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Erythromycin, Clarithromycin, and Azithromycin: Use of Frequency Distribution Curves, Scattergrams, and Regression Analyses To Compare In Vitro Activities and Describe Cross-Resistance

ROBERT J. FASS

Division of Infectious Diseases, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, Ohio 43210

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MICs of erythromycin, clarithromycin, and azithromycin for 852 recent clinical isolates were determined by broth microdilution methods. Frequency distribution curves, scattergrams, and regression analyses were used to compare in vitro activities and describe cross-resistance. Clarithromycin was the most active drug against *Bacteroides* spp. but the least active against *Haemophilus influenzae*. Azithromycin was most active against *H. influenzae*, *Moraxella catarrhalis*, *Pasteurella multocida*, and *Fusobacterium* spp. but the least active against *Streptococcus* spp. and *Enterococcus* spp. All three drugs had equivalent activities against *Staphylococcus* spp. and gram-positive anaerobes. None of the three drugs was particularly active against members of the family *Enterobacteriaceae* or nonfermentative gram-negative bacilli, although concentrations of 4 μg of azithromycin per ml inhibited some strains of the family *Enterobacteriaceae* (particularly *Escherichia coli* and *Citrobacter diversus*) and *Acinetobacter baumannii*. Although relative drug activities varied by organism, organisms relatively susceptible to one were relatively susceptible to all and organisms relatively resistant to one were relatively resistant to all; an exception was fusobacteria, which were usually susceptible only to azithromycin. Cross-susceptibility and cross-resistance were, therefore, the rule (except for *Fusobacterium* spp.), although the percentage of susceptible organisms could be varied considerably on the basis of the selection of breakpoints.

Erythromycin has been a popular drug for the treatment of respiratory and skin or soft tissue infections. However, gastrointestinal intolerance has been common, its efficacy in treating infections caused by *Haemophilus influenzae* and anaerobes has been uncertain, and the emergence of staphylococcal resistance has been problematic. Gastrointestinal tolerance of clarithromycin (a new macrolide) and azithromycin (a new azalide) is improved, and both of these drugs have favorable pharmacokinetic profiles, with high achievable concentrations in tissue and desirable spectra of in vitro activity (5, 6).

In the present study, the MICs of erythromycin, clarithromycin, and azithromycin for 852 recent clinical isolates were determined. Frequency distribution curves, scattergrams,

TABLE 1. In vitro activities of erythromycin, clarithromycin, and azithromycin against gram-negative organisms, excluding members of the family *Enterobacteriaceae* and nonfermenters

Organism (no. of strains)	Drug	MIC (μg/ml)[a]			Cum % S at drug concn (μg/ml) of[b]:		
		Range	50%	90%	0.5	2	4
Haemophilus influenzae AS[c] (20)	Erythromycin	2–4	2	4	0	70	100
	Clarithromycin	2–16	4	8	0	5	75
	Azithromycin	0.5–2	1	1	10	100	100
Haemophilus influenzae AR[d] (25)	Erythromycin	0.5–4	2	4	4	84	100
	Clarithromycin	1–8	4	8	0	16	84
	Azithromycin	0.25–2	1	1	44	100	100
Moraxella catarrhalis (22)	Erythromycin	0.03–0.5	0.12	0.25	100	100	100
	Clarithromycin	0.03–0.25	0.12	0.25	100	100	100
	Azithromycin	0.03–0.06	0.06	0.06	100	100	100
Pasteurella multocida (21)	Erythromycin	0.5–8	2	4	5	76	90
	Clarithromycin	0.5–8	2	4	5	67	90
	Azithromycin	0.25–2	1	2	33	100	100

[a] 50% and 90%, MICs required to inhibit 50 and 90% of the isolates, respectively.
[b] Cum % S, cumulative percent susceptible; 98 and 100% of *H. influenzae* strains were susceptible to 8 and 16 μg of clarithromycin per ml, respectively, which are the breakpoints of the National Committee for Clinical Laboratory Standards for defining susceptible and intermediate.
[c] AS, ampicillin susceptible.
[d] AR, ampicillin resistant.

