

Reappraisal of the Antimicrobial Susceptibilities of *Chryseobacterium* and *Flavobacterium* Species and Methods for Reliable Susceptibility Testing

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Several *Flavobacterium* species, comprising a heterogeneous group of gram-negative bacilli that are capable of causing opportunistic infections in humans, have recently been reclassified as *Chryseobacterium* or *Myroides* species. Intrinsically resistant to a number of antibiotics, these organisms have been reported to be susceptible to vancomycin and certain other drugs that are normally active against gram-positive bacteria. By using the National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution procedure, 58 clinical isolates of former flavobacteria (36 *Chryseobacterium meningosepticum* isolates, 11 *C. indologenes* isolates, 3 *C. gleum* isolates, 4 unspiciated former members of *Flavobacterium* group IIb, and 4 *Myroides odoratum* isolates) were tested with 23 antibiotics, including conventional and investigational agents. In addition, the broth microdilution results were compared to those generated by agar dilution, E-test, and disk diffusion for vancomycin and piperacillin-tazobactam. Compared to the NCCLS microdilution results, there were 7.1 and 17.9% very major errors with piperacillin-tazobactam by agar dilution and E-test, respectively. In addition, there were from 12.1 to 48.3% minor errors with both procedures with vancomycin and piperacillin-tazobactam. The very major and minor error rates were unacceptably high with disk testing of piperacillin-tazobactam; the use of enterococcal vancomycin disk breakpoints (zone diameter of ≥ 17 mm = susceptible) resulted in >20% minor errors but only one very major error. All of the isolates were susceptible to minocycline; over 90% were susceptible to sparfloxacin, levofloxacin, and clinafloxacin; and 88% were susceptible to rifampin. None was susceptible to vancomycin. When *Chryseobacterium* or *Myroides* species are isolated from serious infections, susceptibility testing by broth microdilution should be performed and therapy should be guided by those results.

Members of the genera *Chryseobacterium* and *Myroides* (formerly classified as *Flavobacterium* species) in the family *Cytophagaceae* comprise a heterogeneous group of nonmotile, oxidase-positive, nonfermentative or slowly fermentative gram-negative bacilli (26, 27). *Chryseobacterium meningosepticum* is the species most commonly associated with infections in humans. It can cause neonatal meningitis, pneumonia, bacteremia, sepsis, and soft tissue and other infections primarily in immunocompromised patients and has been a well-documented cause of outbreaks in neonatal and adult intensive care units (6, 7, 11). The other former flavobacteria have been isolated from a variety of clinical and environmental sources. The most common of these former flavobacteria are *Myroides odoratum* (4, 10, 12, 14) and members of *Flavobacterium* group IIb, including *Chryseobacterium indologenes* (13) and *Chryseobacterium gleum* (27).

All of these species are known to be resistant to a number of antimicrobial agents. *C. meningosepticum* has the unusual reputation of being susceptible to vancomycin (11) and to other agents that are commonly used to treat infections caused by gram-positive bacteria, such as erythromycin (2, 11, 20, 21) and clindamycin (8, 9).

In prior studies with these bacteria, the results of disk diffusion susceptibility tests agreed poorly with MIC determinations, particularly in the interpretation of results for vanco-

mycin (1, 8, 28). In their recent comprehensive review of *C. meningosepticum*, Bloch et al. (6) described a complete failure of vancomycin in vitro for their series of isolates; after a review of the literature, they found that only 65% of organisms demonstrated in vitro susceptibility to vancomycin. In many of their cited references, disk diffusion susceptibility testing was employed.

Other more recent reports provide conflicting data regarding the susceptibilities of chryseobacteria to drugs that are generally considered to be effective against gram-negative bacilli, including piperacillin and piperacillin-tazobactam (4, 8, 9, 13, 16, 23, 29). In our own recent experience with a few clinical isolates, we found them to be susceptible to piperacillin-tazobactam by disk diffusion criteria.

