |
|                                     | Optochin               | 64-128                                | 128          | 128          |
|                                     | Fosfomycin             | 256->256                              | >256         | >256         |
|                                     | Nitrofurantoin         | 32-256                                | 128          | 256          |
| <i>C. striatum</i> (11)             | Ampicillin             | 0.250-2                               | 0.5          | 2            |
|                                     | Oxacillin              | 2-32                                  | 8            | 32           |
|                                     | Cephalothin            | 0.125-16                              | 0.250        | 2            |
|                                     | Cefuroxime             | $\leq 0.015$ -4                       | 1            | 4            |
|                                     | Imipenem               | $\leq 0.003$ -0.250                   | 0.030        | 0.125        |
|                                     | Tetracycline           | 0.5-64                                | 8            | 64           |
|                                     | Doxycycline            | 0.125-16                              | 0.5          | 2            |
|                                     | Erythromycin           | $\leq 0.015$ ->256                    | 8            | 256          |
|                                     | Azithromycin           | 0.060->256                            | 256          | >256         |
|                                     | Clindamycin            | 1->256                                | >256         | >256         |

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TABLE 1—Continued

| Organism<br>(no. of isolates) | Antimicrobial<br>agent | MIC ( $\mu\text{g/ml}$ ) <sup>b</sup> |              |       |
|-------------------------------|------------------------|---------------------------------------|--------------|-------|
|                               |                        | Range                                 | 50%          | 90%   |
|                               | Rifampin               | $\leq 0.003$ –>256                    | 2            | >256  |
|                               | Fusidic acid           | $\leq 0.015$ –0.5                     | 0.030        | 0.250 |
|                               | Ciprofloxacin          | 0.060–32                              | 0.250        | 16    |
|                               | Gentamicin             | 0.030–4                               | 2            | 2     |
|                               | Vancomycin             | 0.250–0.5                             | 0.250        | 0.5   |
|                               | Optochin               | 16–256                                | 128          | 128   |
|                               | Fosfomycin             | >256                                  | >256         | >256  |
|                               | Nitrofurantoin         | 16–256                                | 256          | 256   |
| <i>C. urealyticum</i> (63)    | Ampicillin             | 0.030–>256                            | >256         | >256  |
|                               | Oxacillin              | 0.125–>256                            | >256         | >256  |
|                               | Cephalothin            | 0.060–>256                            | 256          | >256  |
|                               | Cefuroxime             | 0.060–>256                            | 256          | >256  |
|                               | Imipenem               | $\leq 0.003$ –>256                    | >256         | >256  |
|                               | Tetracycline           | 0.250–256                             | 16           | 128   |
|                               | Doxycycline            | 0.125–32                              | 0.5          | 4     |
|                               | Erythromycin           | $\leq 0.015$ –>256                    | 16           | >256  |
|                               | Azithromycin           | 0.030–>256                            | 128          | >256  |
|                               | Clindamycin            | 0.030–>256                            | >256         | >256  |
|                               | Rifampin               | $\leq 0.003$ –>256                    | 0.015        | 4     |
|                               | Fusidic acid           | $\leq 0.015$ –2                       | 0.125        | 1     |
|                               | Ciprofloxacin          | 0.125–64                              | 1            | 32    |
|                               | Gentamicin             | 0.060–>256                            | >256         | >256  |