TABLE 2. In vitro activities of erythromycin, clarithromycin, and azithromycin against gram-positive organisms

Organism (no. of strains)	Drug	MIC (μg/ml)[a]			Cum % S at drug concn (μg/ml) of[b]:		
		Range	50%	90%	0.5	2	4
Staphylococcus aureus MS[c] (21)	Erythromycin	0.12–0.25	0.25	0.25	100	100	100
	Clarithromycin	0.12–0.25	0.25	0.25	100	100	100
	Azithromycin	0.25	0.25	0.25	100	100	100
Staphylococcus aureus MR[d] (20)	Erythromycin	0.25–>8	>8	>8	5	5	5
	Clarithromycin	0.25–>32	>32	>32	5	5	5
	Azithromycin	0.25–>32	32	>32	5	5	5
Staphylococcus epidermidis MS (20)	Erythromycin	0.12–>8	0.25	>8	70	70	70
	Clarithromycin	0.12–>32	0.12	>32	70	70	70
	Azithromycin	0.12–>32	0.12	>32	70	70	70
Staphylococcus epidermidis MR (21)	Erythromycin	0.12–>8	>8	>8	29	29	29
	Clarithromycin	0.06–>32	>32	>32	29	29	29
	Azithromycin	0.12–>32	>32	>32	29	29	29
Staphylococcus haemolyticus MS (20)	Erythromycin	0.12–>8	0.25	>8	80	80	80
	Clarithromycin	0.06–>32	0.12	32	80	80	80
	Azithromycin	0.12–>32	0.25	>32	80	80	80
Staphylococcus haemolyticus MR (20)	Erythromycin	0.25–>8	>8	>8	10	10	10
	Clarithromycin	0.25–>32	>32	>32	10	10	10
	Azithromycin	0.25–>32	>32	>32	10	10	10
Staphylococcus hominis MS (10)	Erythromycin	0.06–>8	0.25	>8	70	70	70
	Clarithromycin	0.06–>32	0.12	>32	70	70	70
	Azithromycin	0.06–>32	0.12	>32	70	70	70
Staphylococcus hominis MR (10)	Erythromycin	0.12–>8	>8	>8	30	30	30
	Clarithromycin	0.12–>32	>32	>32	30	30	30
	Azithromycin	0.12–>32	>32	>32	30	30	30
Staphylococcus saprophyticus (12)	Erythromycin	0.25–>8	0.5	0.5	92	92	92
	Clarithromycin	0.25–>32	0.5	0.5	92	92	92
	Azithromycin	0.25–>32	0.5	1	83	92	92
Streptococcus pyogenes (20)	Erythromycin	0.12–0.25	0.25	0.25	100	100	100
	Clarithromycin	0.12–0.25	0.25	0.25	100	100	100
	Azithromycin	0.25–1	0.5	1	65	100	100
Streptococcus pneumoniae (20)	Erythromycin	0.06–0.25	0.12	0.25	100	100	100
	Clarithromycin	0.06–0.25	0.12	0.25	100	100	100
	Azithromycin	0.25–0.5	0.25	0.5	100	100	100
Streptococcus agalactiae (18)	Erythromycin	0.03–0.12	0.06	0.12	100	100	100
	Clarithromycin	0.03–0.06	0.06	0.06	100	100	100
	Azithromycin	0.06–0.12	0.12	0.12	100	100	100
Streptococcus bovis (20)	Erythromycin	≤0.015–>8	0.03	1	85	95	95
	Clarithromycin	≤0.015–>32	0.03	0.5	95	95	95
	Azithromycin	0.03–>32	0.06	1	85	95	95
Viridans group streptococci (16)	Erythromycin	0.12–2	0.12	1	81	100	100
	Clarithromycin	0.12–2	0.12	0.5	88	100	100
	Azithromycin	0.25–4	0.25	2	75	94	100
Enterococcus faecalis (20)	Erythromycin	0.25–>8	1	>8	20	65	65
	Clarithromycin	0.25–>32	1	>32	25	65	65
	Azithromycin	0.25–>32	2	>32	15	60	65
Enterococcus faecium (19)	Erythromycin	0.06–>8	>8	>8	5	21	42
	Clarithromycin	0.06–>32	32	>32	5	16	37
	Azithromycin	0.06–>32	>32	32	5	5	21
Enterococcus avium (15)	Erythromycin	0.12–>8	0.5	>8	53	53	53
	Clarithromycin	0.12–>32	0.12	>32	53	53	53
	Azithromycin	0.25–>32	0.5	>32	53	53	53
Enterococcus durans (15)	Erythromycin	0.25–>8	4	>8	13	33	60
	Clarithromycin	0.25–>32	4	>32	13	40	60
	Azithromycin	0.25–>32	8	>32	13	13	27

[a] 50% and 90%, MICs required to inhibit 50 and 90% of the isolates, respectively.
[b] Cum % S, cumulative percent susceptible.
[c] MS, methicillin susceptible.
[d] MR, methicillin resistant.