We undertook our study in order to confirm the previously reported susceptibilities of these former flavobacteria, corroborate the results of prior studies which concluded that disk diffusion susceptibility testing is unreliable for these isolates, explore the potential activities of newer antimicrobial agents against a substantial number of isolates, and assist clinicians with decisions regarding empiric antibiotic choices for their patients with infections caused by *Chryseobacterium* and *Myroides* species.

MATERIALS AND METHODS

Isolates. Frozen, lyophilized, and stock cultures of clinical origin and fresh clinical isolates were employed for this study. The identities of all isolates were confirmed by the Vitek system, incorporating GNI cards (bioMérieux Vitek, Hazelwood, Mo.) and/or apiNFT (bioMérieux). The 36 *C. meningosepticum*, 11 *C. indologenes*, 3 *C. gleum*, and 4 *M. odoratum* isolates were identified by one or both systems. Four isolates with characteristic production of an insoluble bright

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yellow pigment, originally stored as *Flavobacterium* group IIb isolates, could not be identified to the species level by either system.

Antimicrobial agents. The following standard susceptibility testing powders were obtained: sparfloxacin and quinupristin-dalfopristin (Rhône-Poulenc-Rorer, Collegeville, Pa.); levofloxacin (Ortho-McNeil Pharmaceutical, Raritan, N.J.); cinafloxacin and chloramphenicol (Parke-Davis, Morris Plains, N.J.); minocycline, rifampin, doxycycline, trimethoprim, and sulfamethoxazole (Sigma Chemical Co., St. Louis, Mo.); ciprofloxacin (Bayer Pharmaceutical Division, West Haven, Conn.); clarithromycin and erythromycin (Abbott Laboratories, Abbott Park, Ill.); piperacillin and tazobactam (Wyeth-Ayerst Laboratories, Philadelphia, Pa.); imipenem (Merck and Co., West Point, Pa.); cefepime (Bristol-Myers Squibb, Wallingford, Conn.); ticarcillin and clavulanic acid (SmithKline Beecham, Philadelphia, Pa.); clindamycin, lincomycin, eperzolid (formerly U-100592), and linezolid (formerly U-100766) (Pharmacia and Upjohn Company, Kalamazoo, Mich.); azithromycin (Pfizer Labs, New York, N.Y.); meropenem (Zeneca Pharmaceuticals, Wilmington, Del.); and vancomycin (Eli Lilly & Co., Indianapolis, Ind.). For β -lactam- β -lactamase inhibitor combinations, constant concentrations of clavulanate (2 μ g/ml) and tazobactam (4 μ g/ml) were combined with twofold dilutions of ticarcillin and piperacillin, respectively. The trimethoprim-sulfamethoxazole combination was tested at a ratio of 1:19. Antibiotic-impregnated disks containing 30 μ g of vancomycin and 100 μ g of piperacillin with 10 μ g of tazobactam were obtained from Becton-Dickinson Microbiology Systems, Cockeysville, Md. E-test strips impregnated with vancomycin and piperacillin-tazobactam were obtained from AB Biodisk, Piscataway, N.J.

Broth microdilution susceptibility tests. Broth microdilution MIC tests were performed by the procedures advocated by the National Committee for Clinical Laboratory Standards (NCCLS) (19), including the use of cation-adjusted Mueller-Hinton broth (Difco, Detroit, Mich.). A final inoculum of 5×10^5 CFU/ml and incubation for 16 to 20 h at 35°C in ambient air were employed.

Agar dilution susceptibility tests. Agar dilution MIC tests were performed as recommended by NCCLS (19) by using Mueller-Hinton agar (Difco), a final inoculum of 10^4 CFU, and incubation for 16 to 20 h at 35°C in ambient air.

E-test susceptibility assays. E-test susceptibility assays were performed as recommended by the manufacturer by using Mueller-Hinton agar (Becton-Dickinson) and incubation for 16 to 20 h at 35°C in ambient air. A 0.5 McFarland suspension served as the inoculum.

