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Evaluation of the In Vitro Activity of Levofloxacin and Moxifloxacin Tested Against *Stenotrophomonas maltophilia*: Can Moxifloxacin Activity Be Predicted by Levofloxacin MIC Results?

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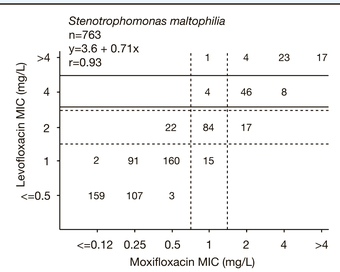
ABSTRACT

Objective: To evaluate the in vitro activity of levofloxacin (LEV) and moxifloxacin (MXF) tested against *S. maltophilia* and the correlation between MIC values for these fluoroquinolones (FQ) compounds in order to assess if LEV susceptible (S) strains could be categorized as MXF-S.
Methods: A total of 763 unique *S. maltophilia* strains collected worldwide through the SENTRY Antimicrobial Surveillance Program (2002-2005) were tested for S against LEV, MXF and selected antimicrobials by broth microdilution methods according to CLSI guidelines. MIC results were interpreted according to CLSI and EUCAST breakpoints. CLSI has LEV breakpoints of (S/resistant [R] in mg/L) <=2/>=8 for *S. maltophilia* and other Gram-negative bacilli (GNB) and no MXF breakpoints except for Gram-positive pathogens; while EUCAST has GNB breakpoints for LEV (<=1/>= 4 for Enterobacteriaceae [ENT], *Acinetobacter* and *P. aeruginosa*) and MXF (<=0.5/>=2 for ENT only).
Results: LEV showed good in vitro activity against *S. maltophilia* (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) with 85.8% S at the CLSI breakpoint, but only 70.3% if EUCAST breakpoints were applied. Scattergram with the correlation between the MXF and LEV MIC results is shown in the comparison Figure. By applying the CLSI LEV breakpoints (<=2/>=8 mg/L) and MXF breakpoints at <=1/>=4 mg/L, the overall categorical agreement was 95.5% with only 0.1% very major (VM; false-S), no major (MA; false-R) and 4.3% minor (MI) errors. Using EUCAST ENT breakpoints (LEV includes *P. aeruginosa* and *Acinetobacter* spp.), the overall agreement was 93.3% with no VM or MA error and 7.7% MI error. S rates for ciprofloxacin were 29.5 and 10.0% when GBN S breakpoints of CLSI and EUCAST were applied, respectively.
Conclusions: The spectrum of LEV against *S. maltophilia* decreases significantly if EUCAST breakpoints are used in preference to CLSI breakpoints. There was an excellent correlation (r=0.93) between LEV and MXF MIC results and categorical results for LEV may be used to predict categorical results for MXF if breakpoints were one doubling dilution lower than that of LEV. However, clinical studies may be necessary to establish the role of these FQs in the treatment of *S. maltophilia* infections, but achieving a critical number of case studies would be difficult.

Figure. Scattergram showing the correlation between levofloxacin and moxifloxacin MIC results determined by broth microdilution method when testing 763 *S. maltophilia* isolates.



INTRODUCTION

Treatment of *Stenotrophomonas maltophilia* infections still represents a significant challenge for clinicians and microbiologists because of high level of intrinsic antimicrobial resistance, methodological difficulties in susceptibility testing, and the paucity of clinical trials to determine the optimal therapy.

Trimethoprim/sulfamethoxazole has been established as the therapeutic choice for treatment of *S. maltophilia* infections. However, this compound shows only bacteriostatic activity against most isolates and resistant strains have been increasingly reported. The fluoroquinolones levofloxacin and moxifloxacin have shown excellent in vitro activity against *S. maltophilia*. However, the Clinical and Laboratory Standards Institute (CLSI) currently provides levofloxacin interpretative criteria for *S. maltophilia* but not for moxifloxacin. Furthermore, some hospitals may have only one of these fluoroquinolones in their formulary.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommends levofloxacin breakpoints for Enterobacteriaceae, *Acinetobacter* spp., and *Pseudomonas aeruginosa*, but not for *S. maltophilia.* In addition, EUCAST has established moxifloxacin breakpoints for Enterobacteriaceae but not for non-fermentative Gram-negative bacilli.