|                               | Vancomycin             | 0.125–0.5                             | 0.5          | 0.5   |
|                               | Optochin               | 64–>256                               | 128          | 256   |
|                               | Fosfomycin             | 128–>256                              | >256         | >256  |
|                               | Nitrofurantoin         | 0.250–>256                            | 256          | >256  |
| <i>C. xerosis</i> (20)        | Ampicillin             | $\leq 0.015$ –>256                    | 0.5          | 256   |
|                               | Oxacillin              | 0.5–>256                              | 8            | >256  |
|                               | Cephalothin            | $\leq 0.015$ –>256                    | 1            | 256   |
|                               | Cefuroxime             | 0.060–256                             | 0.5          | 256   |
|                               | Imipenem               | $\leq 0.015$ –64                      | 0.060        | 8     |
|                               | Tetracycline           | 0.030–8                               | 1            | 4     |
|                               | Doxycycline            | 0.030–1                               | 0.5          | 1     |
|                               | Erythromycin           | $\leq 0.015$ –>256                    | 256          | >256  |
|                               | Azithromycin           | $\leq 0.015$ –>256                    | >256         | >256  |
|                               | Clindamycin            | 0.125–>256                            | >256         | >256  |
|                               | Rifampin               | $\leq 0.003$ –32                      | $\leq 0.003$ | 4     |
|                               | Fusidic acid           | $\leq 0.015$ –0.250                   | 0.030        | 0.030 |
|                               | Ciprofloxacin          | 0.030–128                             | 4            | 128   |
|                               | Gentamicin             | $\leq 0.015$ –>256                    | 4            | >256  |
|                               | Vancomycin             | 0.250–2                               | 0.5          | 0.5   |
|                               | Optochin               | 8–>256                                | 64           | 128   |
|                               | Fosfomycin             | 256–>256                              | >256         | >256  |
|                               | Nitrofurantoin         | 0.030–256                             | 128          | 256   |
| CDC groups (31)               | Ampicillin             | $\leq 0.015$ –4                       | 0.250        | 2     |
|                               | Oxacillin              | 0.030–16                              | 2            | 16    |
|                               | Cephalothin            | $\leq 0.015$ –16                      | 0.125        | 1     |
|                               | Cefuroxime             | $\leq 0.015$ –4                       | 0.250        | 2     |
|                               | Imipenem               | $\leq 0.003$ –4                       | 0.030        | 1     |
|                               | Tetracycline           | 0.125–32                              | 1            | 16    |
|                               | Doxycycline            | $\leq 0.015$ –16                      | 0.125        | 4     |
|                               | Erythromycin           | $\leq 0.015$ –>256                    | 0.250        | 8     |
|                               | Azithromycin           | $\leq 0.015$ –>256                    | 0.5          | >256  |
|                               | Clindamycin            | 0.030–>256                            | 2            | >256  |
|                               | Rifampin               | $\leq 0.003$ –256                     | 0.007        | 0.060 |
|                               | Fusidic acid           | $\leq 0.015$ –4                       | 0.125        | 1     |
|                               | Ciprofloxacin          | 0.030–32                              | 0.125        | 1     |
|                               | Gentamicin             | $\leq 0.015$ –64                      | 0.060        | 2     |
|                               | Vancomycin             | 0.060–4                               | 0.250        | 1     |
|                               | Optochin               | 16–>256                               | 256          | >256  |
|                               | Fosfomycin             | 64–>256                               | >256         | >256  |
|                               | Nitrofurantoin         | 8–>256                                | 32           | 256   |