TABLE 3. In vitro activities of erythromycin, clarithromycin, and azithromycin against anaerobic organisms

Organism (no. of strains)	Drug	MIC (μg/ml)[a]			Cum % S at drug concn (μg/ml) of[b]:		
		Range	50%	90%	0.5	2	4
Bacteroides fragilis (15)	Erythromycin	0.5–>8	8	>8	7	13	40
	Clarithromycin	0.25–>32	1	4	20	87	93
	Azithromycin	0.5–>32	8	16	0	7	20
Bacteroides thetaiotaomicron (15)	Erythromycin	1–>8	4	8	0	20	73
	Clarithromycin	0.25–>32	1	4	27	87	93
	Azithromycin	0.5–>32	8	16	7	20	33
Prevotella melaninogenicus (15)	Erythromycin	≤0.015–8	0.5	4	60	73	93
	Clarithromycin	≤0.015–4	0.12	1	73	93	100
	Azithromycin	≤0.015–16	0.25	8	73	73	80
Peptostreptococcus spp. (20)	Erythromycin	0.12–>8	2	>8	20	50	85
	Clarithromycin	0.06–>32	2	>32	25	80	85
	Azithromycin	0.5–>32	2	>32	25	75	85
Clostridium perfringens (15)	Erythromycin	1–>8	4	4	0	40	93
	Clarithromycin	0.5–>32	2	4	13	87	93
	Azithromycin	0.5–>32	2	4	7	80	93
Fusobacterium spp.[c] (15)	Erythromycin	0.5–>8	>8	>8	7	33	40
	Clarithromycin	0.25–>32	16	>32	7	47	47
	Azithromycin	0.03–16	0.25	16	67	67	73

[a] 50% and 90%, MICs required to inhibit 50 and 90% of the isolates, respectively.
[b] Cum % S, cumulative percent susceptible.
[c] Three strains each of *F. nucleatum*, *F. necropherum*, *F. naviforme*, and *F. mortiferum*; two strains of *F. gonidiaformans*; one strain of *F. varium*.

and regression analyses were used to compare in vitro activities and describe cross-resistance.

MATERIALS AND METHODS

Organisms. The organisms studied included 852 bacterial strains arbitrarily selected from recent isolates at the Ohio State University Hospitals. Duplicate isolates from the same patients were excluded.

Antimicrobial agents. Erythromycin was obtained from Eli Lilly & Co., Indianapolis, Ind., clarithromycin was obtained from Abbott Laboratories, Abbott Park, Ill., and azithromycin was obtained from Pfizer Inc., Groton, Conn.

Laboratory standards were diluted in accordance with the manufacturers' recommendations and were dispensed into microdilution plates by using an MIC-2000 dispensing machine (Dynatech Laboratories, Inc., Chantilly, Va.) in $\log_2$ dilution steps from 0.015 to 8 μg/ml for erythromycin and 0.015 to 32 μg/ml for clarithromycin and azithromycin. Plates were stored at −70°C until they were used.

Susceptibility tests. MICs for nonfastidious organisms and *H. influenzae* were determined by a standardized microdilution method (9) in 0.1-ml volumes of cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) or Haemophilus Test Medium, respectively. For *Streptococcus pyogenes*, *Streptococcus pneumoniae*, viridans group streptococci, and anaerobes, methods similar to those described above were used, but with Schaedler broth (Difco) supplemented with 1% heat-inactivated horse serum and 0.5 μg of vitamin K_1 per ml. Microdilution plates were inoculated with disposable inoculators (Dynatech) so that the final inoculum was approximately 5×10^5 CFU/ml. For streptococci, incubation was in room air for approximately 20 h, and for anaerobes, incubation was in 85% N_2–10% H_2–5% CO_2 for approximately 40 h. Recommended control strains (9) were used.

