Antimicrobial Susceptibility and Synergy Studies of *Stenotrophomonas maltophilia* Isolates from Patients with Cystic Fibrosis

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Stenotrophomonas maltophilia is a newly emerging pathogen being detected with increasing frequency in patients with cystic fibrosis (CF). The impact of this multidrug-resistant organism on lung function is uncertain. The optimal treatment for *S. maltophilia* in CF patients is unknown. We studied the in vitro activity of ten antimicrobial agents, and conducted synergy studies by using checkerboard dilutions of eight pairs of antimicrobial agents against strains isolated from 673 CF patients from 1996 to 2001. This represents approximately 7 to 23% of the CF patients in the United States who harbor *S. maltophilia* annually. Doxycycline was the most active agent and inhibited 80% of 673 initial patient isolates, while trimethoprim-sulfamethoxazole inhibited only 16%. High concentrations of colistin proved more active than high concentrations of tobramycin and gentamicin. Serial isolates ($n = 151$) from individual patients over time (median, 290 days) showed minimal changes in resistance. Synergistic or additive activity was demonstrated by trimethoprim-sulfamethoxazole paired with ticarcillin-clavulanate (65% of strains), ciprofloxacin paired with ticarcillin-clavulanate (64% of strains), ciprofloxacin paired with piperacillin-tazobactam (59% of strains), trimethoprim-sulfamethoxazole paired with piperacillin-tazobactam (55% of strains), and doxycycline paired with ticarcillin-clavulanate (49% of strains). In all, 522 (78%) isolates were multidrug resistant (i.e., resistant to all agents in two or more antimicrobial classes) but 473 (91%) of these were inhibited by at least one antimicrobial combination (median, four; range, one to eight). To determine appropriate treatment for patients with CF, it is important to monitor the prevalence, antimicrobial susceptibility, and clinical impact of *S. maltophilia* in this patient population.

Cystic fibrosis (CF) is the most common, autosomal recessive, life-shortening genetic disorder in Caucasians (26, 30). The gene responsible for CF, the CF transmembrane conductance regulator, functions as a Cl^- channel, but the role of the CF transmembrane conductance regulator in the pathogenesis of chronic lung infections in CF patients remains largely unknown (22). CF patients are infected by a predictable cascade of pathogens, and chronic lung disease is the most common cause of morbidity and mortality. Young infants are initially infected with *Haemophilus influenzae*, *Staphylococcus aureus*, and/or *Pseudomonas aeruginosa* (30). During the first decade of life, *P. aeruginosa* becomes increasingly prevalent, and by 18 years of age, 80% of CF patients are infected with this pathogen (9–14, 17). In efforts to treat pulmonary exacerbations and slow the progression of lung disease, CF patients receive multiple courses of oral, intravenous, and aerosolized antibiotics. As the life expectancy of CF patients has increased and microbiology laboratories are using more selective media (37), newly emerging pathogens are being detected with increasing frequency and include *Burkholderia cepacia* complex (5), nontuberculous mycobacteria (28, 29), *Achromobacter xylosoxidans*, and *Stenotrophomonas maltophilia* (6).

Isolation of *S. maltophilia* was first reported from CF patients during the early 1980s (23) and, as reported to the CF Foundation National Patient Registry from 1996 to 2001, *S. maltophilia* was harbored by 4 to 8% of patients in the United

States (9–14). The impact of *S. maltophilia* on lung function is uncertain; in some CF patients, *S. maltophilia* appears to be responsible for a decline in pulmonary function, while in others, *S. maltophilia* may merely colonize damaged lungs. *S. maltophilia* is highly resistant to most antimicrobial agents because of innate and acquired mechanisms of resistance (1, 41). Treatment options are limited, and there have been few recent surveys of the antimicrobial susceptibility patterns of this organism. We studied the in vitro activity of antimicrobial agents, including higher concentrations of gentamicin, tobramycin, and colistin, such as may be achieved by aerosolization, and the activity of combinations of antimicrobial agents against *S. maltophilia* strains isolated from CF patients.