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TABLE 1—Continued

| Organism<br>(no. of isolates)                 | Antimicrobial<br>agent | MIC ( $\mu\text{g/ml}$ ) <sup>b</sup> |              |              |
|---|------------------------|---------------------------------------|--------------|--------------|
|   |                        | Range                                 | 50%          | 90%          |
| <i>Corynebacterium</i> spp. (20) <sup>c</sup> | Ampicillin             | $\leq 0.015-8$                        | 0.125        | 2            |
|   | Oxacillin              | $\leq 0.015-64$                       | 2            | 64           |
|   | Cephalothin            | $\leq 0.015-8$                        | 0.125        | 4            |
|   | Cefuroxime             | 0.030-8                               | 0.5          | 4            |
|   | Imipenem               | $\leq 0.015-4$                        | 0.030        | 1            |
|   | Tetracycline           | 0.060-4                               | 0.5          | 4            |
|   | Doxycycline            | 0.030-0.125                           | 0.060        | 0.125        |
|   | Erythromycin           | $\leq 0.015-0.06$                     | $\leq 0.015$ | 0.060        |
|   | Azithromycin           | $\leq 0.015-0.125$                    | 0.060        | 0.125        |
|   | Clindamycin            | $\leq 0.015-4$                        | 0.250        | 4            |
|   | Rifampin               | $\leq 0.003-0.015$                    | $\leq 0.003$ | 0.007        |
|   | Fusidic acid           | $\leq 0.015-1$                        | 0.030        | 1            |
|   | Ciprofloxacin          | 0.030-8                               | 0.060        | 1            |
|   | Gentamicin             | 0.060-2                               | 0.5          | 2            |
|   | Vancomycin             | 0.250-8                               | 0.5          | 4            |
|   | Optochin               | 32-256                                | 128          | 256          |
|   | Fosfomycin             | 64->256                               | >256         | >256         |
| Nitrofurantoin                                | 4->256                 | 64                                    | >256         |              |
| <i>A. hemolyticum-A. pyogenes</i> (12)        | Ampicillin             | 0.030-0.250                           | 0.060        | 0.250        |
|   | Oxacillin              | 0.125-1                               | 1            | 1            |
|   | Cephalothin            | $\leq 0.015-0.060$                    | $\leq 0.015$ | 0.060        |
|   | Cefuroxime             | $\leq 0.015-0.250$                    | 0.125        | 0.250        |
|   | Imipenem               | $\leq 0.007-0.030$                    | 0.015        | 0.030        |
|   | Tetracycline           | 0.125-2                               | 0.250        | 1            |
|   | Doxycycline            | 0.060-2                               | 0.125        | 1            |
|   | Erythromycin           | $\leq 0.015$                          | $\leq 0.015$ | $\leq 0.015$ |
|   | Azithromycin           | $\leq 0.015$                          | $\leq 0.015$ | $\leq 0.015$ |
|   | Clindamycin            | $\leq 0.015-0.030$                    | $\leq 0.015$ | 0.030        |
|   | Rifampin               | $\leq 0.003-0.007$                    | $\leq 0.003$ | 0.007        |
|   | Fusidic acid           | 0.060-0.5                             | 0.125        | 0.125        |
|   | Ciprofloxacin          | 0.125-0.5                             | 0.250        | 0.5          |
|   | Gentamicin             | 0.060-1                               | 0.5          | 1            |
|   | Vancomycin             | 0.250-0.5                             | 0.250        | 0.5          |
|   | Optochin               | 32-256                                | 256          | 256          |
|   | Fosfomycin             | 32-128                                | 128          | 128          |
| Nitrofurantoin                                | 1-64                   | 32                                    | 32           |              |
| <i>R. equi</i> (8)                            | Ampicillin             | 2-16                                  | 8            |              |
|   | Oxacillin              | 32-64                                 | 32           |              |
|   | Cephalothin            | 4->256                                | 64           |              |
|   | Cefuroxime             | 2->256                                | 4            |              |
|   | Imipenem               | 0.125-0.250                           | 0.250        |              |
|   | Tetracycline           | 4-16                                  | 8            |              |
|   | Doxycycline            | 0.250-0.5                             | 0.5          |              |
|   | Erythromycin           | 0.250-0.5                             | 0.5          |              |
|   | Azithromycin           | 1-2                                   | 2            |              |
|   | Clindamycin            | 2-8                                   | 4            |              |
|   | Rifampin               | 0.030-0.06                            | 0.030        |              |
|   | Fusidic acid           | 1-4                                   | 1            |              |
|   | Ciprofloxacin          | 0.5-1                                 | 0.5          |              |
|   | Gentamicin             | 0.125-1                               | 0.5          |              |
|   | Vancomycin             | 0.5                                   | 0.5          |              |
|   | Optochin               | 256                                   | 256          |              |
|   | Fosfomycin             | >256                                  | >256         |              |
| Nitrofurantoin                                | 64-128                 | 64                                    |              |              |
| <i>L. monocytogenes</i> (16)                  | Ampicillin             | 0.250-1                               | 0.5          | 1            |
|   | Oxacillin              | 4-8                                   | 8            | 8            |
|   | Cephalothin            | 2-8                                   | 4            | 8            |
|   | Cefuroxime             | 32-256                                | 128          | 256          |
|   | Imipenem               | 0.125-0.250                           | 0.125        | 0.250        |
|   | Tetracycline           | 0.5-4                                 | 2            | 4            |
|   | Doxycycline            | 0.060-0.125                           | 0.060        | 0.125        |
|   | Erythromycin           | 0.060-0.250                           | 0.250        | 0.250        |
|   | Azithromycin           | 0.5-1                                 | 1            | 1            |
|   | Clindamycin            | 2-4                                   | 2            | 4            |