Disk susceptibility tests. Disk susceptibility tests were performed as recommended by NCCLS (19) by using Mueller-Hinton agar (Becton-Dickinson) and incubation for 16 to 20 h at 35°C in ambient air. A 0.5 McFarland suspension served as the inoculum.

Disk diameters and all MIC results were interpreted by using NCCLS interpretive standards, if available, for nonfastidious gram-negative bacteria. For vancomycin, erythromycin, and clindamycin, gram-positive bacteria breakpoints were employed; for vancomycin disk susceptibilities, both staphylococcal and enterococcal criteria of NCCLS were applied for interpretation.

RESULTS

We tested a total of 58 clinical isolates of *Chryseobacterium* and *Myroides* species with 23 antibiotics, including traditional agents as well as new and investigational agents. The broth microdilution MIC determinations for 36 *C. meningosepticum*, 18 former *Flavobacterium* group IIb (11 *C. indologenes*, 3 *C. gleum*, and 4 unspiciated), and 4 *M. odoratum* isolates are shown in Table 1. The pattern of growth at the bottoms of piperacillin-tazobactam and cefepime wells was frequently atypical, appearing somewhat filmy or diaphanous at higher concentrations of antibiotic, possibly suggesting partial inhibition of β -lactamase. In some cases, the endpoints (>80% inhibition) for trimethoprim-sulfamethoxazole were difficult to read.

Minocycline, sparfloxacin, levofloxacin, cinafloxacin, and rifampin were the most active drugs tested. The 58 isolates examined demonstrated very similar susceptibility patterns, with a few exceptions; 35 of 36 *C. meningosepticum* isolates were susceptible to rifampin, but only 73% of isolates of other species were fully susceptible. Only one-quarter of *C. meningosepticum* and *M. odoratum* isolates were susceptible to ciprofloxacin, but 94% of the former *Flavobacterium* group IIB isolates were susceptible. Thirty-five *C. meningosepticum* isolates were resistant to imipenem, and all were resistant to meropenem and cefepime. All three isolates of *C. gleum* were susceptible to cefepime at low concentrations, and two of the unspiciated group IIb isolates were susceptible at somewhat higher concentrations.

TABLE 1. Activities (in descending order) of 23 antimicrobial agents tested by NCCLS broth microdilution against 58 clinical isolates of *Chryseobacterium* and *Myroides* species^a

Antimicrobial agent	MIC ₅₀ ^b	MIC ₉₀ ^b	MIC range (μ g/ml)	% of isolates	
				Susceptible ^c	Resistant ^c
Minocycline	1	2	≤ 0.25 -4	100 (≤ 4)	0 (≥ 16)
Levofloxacin	1	2	0.5-8	98 (≤ 2)	2 (≥ 8)
Sparfloxacin	0.25	1	≤ 0.12 -2	97 (≤ 1)	0 (≥ 4)
Cinafloxacin ^d	0.25	1	≤ 0.12 -2		
Rifampin	1	2	≤ 0.12 -4	88 (≤ 1)	2 (≥ 4)
Ciprofloxacin	2	8	0.5-16	48 (≤ 1)	31 (≥ 4)
Doxycycline	8	16	2-32	47 (≤ 4)	19 (≥ 16)
Trimethoprim-sulfamethoxazole ^e	4	8	≤ 0.5 ->32	33 (≤ 2)	67 (≥ 4)
Piperacillin-tazobactam ^f	64	>128	≤ 2 ->128	29 (≤ 16)	22 (≥ 128)
Clarithromycin	8	16	≤ 1 ->32	29 (≤ 2)	57 (≥ 8)
Imipenem	>16	>16	2->16	17 (≤ 4)	78 (≥ 16)
Cefepime	>64	>64	≤ 1 ->64	10 (≤ 4)	72 (≥ 32)
Meropenem	>16	>16	2->16	7 (≤ 4)	69 (≥ 16)
Azithromycin	>32	>32	2->32	3 (≤ 2)	91 (≥ 8)
Clindamycin	8	16	≤ 0.5 -32	2 (≤ 0.5)	76 (≥ 4)
Ticarcillin-clavulanate ^g	>128	>128	16->128	2 (≤ 16)	97 (≥ 128)
Vancomycin	32	>64	16->64	0 (≤ 4)	79 (≥ 32)
Erythromycin	>32	>32	2->32	0 (≤ 0.5)	91 (≥ 8)
Chloramphenicol	64	>64	16->64	0 (≤ 8)	93 (≥ 32)
Lincomycin ^d	>32	>32	8->32		
Quinupristin-dalfopristin ^d	>8	>8	>8		
Linezolid ^d	>16	>16	8->16		
Eperzolid ^d	>16	>16	≥ 16		