The breakpoints recommended by the National Committee for Clinical Laboratory Standards (10) for defining susceptible, intermediate, and resistant strains were ≤0.5, 1 to 4, and ≥8 μg/ml, respectively, for erythromycin and ≤2, 4, and ≥8 μg/ml, respectively, for clarithromycin and azithromycin. For *H. influenzae*, the National Committee for Clinical Laboratory Standards provides no recommended breakpoints for erythromycin, states that all strains are inhibited by ≤4 μg of azithromycin per ml and are considered to be susceptible, and recommends respective breakpoints of ≤8, 16, and ≥32 μg/ml for clarithromycin. The higher clarithromycin breakpoints are based on the observation that 14-hydroxy-clarithromycin, its major metabolite, enhances the activity of the parent compound against *H. influenzae* (4). There are no generally accepted recommendations for testing the susceptibilities of anaerobes to these drugs.

Frequency distribution curves, scattergrams, and regression analyses. MICs were entered into a Macintosh IIci computer by using FileMaker Pro software. The MICs were converted to $\log_2$ values, grouped, and then exported for subsequent analysis. To describe the relationships of the activities of individual study drugs against individual species or groups of organisms, frequency distribution curves of MICs and scattergrams comparing MICs for all possible drug pairs were plotted with CricketGraph III. For regression analyses, lines of best fit were calculated by using the organisms that had on-scale values (0.03 to 8 μg/ml for all three drugs). r^2, the coefficient of determination, indicated the proportion of the total variance in y which could be explained by the variance in x. For example, if $r^2 = 0.85$,

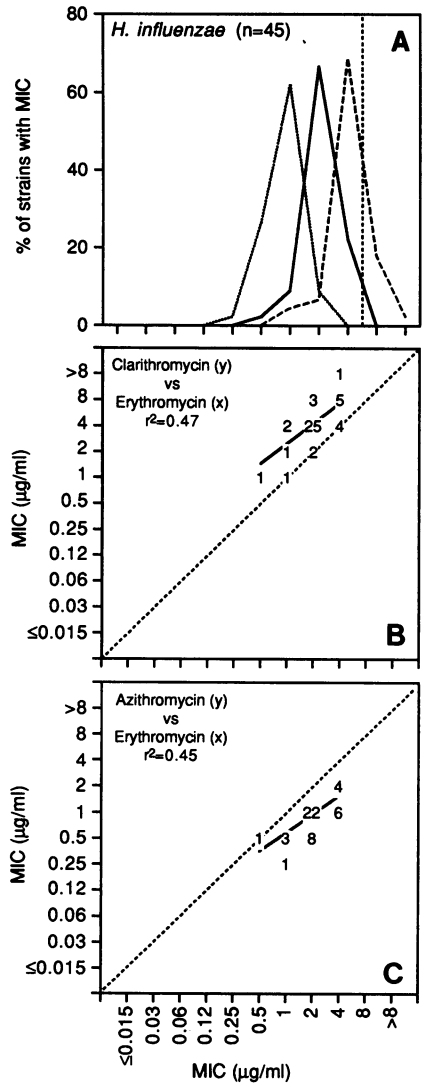

FIG. 1. (A) MIC frequency distribution curves for *H. influenzae*: erythromycin (——), clarithromycin (– – –), and azithromycin (.....). Dashed vertical line separates organisms for which MICs were ≥8 μg/ml from those for which MICs were ≤4 μg/ml. (B and C) Scattergrams comparing clarithromycin-erythromycin and azithromycin-erythromycin, respectively; azithromycin-clarithromycin was similar to azithromycin-erythromycin and is not shown. Each number represents the number of strains for which the specific MICs were as indicated. Dashed diagonal lines indicate lines of identity. Solid diagonal lines indicate lines of best fit calculated by using on-scale values (0.03 to 8 μg/ml for all three drugs). r^2 represents the coefficient of determination.