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TABLE 1—Continued

| Organism<br>(no. of isolates) | Antimicrobial<br>agent      | MIC ( $\mu\text{g/ml}$ ) <sup>b</sup> |              |       |  |
|-------------------------------|-----------------------------|---------------------------------------|--------------|-------|--|
|                               |                             | Range                                 | 50%          | 90%   |  |
|                               | Rifampin                    | $\leq 0.003$ –0.125                   | $\leq 0.003$ | 0.125 |  |
|                               | Fusidic acid                | 8                                     | 8            | 8     |  |
|                               | Ciprofloxacin               | 0.5–8                                 | 1            | 1     |  |
|                               | Gentamicin                  | 0.125–1                               | 0.5          | 0.5   |  |
|                               | Vancomycin                  | 0.5–1                                 | 1            | 1     |  |
|                               | Optochin                    | 256–>256                              | >256         | >256  |  |
|                               | Fosfomycin                  | >256                                  | >256         | >256  |  |
|                               | Nitrofurantoin              | 8–32                                  | 16           | 32    |  |
|                               | <i>E. rhusiopathiae</i> (5) | Ampicillin                            | 0.125–0.250  | 0.250 |  |
|                               |                             | Oxacillin                             | 0.125–0.250  | 0.250 |  |
| Cephalothin                   |                             | 0.125–1                               | 1            |       |  |
| Cefuroxime                    |                             | 2–8                                   | 4            |       |  |
| Imipenem                      |                             | 0.006                                 | 0.006        |       |  |
| Tetracycline                  |                             | 0.5–1                                 | 1            |       |  |
| Doxycycline                   |                             | 0.125–0.250                           | 0.250        |       |  |
| Erythromycin                  |                             | 0.125                                 | 0.125        |       |  |
| Azithromycin                  |                             | 0.030–0.060                           | 0.060        |       |  |
| Clindamycin                   |                             | $\leq 0.015$ –0.060                   | 0.030        |       |  |
| Rifampin                      |                             | 64–256                                | 128          |       |  |
| Fusidic acid                  |                             | 0.125–0.250                           | 0.250        |       |  |
| Ciprofloxacin                 |                             | 0.030–0.060                           | 0.030        |       |  |
| Gentamicin                    |                             | 2–4                                   | 4            |       |  |
| Vancomycin                    |                             | 16–64                                 | 64           |       |  |
| Optochin                      |                             | 128–256                               | 256          |       |  |
| Fosfomycin                    | 16–64                       | 32                                    |              |       |  |
| Nitrofurantoin                | 4–8                         | 4                                     |              |       |  |
| <i>Oerskovia</i> spp. (4)     | Ampicillin                  | 8                                     | 8            |       |  |
|                               | Oxacillin                   | 64                                    | 64           |       |  |
|                               | Cephalothin                 | 4–8                                   | 4            |       |  |
|                               | Cefuroxime                  | 8                                     | 8            |       |  |
|                               | Imipenem                    | 1–2                                   | 1            |       |  |
|                               | Tetracycline                | 8                                     | 8            |       |  |
|                               | Doxycycline                 | 0.250                                 | 0.250        |       |  |
|                               | Erythromycin                | 1–2                                   | 1            |       |  |
|                               | Azithromycin                | 0.5                                   | 0.5          |       |  |
|                               | Clindamycin                 | 4                                     | 4            |       |  |
|                               | Rifampin                    | $\leq 0.003$ –2                       | $\leq 0.003$ |       |  |
|                               | Fusidic acid                | 1                                     | 1            |       |  |
|                               | Ciprofloxacin               | 1–8                                   | 8            |       |  |
|                               | Gentamicin                  | 1–4                                   | 2            |       |  |
|                               | Vancomycin                  | 0.125                                 | 0.125        |       |  |
|                               | Optochin                    | 64–256                                | 256          |       |  |
| Fosfomycin                    | >256                        | >256                                  |              |       |  |
| Nitrofurantoin                | 256                         | 256                                   |              |       |  |