The main objective of this study was to evaluate the susceptibility pattern of contemporary clinical strains of *S. maltophilia.* We also evaluated, the correlation between levofloxacin and moxifloxacin MIC results in order to determine if levofloxacin susceptibility can predict moxifloxacin susceptibility.

MATERIALS AND METHODS

A total of 763 unique *S. maltophilia* clinical strains collected worldwide between January 2002 and December 2005 through the SENTRY Antimicrobial Surveillance Program were studied. Species identification was performed at the participating institution by the routine methodology in use at each laboratory. Antimicrobial susceptibility testing was performed by CLSI broth microdilution method using panels manufactured by TREK Diagnostics (Cleveland, USA). Quality control was performed by testing *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

MIC results for ceftazidime, levofloxacin, minocycline, ticarcillin/clavulanate, and trimethoprim/sulfamethoxazole were interpreted according to the CLSI breakpoints for *S. maltophilia* (M100-S17; Table 2B-4), while the CLSI breakpoints for non-Enterobacteriaceae (M100-S17; Table 2B-1) were applied for other antimicrobials. Moxifloxacin results were interpreted according to CLSI breakpoints for *Streptococcus pneumoniae* (≤1 mg/L susceptible/ ≥4 mg/L resistant) for comparison purpose only. Levofloxacin and moxifloxacin MIC values were also interpreted according to the breakpoints recommended by the EUCAST for Enterobacteriaceae since EUCAST does not have any breakpoints specifically established for *S. maltophilia*. EUCAST susceptible/resistant breakpoints are ≤1/≥4 mg/L and ≤0.5/≥2 mg/L for levofloxacin and moxifloxacin, respectively.

The MIC results of moxifloxacin were compared to those of levofloxacin by linear regression analysis. Categorical agreement and errors were calculated using CLSI and EUCAST breakpoints. Very major error (false-susceptible) was defined as susceptibility to levofloxacin and resistance to moxifloxacin, while major error (false-resistance) was defined as resistance to levofloxacin and susceptibility to moxifloxacin. Any discordant results involving the intermediate category was classified as minor error.

RESULTS

- *S. maltophilia* isolates were collected mainly from bloodstream (467; 61.2%) and respiratory tract (165; 21.6%). The strains were from Europe (36.7%), North America (32.9%), Latin America (25.3%) and Asia-Western Pacific region (5.1%).
- Minocycline (100.0%) and doxycycline (99.6%) exhibited the highest susceptibility rates followed by trimethoprim/sulfamethoxazole (97.8%), tigecycline (93.7%), polymyxin B (88.0%), levofloxacin (86.5%) and ticarcillin/clavulanate (82.0%; Table 1).
- Among the fluoroquinolones, levofloxacin (MIC_{50}, 1 mg/L; 86.5% susceptible) was two-fold more potent than ciprofloxacin (MIC_{50}, 2 mg/L; 29.5% susceptible) and two-fold less potent than moxifloxacin (MIC_{50}, 0.5 mg/L).
- Utilizing CLSI breakpoints, 86.5% of *S. maltophilia* strains were susceptible to levofloxacin while 84.9% were inhibited at moxifloxacin concentrations of 1 mg/L or less (Table 1).
- Utilizing EUCAST breakpoints for Enterobacteriaceae, 70.3 and 71.3% of strains were susceptible to levofloxacin and moxifloxacin, respectively. EUCAST breakpoints correlate best with the PK/PD characteristics of these fluoroquinolones when compared to CLSI and US-FDA breakpoints.
- The linear regression showed an excellent correlation between levofloxacin and moxifloxacin MIC results (r=0.93; Figures 1a and 1b).
- By applying the CLSI levofloxacin (≤2 mg/L and ≥8 mg/L) and suggested moxifloxacin breakpoints (≤1 mg/L and ≥4 mg/L), the overall categorical agreement was 95.5% with no very major errors, only 0.1% major error, and only 4.3% minor errors (Figure 1a).
- When the EUCAST Enterobacteriaceae breakpoints were applied, the overall agreement was 93.3% with no very major or major errors, and 7.7% minor errors (Figure 1b).