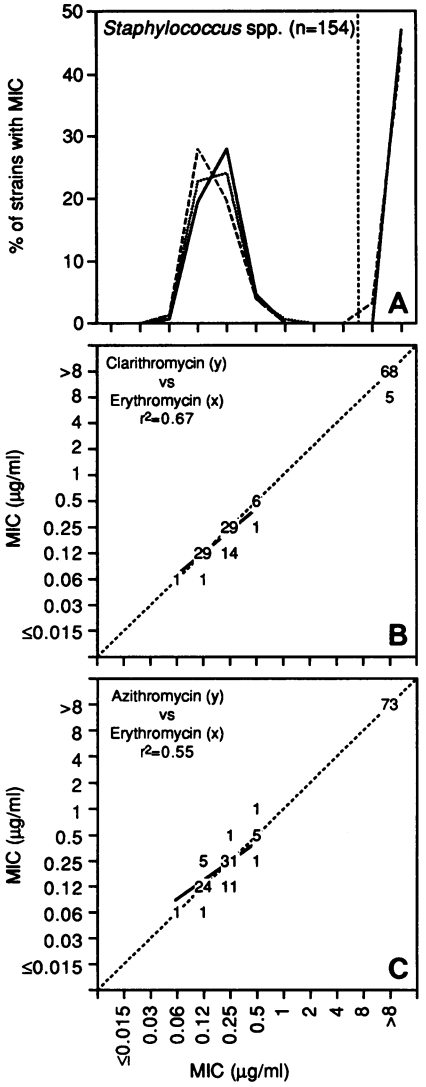

FIG. 2. (A) MIC frequency distribution curves for *Staphylococcus* spp.: erythromycin (——), clarithromycin (– – –), and azithromycin (.....). Dashed vertical line separates organisms for which MICs were ≥8 μg/ml from those for which MICs were ≤4 μg/ml. (B and C) Scattergrams comparing clarithromycin-erythromycin and azithromycin-erythromycin; azithromycin-clarithromycin was similar to azithromycin-erythromycin and is not shown. Each number represents the number of strains for which the specific MICs were as indicated. Dashed diagonal lines indicate lines of identity. Solid diagonal lines indicate lines of best fit calculated by using on-scale values (0.03 to 8 μg/ml for all three drugs). r^2 represents the coefficient of determination.

85% of the total variance in the MIC of drug *y* would be determined by the MIC of drug *x*.

RESULTS

The MICs of erythromycin, clarithromycin, and azithromycin for 500 of the isolates tested are shown in traditional format in Tables 1 to 3 (data for members of the family *Enterobacteriaceae* and nonfermentative gram-negative bacilli are excluded). None of the three drugs was particularly active against members of the family *Enterobacteriaceae* (*n* = 262), *Pseudomonas aeruginosa* (*n* = 50), *Xanthomonas maltophilia* (*n* = 20), or *Acinetobacter baumannii* (*n* = 20), although concentrations of 4 μg of azithromycin per ml inhibited some strains of *Enterobacteriaceae* (particularly *Escherichia coli* and *Citrobacter diversus*) and *A. baumannii* (data not shown).

MIC frequency distribution curves and scattergrams comparing the MICs of the study drugs for representative organisms including *H. influenzae*, *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., *Bacteroides* spp., and *Fusobacterium* spp. are shown in Fig. 1 to 6, respectively.

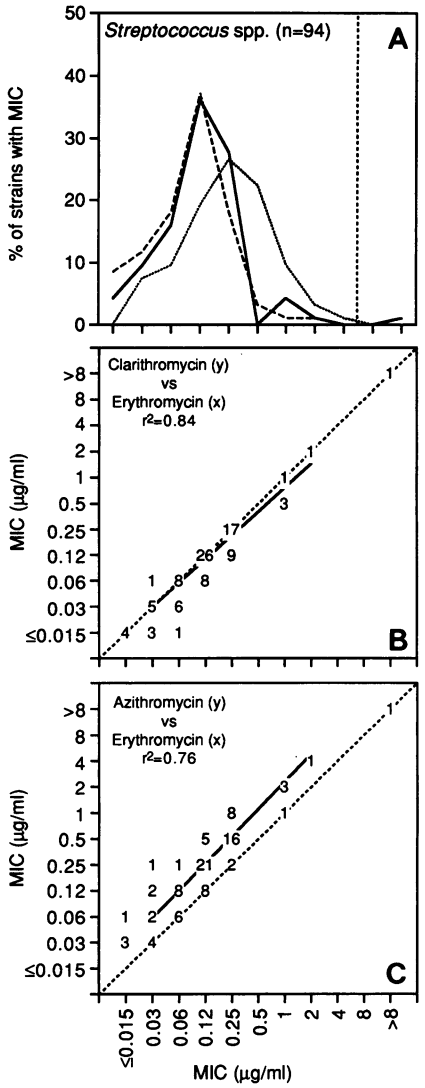

FIG. 3. (A) MIC frequency distribution curves for *Streptococcus* spp.: erythromycin (——), clarithromycin (– – –), and azithromycin (.....). Dashed vertical lines separate organisms for which MICs were ≥8 μg/ml from those for which MICs were ≤4 μg/ml. (B and C) Scattergrams comparing clarithromycin-erythromycin and azithromycin-erythromycin, respectively; azithromycin-clarithromycin was similar to azithromycin-erythromycin and is not shown. Each number represents the number of strains for which the specific MICs were as indicated. Dashed diagonal lines indicate lines of identity. Solid diagonal lines indicate lines of best fit calculated by using on-scale values (0.03 to 8 μg/ml for all three drugs). r^2 represents the coefficient of determination.