<sup>a</sup> A total of 265 isolates were tested.

<sup>b</sup> 50% and 90%, MICs at which 50 and 90% of isolates are inhibited, respectively.

<sup>c</sup> *C. aquaticum* (n = 4), *C. diphtheriae* (n = 2), *C. ulcerans* (n = 6), *C. pseudotuberculosis* (n = 4), and *C. renale* group (n = 4).

against many isolates, but again, resistance was common among strains of *C. jeikeium*, *C. urealyticum*, *C. xerosis*, and *Oerskovia* spp. Tetracycline and especially doxycycline were very active against most strains tested, with all MICs at which 90% of isolates are inhibited being equal to or less than 4  $\mu\text{g/ml}$ . Only a few strains of *C. jeikeium*, *C. urealyticum*, and *C. striatum* and several strains from the CDC groups of coryneforms were resistant to doxycycline. Fusidic acid was also active against most organisms tested, with only a few strains of *C. jeikeium* and *L. monocytogenes* being resistant to this drug at concentrations greater than 4  $\mu\text{g/ml}$ . Gentamicin was active against most organisms except *C. jeikeium* and *C. urealyticum* and some strains of *C. xerosis* and *C. minutissimum*. Vancomycin was the most active antibiotic against these organisms, which, with the exception of *E. rhusiopathiae*, were all inhibited

by 4  $\mu\text{g}$  of vancomycin per ml. Finally, optochin, fosfomycin, and nitrofurantoin showed little activity against the organisms tested, although nitrofurantoin was active against a few strains of *C. xerosis*, *C. urealyticum*, *C. minutissimum*, *C. diphtheriae*-*C. ulcerans*, *C. jeikeium*, *E. rhusiopathiae*, and *A. hemolyticum*-*A. pyogenes*. Although any breakpoint for susceptibility to optochin was not defined, the MICs at which 50% of all strains are inhibited were  $\geq 64$   $\mu\text{g/ml}$ . Multiple antibiotic resistance was common not only in *C. jeikeium* and *C. urealyticum* but also in *C. xerosis* and *C. minutissimum*.

## DISCUSSION

The most active antibiotics against *Corynebacterium* species and other non-spore-forming gram-positive bacilli were vanco-

mycin, doxycycline, and fusidic acid. The resistance of *E. rhusiopathiae* to vancomycin is an important point to consider, since vancomycin is frequently recommended as empiric therapy for serious gram-positive infections (6), with it being practically the only organism resistant to this antibiotic. Resistance to vancomycin has been recently reported in *C. aquaticum* and CDC group B1 (30). A few strains of *C. jeikeium*, *C. urealyticum*, *C. striatum*, and CDC groups of coryneforms were also resistant to doxycycline, which was more active than tetracycline. For only *L. monocytogenes* and a few strains of *C. jeikeium* were the MICs of fusidic acid equal to or greater than 8 µg/ml, but all other organisms were inhibited by 2 µg of fusidic acid per ml.