MATERIALS AND METHODS

Clinical isolates. Since 1992, the CF Foundation has funded the CF Referral Center for Susceptibility and Synergy Studies (CF Referral Center) at Columbia University (<http://healthsciences.columbia.edu/dept/synergy>) to study the antimicrobial susceptibilities of multidrug-resistant organisms and to study the activity of antibiotics in combination (36). The CF Referral Center solicits multidrug-resistant clinical isolates from CF patients cared for at accredited CF centers throughout the United States (17). Clinicians in CF care centers have been informed about the CF Referral Center's services by the U.S. CF Foundation in both written communications and formal presentations by the CF Referral Center staff at national meetings. In 1995, studies of *S. maltophilia* were initiated in response to increasing requests to the CF Referral Center from CF clinicians. The CF Foundation maintains a CF Patient Registry wherein demographic, morbidity (including respiratory tract microbiology), and mortality data are collected (17).

Clinical isolates received at the CF Referral Center from 1996 to 2001 and identified by the referring clinical microbiology laboratories as *S. maltophilia* were selected for this study. Isolates were confirmed at the CF Referral Center as *S. maltophilia* using phenotypic characteristics to distinguish *S. maltophilia*

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TABLE 1. CF patients in the United States with *S. maltophilia* as processed by the CF Referral Center, 1996 to 2001

Yr	No. of patients with respiratory tract cultures ^a	No. (%) of patients with <i>S. maltophilia</i> ^a	No. (%) of patients with <i>S. maltophilia</i> processed by CF Referral Center ^b
1996	17,620	683 (4)	47 (7)
1997	17,996	926 (5)	115 (12)
1998	17,794	595 (3)	138 (23)
1999	18,466	1,182 (6)	150 (13)
2000	19,185	1,285 (7)	167 (13)
2001	22,732	1,909 (8)	198 (10)

^a Data from U.S. CF Foundation National Patient Registry represent unique patients, but patients contribute microbiology data annually.

^b Number of unique patient isolates of *S. maltophilia* processed at the CF Referral Center/number of patients with *S. maltophilia* reported to the CF Foundation National Patient Registry.

from *B. cepacia* complex, *A. xylosoxidans*, or *P. aeruginosa*. Strains were plated on several agar media, including Biplate medium (Remel, Lenexa, Kans.), Mueller-Hinton agar (BBL, Cockeysville, Md.), oxidative-fermentative-polymyxin B-bacitracin-lactose medium (Remel), and DNase medium (BBL). Plates were incubated at 35°C for 18 to 24 h and for 48 h to accommodate slowly growing strains. Isolates confirmed as *S. maltophilia* grew on Biplate medium and Mueller-Hinton agar without pigment production and demonstrated DNase production. The susceptibility of 50 of these strains has been previously reported (34).

Antimicrobial susceptibility and synergy studies. The activity of 10 antimicrobial agents was determined with a broth microdilution assay using commercially prepared microtiter plates (Microtech Medical Systems, Inc., Aurora, Colo.). This method has been shown to be comparable to agar dilution for testing the antimicrobial susceptibility of *P. aeruginosa* isolates from CF patients (33). The following antimicrobial agents were tested in serial twofold dilutions: ciprofloxacin (0.25 to 8 µg/ml), doxycycline (1 to 32 µg/ml), ticarcillin-clavulanate (ticarcillin component, 4 to 128 µg/ml), piperacillin (4 to 128 µg/ml), piperacillin-tazobactam (piperacillin component, 4 to 128 µg/ml), trimethoprim-sulfamethoxazole (0.5 to 16 µg/ml), and imipenem (0.5 to 16 µg/ml). The National Committee for Clinical Laboratory Standards (NCCLS) has established general interpretative criteria for susceptibility breakpoints for nonmembers of the family *Enterobacteriaceae*, including *S. maltophilia* (27). In addition, the activities of higher concentrations (100 and 200 µg/ml) of gentamicin, tobramycin, and colistin, such as could be achieved by aerosolization, were tested (2, 31). While there are no NCCLS recommendations for the optimal method for susceptibility testing of colistin, this agent was tested by using the broth microdilution assay. Plates were incubated at 35°C for 18 to 24 h and examined for inhibition of growth. Strains with inadequate growth at 24 h were incubated for an additional 18 to 24 h.

Synergy studies using checkerboard dilutions of pairs of antimicrobial agents

tested at clinically achievable concentrations were performed. Fractional inhibitory concentrations (FIC) were calculated as previously described (15, 18). FIC of ≤0.5 were interpreted as synergistic, FIC of >0.5 to 1.0 were interpreted as additive, FIC of >1.0 to ≤4.0 were interpreted as indifferent, and FIC of >4 were interpreted as antagonistic (16, 21).