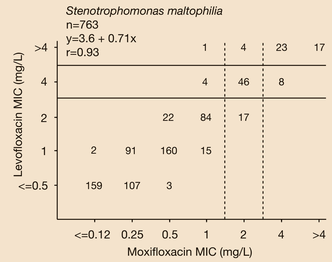
Table 1. Antimicrobial activity of selected compounds tested against 763 *Stenotrophomonas maltophilia* strains by the SENTRY Antimicrobial Surveillance Program (2002-2005).

Antimicrobial agent	MIC (mg/L)[a] MIC_{50}	MIC_{90}	Range	% Susceptible	% Resistant
Amikacin	>32	>32	0.5-32	11.1	88.8
Cefepime	16	>16	0.25->16	18.9	49.8
Ceftazidime	16	>16	≤1->16	49.1	37.7
Ciprofloxacin	2	>4	≤0.03->4	29.5	35.9
Doxycycline[b]	≤1	4	≤1-8	99.6	0.0
Gentamicin	>8	>8	≤2->8	10.5	89.4
Levofloxacin	1	4	≤0.03->4	86.5	5.9
Minocycline[b]	≤0.25	1	≤0.25-4	100.0	0.0
Moxifloxacin	0.5	2	≤0.03->4	84.9[c]	6.3[c]
Piperacillin/tazobactam	>64	>64	2->64	38.4	61.6
Polymyxin B	≤1	4	≤1-4	88.0	0.5
Tetracycline	>8	>8	≤0.25->8	5.9	62.8
Ticarcillin	128	>128	≤16->128	32.0	68.0
Ticarcillin/clavulanate	32	128	≤16->128	82.0	18.0
Tigecycline	1	2	0.06-8	93.7	1.2
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5->2	97.8	2.2

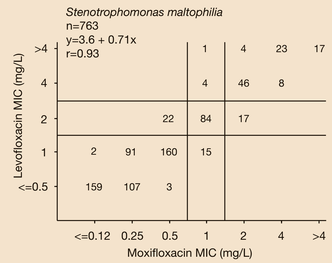
a. MIC determined by broth microdilution methods and interpreted according to CLSI guidelines (2007), where available.
b. Only strains collected in 2004 (230 strains) were tested against doxycycline and minocycline.
c. Interpreted according to CLSI breakpoints for *S. pneumoniae* (≤1 mg/L for susceptible and ≥4 mg/L for resistant).

Figure 1. Scattergram showing the correlation between levofloxacin and moxifloxacin MIC results determined by broth microdilution method when testing 763 *S. maltophilia* isolates.

1a. Applying CLSI breakpoints for levofloxacin when testing *S. maltophilia* (solid line) and for moxifloxacin when testing *S. pneumoniae* (broken lines).



1b. Applying EUCAST breakpoints for Enterobacteriaceae.



CONCLUSIONS

- Tetracyclines derivatives, such as minocycline and doxycycline, and the new glycylcycline tigecycline, may constitute alternative therapeutic agents for *S. maltophilia* infections due to their high in vitro potency; however, expanded clinical studies are necessary to define the role of these antimicrobials in the treatment of such infections.
- The fluoroquinolones levofloxacin and moxifloxacin showed a potent in vitro activity against *S. maltophilia.* However, the spectrum of these compounds against *S. maltophilia* decreases significantly if EUCAST breakpoints are used in preference to CLSI breakpoints.
- An acceptable categorical agreement between levofloxacin and moxifloxacin was obtained using CLSI or EUCAST breakpoints. Thus, *S. maltophilia* susceptibility to moxifloxacin may be predicted based on susceptibility to levofloxacin.

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