All β-lactam antibiotics except oxacillin were active against many organisms, although many strains of *C. jeikeium* and *C. urealyticum* were highly resistant to these drugs, as has been reported previously (3, 5, 19, 23). *C. striatum*, *Rhodococcus equi*, and *Oerskovia* spp. were not susceptible or were only marginally susceptible to several β-lactam antibiotics, and of particular concern is the increasing number of *C. xerosis*, *C. minutissimum*, and *C. striatum* isolates resistant to β-lactam antibiotics. These organisms had been considered susceptible to penicillins, but our results and other scattered reports (10, 13, 17, 18, 20, 27, 28, 31) suggest that penicillin-resistant strains are appearing. The dissociated susceptibility of *L. monocytogenes* to cephalothin and cefuroxime has been described previously, and this organism is also resistant to ceftazidime (11). Our results show an increase in the MICs of ampicillin for *L. monocytogenes* in comparison with those given in other reports (21). Although the inoculum size and the media used to determine antimicrobial susceptibility in *L. monocytogenes* seem to affect the results (11), a careful follow-up of the susceptibilities over time should be carried out.

Lincosamides and macrolides had been considered good therapeutic alternatives, but numerous resistant strains have now appeared among many organisms. Nevertheless, macrolide antibiotics (erythromycin and azithromycin) were more active than clindamycin against most strains tested. Several scattered reports have shown resistance to these antibiotics in *C. pseudodiphtheriticum* (1, 12), *C. xerosis* (9, 10, 31), *C. striatum* (18, 22, 28), *C. minutissimum* (27), and *A. pyogenes* (4). Rifampin was also very active against most organisms tested except *E. rhusiopathiae* and *C. striatum*. A case of recurrent pneumonia caused by a rifampin-resistant *Rhodococcus equi* strain in a patient infected with human immunodeficiency virus has been described (16). Ciprofloxacin was very active against many isolates, but again, resistant strains appeared in several species, mainly *C. jeikeium*, *C. urealyticum*, *C. xerosis*, *C. minutissimum*, and *C. striatum*, suggesting that resistance to this drug is apparently increasing (10, 18, 28).

Gentamicin was very active against most isolates, although resistance was quite common mainly in *C. jeikeium*, *C. urealyticum*, *C. xerosis*, and *C. minutissimum*, as has been reported previously (3, 9, 10, 19, 23, 27). Aminoglycoside antibiotics are probably not the drugs of choice for the treatment of most infections caused by these organisms but could be useful in combination with other antibiotics, particularly β-lactams, for some severe infections such as endocarditis (14).

Optochin, fosfomicin, and nitrofurantoin showed little activity against most isolates. Fosfomicin and the nitrofurans have been proposed as selective agents in some selective media that can be used to isolate corynebacteria (24, 29). Nevertheless, we must take into account the fact that some strains of *C. xerosis*, *C. urealyticum*, *C. minutissimum*, *C. diphtheriae*-*C. ulcerans*, *E. rhusiopathiae*, and *A. hemolyticum*-*A. pyogenes* may be inhibited by low concentrations of nitrofurantoin.

The organisms included in the present study may be mainly involved in cases of bacteremia, endocarditis, meningitis, and respiratory, skin, soft tissue, and urinary tract infections. In the early 1980s, because of the limited information available on the susceptibilities of corynebacteria to antimicrobial agents, erythromycin was suggested as the drug of choice for therapy of disease caused by all species of corynebacteria except *C. jeikeium* (9). We agree with a previous report recommending that vancomycin be used to treat serious infections caused by corynebacteria until susceptibility testing has been performed (31). *C. jeikeium*, *C. urealyticum*, *C. xerosis*, and *C. minutissimum* are, among the true *Corynebacterium* species, those having multiple antibiotic resistances. The antimicrobial susceptibilities of many of the organisms tested are therefore not always predictable; resistance to many antibiotics is increasing, and so determination of their susceptibilities may be necessary in order to obtain the best therapeutic results. The ultimate therapeutic regimen must be chosen according to the in vitro results, the location of the infection, and previous clinical experience. Our results may be of utility when prescribing antibiotics in cases in which any of the organisms tested in the present study are involved in clinical infections.

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