RESULTS

Comparison with national data. From 1996 to 2001, the CF Referral Center processed 1,418 to 3,330 multidrug-resistant isolates per year, of which 4 to 14% were identified as *S. maltophilia*. Over the 6-year study period, the CF Referral Center processed at least one isolate of *S. maltophilia* from 7 to 23% of all CF patients who harbored *S. maltophilia*, as reported to the CF Foundation Patient Registry (Table 1).

Antimicrobial susceptibility testing. The CF Referral Center received 955 strains of *S. maltophilia* from January 1996 to December 2001. These strains were from 673 patients (range, one to eight strains per patient). The antimicrobial susceptibilities of the initial strain of each patient are shown in Table 2. Doxycycline was most active, inhibiting 80% of the strains, while trimethoprim-sulfamethoxazole inhibited only 16% of the strains. High concentrations of colistin (200 µg/ml) proved more active than high concentrations of gentamicin and tobramycin (200 µg/ml), as 87% of the isolates were inhibited by colistin while only 35% were inhibited by gentamicin and 26% and were inhibited by tobramycin.

More than one isolate was received from 151 (22%) patients. The susceptibilities of the first and last isolates of *S. maltophilia* from individual patients were compared (median time between isolates, 290 days; range, 7 to 1,918 days). Thirty-three (22%) of these patients had strains that became resistant to at least two antimicrobial agents. A 13% increase in resistance over time was noted for ticarcillin-clavulanate, while minimal increases in resistance were noted for ciprofloxacin (7%), piperacillin-tazobactam (6%), trimethoprim-sulfamethoxazole (6%), tobramycin (5%), gentamicin (6%), and piperacillin (3%). No increased resistance to doxycycline was detected.

Synergistic or additive activity was demonstrated by most pairs of antimicrobial agents, as shown in Table 3. Trimethoprim-sulfamethoxazole paired with ticarcillin-clavulanate inhibited 65% of the strains, while ciprofloxacin paired

TABLE 2. Activities of antimicrobial agents against 673 *S. maltophilia* strains isolated from patients with cystic fibrosis, 1996 to 2001

Antimicrobial agent	MIC (µg/ml)			% (no.) of strains		
	Range ^a	50% of strains	90% of strains	Susceptible	Intermediate	Resistant
Ciprofloxacin	0.25–>8	>8	>8	4 (25)	11 (73)	85 (575)
Doxycycline	1–>32	2	8	80 (538)	10 (71)	11 (64)
Imipenem	0.5–>16	>16	>16	2 (11)	1 (7)	97 (655)
Piperacillin	4–>128	>128	>128	1 (10)	7 (45)	92 (618)
Piperacillin-tazobactam	4–>128	>128	>128	3 (20)	5 (35)	92 (618)
Ticarcillin-clavulanate	4–>128	128	>128	27 (179)	23 (158)	50 (336)
Trimethoprim-sulfamethoxazole	0.5–>16	16	>16	16 (109)	NA ^b	84 (564)
High-dose gentamicin	100–>200	>200	>200	35 (234)	NA	65 (439)
High-dose colistin	100–>200	100	>200	87 (585)	NA	19 (88)
High-dose tobramycin	100–>200	>200	>200	26 (176)	NA	74 (497)

^a Breakpoints from reference 27.

^b NA, not applicable.

TABLE 3. Synergistic activity of pairs of antimicrobial agents against *S. maltophilia* strains from patients with CF

