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A Changing Pattern of Susceptibility of *Xanthomonas maltophilia* to Antimicrobial Agents: Implications for Therapy

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The in vitro susceptibilities of 130 *Xanthomonas maltophilia* isolates to 12 antibiotics—trimethoprim-sulfamethoxazole, minocycline, ticarcillin-clavulanate, ceftazidime, cefoperazone, cefoperazone-sulbactam, imipenem, ciprofloxacin, and the investigational quinolones PD 117558, PD 117596, PD 127391, and sparfloxacin—were determined by a microtiter broth dilution technique. Other than the investigational quinolones, the most active antibiotics were minocycline, trimethoprim-sulfamethoxazole, and ticarcillin-clavulanate, in order. However, the first two were not bactericidal, while about half of the isolates exhibited intermediate susceptibility to ticarcillin-clavulanate. Patterns of susceptibility to trimethoprim-sulfamethoxazole and ciprofloxacin relative to the years of isolation of these strains reflected the development of resistance to the antibiotic prophylaxis practices in the hospital. We recommend that a combination of antibiotics, such as trimethoprim-sulfamethoxazole, minocycline, and ticarcillin-clavulanate, at or close to the maximum tolerated doses be used in the treatment of serious *X. maltophilia* infections.

Xanthomonas maltophilia has emerged as a significant cause of morbidity and mortality in cancer patients (5, 6, 18). This organism is capable of causing life-threatening infections (5, 25) and is usually resistant to multiple antimicrobial agents, particularly to those of the beta-lactam class (25). The standard therapy for infections by this organism is trimethoprim-sulfamethoxazole. The newly developed quinolones, which have broad antimicrobial activity, are now being used in both prophylaxis and therapy of infections in cancer patients. However, at The University of Texas M. D. Anderson Cancer Center, we have cared for patients with serious *X. maltophilia* infections that developed during quinolone prophylaxis. Because of our concern for the emergence of resistance of *X. maltophilia* to quinolones and the limited therapeutic options available to treat this potentially life-threatening infection, we studied the in vitro activities of various antimicrobial agents, including quinolones, against 130 clinical isolates of *X. maltophilia.*

The strains of *X. maltophilia* used in this study were single patient isolates from the clinical microbiology laboratory at M. D. Anderson Cancer Center. Eighty-nine of the cultures were isolated from patients' bloodstreams, 24 were from urine, 12 were from sputum or the throat, and 5 were from miscellaneous sources. These isolates had been collected in the infectious disease laboratories since 1981 for their clinical significance. The bacteria were identified as *X. maltophilia* by various biochemical tests using the API 20C system (Analytab Products, Plainview, N.Y.). Organisms were stored in the laboratory at −70°C.

All antimicrobial agents were obtained in the form of standard laboratory powders and were stored at −70°C before use. The drugs tested were trimethoprim-sulfamethoxazole (Hoffmann-La Roche, Montclair, N.J.); minocycline (Lederle, Pearl River, N.Y.); ciprofloxacin (Miles, West Haven, Conn.); the four investigational quinolones, sparfloxacin (Parke-Davis, Ann Arbor, Mich.), PD 117558 (Parke-Davis), PD 117596 (Parke-Davis), and PD 127391 (Parke-Davis); ceftazidime (Eli Lilly, Indianapolis, Ind.); cefoperazone (Pfizer, Groton, Conn.); cefoperazone-sulbactam (Pfizer); imipenem (Merck Sharp & Dohme, West Point, Pa.); and ticarcillin-clavulanate (Beecham, Bristol, Tenn.).

Susceptibility testing was performed by a previously described microtiter broth dilution method according to guidelines established by the National Committee for Clinical Laboratory Standards (27). Briefly, the organisms were incubated for 20 h in Mueller-Hinton broth, and appropriate dilutions were made to obtain a final inoculum of 5×10^5 CFU/ml. Antibiotics were prepared manually in cation-supplemented Mueller-Hinton broth and were dispensed automatically with an MIC-2000 dispenser (Dynatech Laboratories, Inc., Alexandria, Va.). Concentrations depended on the antibiotic tested and ranged from 512 to less than 0.0125 μg/ml. *Staphylococcus aureus* ATCC 25932 and *Escherichia coli* ATCC 25922 were used as control organisms. The MIC was described at the lowest concentration of drug that prevented visible growth after 18 h of incubation. Susceptibility interpretations were made according to guidelines established by the National Committee for Clinical Laboratory Standards (26, 28). The breakpoint recommended for ciprofloxacin was also used for the investigational quinolones as was done in prior reports. After thorough mixing of all the wells that showed no visible turbidity, a 0.01-ml sample was removed and spread on blood agar plates. The MBC was defined as the lowest concentration of antimicrobial agent that killed at least 99.9% of the original inoculum on the basis of colony counts. MBCs were determined for 48 randomly chosen isolates. The MICs and MBCs for 50% of the isolates (MIC_{50} and MBC_{50}, respectively) and for 90% of the isolates (MIC_{90} and MBC_{90}, respectively) were calculated.