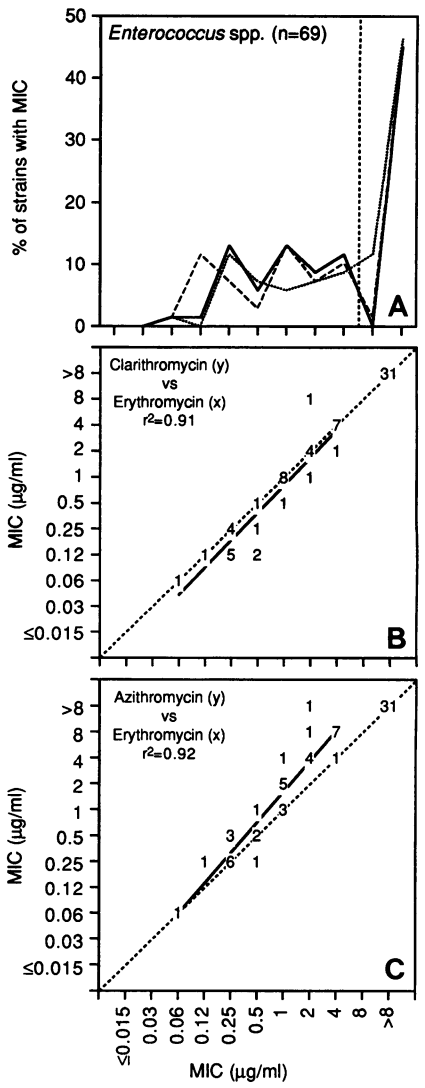

FIG. 4. (A) MIC frequency distribution curves for *Enterococcus* spp.: erythromycin (——), clarithromycin (– – –), and azithromycin (.....). Dashed vertical lines separate organisms for which MICs were ≥8 μg/ml from those for which MICs were ≤4 μg/ml. (B and C) Scattergrams comparing clarithromycin-erythromycin and azithromycin-erythromycin, respectively; azithromycin-clarithromycin was similar to azithromycin-erythromycin and is not shown. Each number represents the number of strains for which the specific MICs were as indicated. Dashed diagonal lines indicate lines of identity. Solid diagonal lines indicate lines of best fit calculated by using on-scale values (0.03 to 8 μg/ml for all three drugs). r^2 represents the coefficient of determination.

DISCUSSION

In the present study, the in vitro activities of erythromycin, clarithromycin, and azithromycin were similar to those observed in previous studies (1–4, 11, 13). In general, clarithromycin was the most active drug against *Bacteroides* spp. but the least active against *H. influenzae*. Azithromycin was the most active against *H. influenzae*, *Moraxella catarrhalis*, *Pasteurella multocida*, and *Fusobacterium* spp. but the least active against *Streptococcus* spp. and *Enterococcus* spp. All three drugs had equivalent activities against *Staphylococcus* spp. and gram-positive anaerobes. None of the three drugs was particularly active against members of the family *Enterobacteriaceae* or nonfermentative gram-negative bacilli; the potentially useful activity of azithromycin against some of these organisms was presumably due to its better penetration of outer membranes (12).

Although the relative activities of the three drugs varied by organism, organisms relatively susceptible to one were relatively susceptible to all, and organisms relatively resistant to one were relatively resistant to all; the exception was fusobacteria, which were usually susceptible only to azithromycin. Cross-susceptibility and cross-resistance were,