Antimicrobial agent pair	Concn ranges tested ($\mu\text{g/ml}$)	No. (%) of strains			
		Synergistic	Additive	Indifferent	Antagonistic
Ciprofloxacin + ticarcillin-clavulanate	(0.5–4)/(4–128)	296 (44)	132 (20)	231 (34)	14 (2)
Ciprofloxacin + piperacillin-tazobactam	(0.5–4)/(4–128)	276 (41)	118 (18)	270 (40)	9 (1)
Doxycycline + ciprofloxacin	(1–8)/(0.25–8)	54 (8)	152 (23)	459 (68)	8 (1)
Doxycycline + ticarcillin-clavulanate	(1–8)/(4–128)	108 (16)	224 (33)	333 (50)	8 (1)
Doxycycline + piperacillin-tazobactam	(1–8)/(4–128)	77 (11)	194 (29)	393 (59)	9 (1)
Trimethoprim-sulfamethoxazole + doxycycline	(0.5–4)/(1–32)	90 (13)	227 (34)	346 (52)	10 (1)
Trimethoprim-sulfamethoxazole + ticarcillin-clavulanate	(0.5–4)/(4–128)	317 (47)	124 (18)	212 (32)	20 (3)
Trimethoprim-sulfamethoxazole + piperacillin-tazobactam	(0.5–4)/(4–128)	275 (41)	96 (14)	286 (43)	16 (2)

with ticarcillin-clavulanate inhibited 64%, ciprofloxacin paired with piperacillin-tazobactam inhibited 59%, trimethoprim-sulfamethoxazole paired with piperacillin-tazobactam inhibited 55%, doxycycline paired with ticarcillin-clavulanate inhibited 49%, and trimethoprim-sulfamethoxazole paired with doxycycline inhibited 47%.

In all, 522 (78%) of the initial isolates were found to be multidrug resistant, defined as resistant to all of the agents in at least two of the antimicrobial classes tested (37). Sixteen (3%) isolates were resistant to all of the antimicrobial agents tested, including high-dose aminoglycosides and colistin. However, 473 (91%) of the multidrug-resistant strains were inhibited (defined as synergistic or additive) by at least one antimicrobial combination (median, four; range, one to eight).

DISCUSSION

This study is the largest survey of *S. maltophilia* isolates from CF patients in which multidrug resistance, longitudinal isolates from single patients, and synergy studies were analyzed. These isolates represented approximately 14% of all CF patients in the United States who harbored *S. maltophilia* annually from 1996 to 2001. In this 6-year study, doxycycline was the most active agent in vitro, as has been noted in previous studies of *S. maltophilia* obtained from patients without CF (32, 40). Most of the combinations that we studied inhibited $\geq 40\%$ of the isolates tested, including half of the isolates that were resistant to all of the single agents tested.

Since the mid-1990s, *S. maltophilia* has been considered an emerging pathogen in patients with CF. *S. maltophilia* is highly resistant to many antimicrobial agents. The three mechanisms of resistance to β -lactam agents have been well studied and include the L1 (specific for penicillins) and L2 (specific for cephalosporins) β -lactamases (38, 39) and the low permeability of the outer membrane due in large part to efflux pumps (25, 41). Resistance to other classes of antibiotics is mediated by changes in the antimicrobial target site, other modifying enzymes, or changes in outer membrane proteins (14).

While no comparative studies have been performed to determine the optimal antimicrobial treatment regimens for infections caused by *S. maltophilia*, experts recommend high doses of trimethoprim-sulfamethoxazole paired with ticarcillin-clavulanate for treatment of patients without CF (19). While in vitro activity has been consistently demonstrated for tetracyclines, there is limited in vivo experience. Furthermore, tetracyclines and trimethoprim-sulfamethoxazole are not bactericidal and resistance may emerge (20, 40).

In general, treatment strategies for *S. maltophilia* in CF patients are similar to those used for *P. aeruginosa* or *B. cepacia* complex, whereby high doses of two or more parenteral agents with different mechanisms of action are used to manage a pulmonary exacerbation. While aerosolized high doses of tobramycin or colistin have proven to be beneficial as suppressive therapy in CF patients chronically infected with *P. aeruginosa* (7), there are no clinical data to support the use of these treatment modalities for *S. maltophilia* (7).

There are some limitations to this study. First, our laboratory solicits multidrug-resistant organisms, which may overestimate resistance in CF isolates. Second, while we used standardized, validated methods for susceptibility testing for *P. aeruginosa* to study these isolates, NCCLS guidelines have not been established for optimal susceptibility testing for *S. maltophilia*, nor for colistin. Third, our studies do not consider in vivo conditions in the CF lung that may have an impact on antimicrobial activity, such as the role of the biofilm, effects of stationary-phase growth, and the inhibitory effect of CF sputum on antimicrobial agents (24). Finally, the epidemiology of *S. maltophilia* in CF patients may be imprecise as this organism may be misidentified as other pathogens (3, 4, 35).

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