As expected, *X. maltophilia* isolates were, in general, not susceptible to imipenem, ceftazidime, cefoperazone, and cefoperazone-sulbactam (Table 1); these agents were active against only 2, 15, 11, and 8% of the tested isolates, respectively. Ciprofloxacin was not as active as expected, with only 16% of the isolates being susceptible (31% of the tested

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TABLE 1. Comparative in vitro activities of various antibiotics against 130 clinical isolates of *X. maltophilia*

Antibiotic	MIC[a] (μg/ml)			% of isolates susceptible[b]
	50%	90%	Range	
Ciprofloxacin	4	32	0.5–128	16
PD 117558	1	4	≤0.25–128	67
PD 117596	0.5	2	≤0.25–8	87
PD 127391	0.5	2	≤0.25–64	87
Sparfloxacin	0.5	2	0.5–64	78
Ceftazidime	64	256	2–>512	15
Cefoperazone	64	256	2–>512	11
Cefoperazone-sulbactam	32	256	2–512	8
Imipenem	512	512	1–>512	2
Ticarcillin-clavulanate	32:2	128:2	<0.25:2–>512:2	43
Trimethoprim-sulfamethoxazole	1:19	4:76	≤0.0125:0.3–>32:608	75
Minocycline	1	4	<0.25–16	97

[a] 50% and 90%, MIC_{50} and MIC_{90}.
[b] Breakpoints used for susceptibility were as follows (in μg/ml): ciprofloxacin, ≤1; PD 117558, ≤1; PD 117596, ≤1; PD 127391, ≤1; sparfloxacin, ≤1; ceftazidime, ≤8; cefoperazone, ≤16; cefoperazone-sulbactam, ≤16:8; imipenem, ≤4; ticarcillin-clavulanate, ≤16:2; trimethoprim-sulfamethoxazole, ≤2:38; minocycline, ≤4.

organisms had intermediate susceptibility). All four investigational quinolones were more active than ciprofloxacin. However, the investigational quinolones were less active against isolates resistant to ciprofloxacin than against susceptible strains. The MIC_{90}s of PD 117558 and PD 117596 for ciprofloxacin-resistant isolates were 8 and 2 μg/ml, respectively. The MIC_{90}s for the remaining isolates were 2 and 0.5 μg/ml, respectively. The results with the other quinolones tested were similar. Forty-three percent of the isolates were susceptible to ticarcillin-clavulanate, with another 44% having intermediate susceptibility. By using the more recent breakpoint of ≤64:2 μg/ml for pseudomonads, 87% of the isolates would have been considered susceptible to ticarcillin-clavulanate (28). The two most active commercially available agents were minocycline and trimethoprim-sulfamethoxazole, with 97% (88% with a breakpoint of 2 μg/ml, which is closer to the peak concentration in serum) and 75% of the strains susceptible, respectively.

An increasing number of *X. maltophilia* isolates have become resistant to ciprofloxacin since the widespread introduction in 1989 of this and other quinolones as therapeutic and, particularly, prophylactic agents in cancer patients (Table 2). On the other hand, the same isolates became more susceptible to trimethoprim-sulfamethoxazole during the period of decreasing usage of this agent at our institution. No significant change in the susceptibility pattern to ticarcillin-clavulanate was seen. In addition, all antibacterial agents tested in this study except for trimethoprim-sulfamethoxazole and minocycline exhibited bactericidal activity against *X. maltophilia*; for example, the MIC_{50} and MIC_{90} of trimethoprim-sulfamethoxazole for the 48 isolates also tested for the MBC of the drug were 1:19 and 8:152 μg/ml, respectively. The MBC_{50} and MBC_{90} for the same organisms were 8:152 and >32:608 μg/ml, respectively. Although 69% of the isolates tested were susceptible to trimethoprim-sulfamethoxazole, only one isolate was killed by the breakpoint concentration. The drug was bacteriostatic against 38 of 48 isolates.

TABLE 2. Susceptibility of *X. maltophilia* to antimicrobial agents according to years of isolation

Isolation yr	No. of isolates[a]	MIC[b] (μg/ml) of:					
		Ciprofloxacin		Trimethoprim-sulfamethoxazole		Ticarcillin-clavulanate	
		50%	90%	50%	90%	50%	90%
1981–1988	26	4	16	1:19	>32:608	64	256
1989–1990	26	2	16	0.5:9.5	4:76	64	256
1991	46	4	32	1:19	4:76	64	512
1992	25	4	64	1:19	8:152	64	512

[a] The years of isolation for seven isolates were unspecified.
[b] 50% and 90%, MIC_{50} and MIC_{90}.