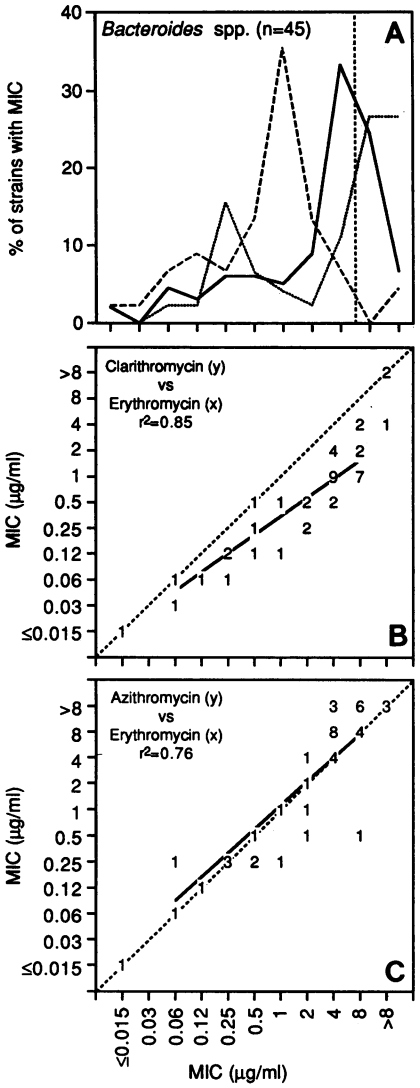

FIG. 5. (A) MIC frequency distribution curves for *Bacteroides* spp.: erythromycin (——), clarithromycin (– – –), and azithromycin (.....). Dashed vertical line separates organisms for which MICs were ≥8 μg/ml from those for which MICs were ≤4 μg/ml. (B and C) Scattergrams comparing clarithromycin-erythromycin and azithromycin-erythromycin, respectively; azithromycin-clarithromycin was similar to azithromycin-erythromycin and is not shown. Each number represents the number of strains for which the specific MICs were as indicated. Dashed diagonal lines indicate lines of identity. Solid diagonal lines indicate lines of best fit calculated by using on-scale values (0.03 to 8 μg/ml for all three drugs). r^2 represents the coefficient of determination.

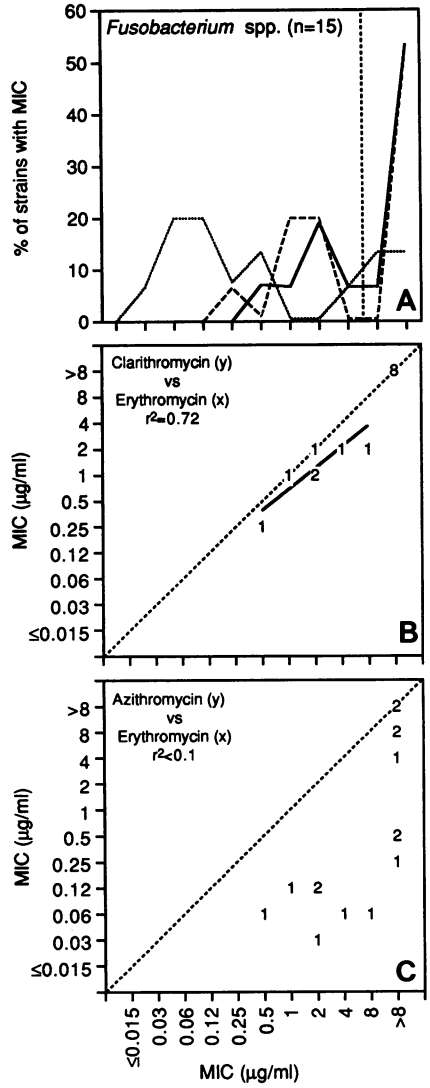

FIG. 6. (A) MIC frequency distribution curves for *Fusobacterium* spp.: erythromycin (——), clarithromycin (– – –), and azithromycin (.....). Dashed vertical line separates organisms for which MICs were ≥8 μg/ml from those for which MICs were ≤4 μg/ml. (B and C) Scattergrams comparing clarithromycin-erythromycin and azithromycin-erythromycin, respectively; azithromycin-clarithromycin was similar to azithromycin-erythromycin and is not shown. Each number represents the number of strains for which the specific MICs were as indicated. Dashed diagonal lines indicate lines of identity. Solid diagonal lines indicate lines of best fit calculated by using on-scale values (0.03 to 8 μg/ml for all three drugs). r^2 represents the coefficient of determination.

therefore, the rule (except for *Fusobacterium* spp.), although the percentage of susceptible organisms could be varied considerably on the basis of the selection of breakpoints.

The mechanisms of resistance to the macrolides and azalides have been well studied (7, 8, 12) and are similar for the three derivatives studied. Evidence that differences in in vitro activity, pharmacokinetics, or achievable concentrations in tissue translate into differences in clinical efficacy is lacking, and differences in therapeutic efficacy will need confirmation by further clinical trials (5).

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