This study represents the largest series of clinical *X. maltophilia* isolates recovered over a long period of time. Our results indicate that the three most active agents against *X. maltophilia* are minocycline, ticarcillin-clavulanate, and trimethoprim-sulfamethoxazole. The last is widely used as the treatment of choice for *X. maltophilia* infections, and several in vitro studies have confirmed its high activity (5, 12, 18, 24, 25, 30). However, at least one study has described a 26% incidence of in vitro resistance (11), and another study has reported the MIC_{50} and MIC_{90} to be at the breakpoint concentration of 2:38 μg/ml (22). The impressive activity exhibited by minocycline against *X. maltophilia* has rarely been described in prior reports (9, 14). In contrast, borderline activity of doxycycline (9, 12, 21) and poor activity of tetracycline (12, 24) have been documented previously.

Ticarcillin-clavulanate has been found to possess good activity in general (8, 37). However, in vitro testing of susceptibility of microorganisms to ticarcillin-clavulanate uses a fixed concentration of clavulanate (2 μg/ml). One study used a fixed ratio of ticarcillin to clavulanate (20:1) rather than a fixed concentration of clavulanate based on pharmacokinetic considerations; it found moderate activity of this antibiotic against *X. maltophilia* (29).

Our results with the other antibiotics tested are in agreement with those of others and confirm the poor activity of ceftazidime, cefoperazone, cefoperazone-sulbactam, and imipenem against *X. maltophilia*. Most other lactam antibiotics (including cephalosporins, penicillins, carbapenems, and monobactams) have been found to possess poor in vitro activity (4, 7, 9, 10, 12, 20, 22, 23, 25, 29, 32); an exception is moxalactam (1, 5, 7, 9, 10, 15, 18). Aminoglycosides have also been reported to display poor activity (4, 9, 10, 12, 22, 25, 29, 32). The increasing resistance of *X. maltophilia* to the commercially available quinolones is worrisome and requires further investigation (3, 4, 10, 12, 16, 17, 21–23, 30, 33). Although the investigational quinolones show good in vitro activity compared with that of ciprofloxacin and other quinolones (3, 13, 17, 19, 21, 22, 29, 30, 32, 33), their clinical usefulness needs to

be determined after further in vitro investigation of, for example, their stability to selection of resistant strains. Clinical experience with the emergence of resistance to ciprofloxacin and the diminished activity of the investigational quinolones against ciprofloxacin-resistant isolates warrant caution in the determination of the clinical usefulness of these investigational quinolones in the treatment of *X. maltophilia* infections. While trimethoprim-sulfamethoxazole, minocycline, and ticarcillin-clavulanate inhibited the majority of *X. maltophilia* isolates, the MIC_{90}s of these agents were high, close to the breakpoint for resistance or higher. In the case of ticarcillin-clavulanate, almost half of the isolates were moderately susceptible. In addition, neither trimethoprim-sulfamethoxazole nor minocycline exhibited bactericidal activity against the tested organisms. Hence, it would be tempting to use high doses of these agents (at or close to the maximum tolerated doses), preferably in combination, in the treatment of serious *X. maltophilia* infections. As an example, administration of trimethoprim at 12 to 15 mg/kg of body weight per day and sulfamethoxazole at 60 to 75 mg/kg/day will maintain maximum serum trimethoprim concentrations of 5 to 10 μg/ml (34, 35, 38); administration of even higher doses, 20 mg of trimethoprim per kg per day and 100 mg of sulfamethoxazole per kg per day, will result in even higher maximum serum drug concentrations of 13.6 and 372 μg/ml, respectively (36). Most *X. maltophilia* isolates would be inhibited at those drug concentrations. In addition, various combinations of antibiotics, including combinations of trimethoprim-sulfamethoxazole with carbenicillin plus rifampin or with colistin or of gentamicin with carbenicillin plus rifampin, have been found to act synergistically in vitro against *X. maltophilia* (2, 31). After empiric high-dose combination antibiotic therapy is initiated, once the infecting strain is shown to be susceptible, the dosage of these agents could be reduced to standard amounts.

The addition of clavulanate to aztreonam (10, 11), sulbactam to cefoperazone (this study), and tazobactam to piperacillin (4, 8) failed to increase significantly the susceptibility of *X. maltophilia* to these agents, except when a 2:1 ratio of aztreonam to clavulanate was used. However, since levels of clavulanate in serum decrease more rapidly than do those of aztreonam, the clinical usefulness of this combination may be limited.

Until 1988, trimethoprim-sulfamethoxazole was the most commonly used antibacterial agent in the prophylaxis of cancer patients at M. D. Anderson Cancer Center. Since then, the quinolones, particularly ciprofloxacin, have replaced it as the agent of choice for bacterial prophylaxis. These practices have translated into an increasing resistance to ciprofloxacin and decreasing resistance to trimethoprim-sulfamethoxazole.

In conclusion, this study shows that *X. maltophilia* remains highly resistant to various classes of antibiotics. Antibiotic usage practices affect the overall susceptibility pattern of *X. maltophilia*. It may be prudent to use antibiotic combinations at doses close to the maximum tolerated doses in the treatment of serious *X. maltophilia* infections. Trimethoprim-sulfamethoxazole, minocycline, and ticarcillin-clavulanate may represent a promising combination, especially if in vitro synergy studies or kill curves demonstrate activity.

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