^a Included were 36 *C. meningosepticum* isolates, 11 *C. indologenes* isolates, 3 *C. gleum* isolates, 4 isolates of unspiciated former members of *Flavobacterium* group IIb, and 4 *M. odoratum* isolates. The breakpoint data for azithromycin, clindamycin, erythromycin, and vancomycin are the standards used for testing gram-positive bacteria.

^b MIC₅₀ and MIC₉₀, MIC (in micrograms per milliliter) of antibiotic at which 50 and 90%, respectively, of the isolates were inhibited.

^c Parenthetical data are concentrations expressed in micrograms per milliliter.

^d Breakpoint susceptibility standards are not yet established or are not available.

^e Data are MICs of trimethoprim at a ratio of 1/19 with sulfamethoxazole.

^f Data are MICs of piperacillin combined with 4 μ g of tazobactam per ml.

^g Data are MICs of ticarcillin combined with 2 μ g of clavulanic acid per ml.

We also tested all 58 isolates with vancomycin and piperacillin-tazobactam by agar dilution, E-test, and disk diffusion techniques and compared the results with those obtained by broth microdilution.

For vancomycin, over 95% of the MICs determined by agar dilution and E-test agreed within 1 log₂ dilution of the results obtained by broth microdilution (Table 2). There were no major or very major errors, but 15.5 and 12.1% minor errors occurred with agar dilution and E-test, respectively. With the disk diffusion method, there were 37% very major errors and 50% minor errors when the staphylococcal zone criteria (≤ 9 mm, resistant; 10 to 11 mm, intermediate; ≥ 12 mm, susceptible) were used for interpretation. However, when we employed the enterococcal zone criteria (≤ 14 mm, resistant; 15 to 16 mm, intermediate; ≥ 17 mm, susceptible), only one very major error and 20.7% minor errors were noted, e.g., an isolate considered resistant by MIC and intermediate by the disk test.

For piperacillin-tazobactam, only 64% of the MICs determined by agar dilution and 53% of the MICs determined by E-test were within 1 log₂ dilution of the results obtained by broth microdilution. There were from 7.1 to 31% very major

TABLE 2. Comparison of agar dilution and E-test MICs and disk diffusion results with the results obtained by broth microdilution for vancomycin and piperacillin-tazobactam with 58 clinical isolates of *Chryseobacterium* and *Myroides* species^a

Antimicrobial agent	Technique	No. of determinations within log ₂ dilution(s) of broth microdilution MIC							Interpretive errors (%)		
		<-2	-2	-1	Same	+1	+2	>+2	Very major ^b	Major ^c	Minor ^d
Vancomycin	Agar dilution	0	3	17	36	2	0	0	0	0	15.5
	E-test	0	1	16	37	3	1	0	0	0	12.1
	Disk diffusion with staphylococcal breakpoints ^e								37	0	50
	Disk diffusion with enterococcal breakpoints ^e								2.2	0	20.7
Piperacillin-tazobactam	Agar dilution	3	9	11	13	13	6	3	7.1	5.9	48.3
	E-test	9	13	10	12	9	4	1	17.9	0	48.3
	Disk diffusion								31	0	53.5

^a See Table 1, footnote a.

^b Calculated as follows: (number of false-susceptible results ÷ number of resistant isolates) × 100.

^c Calculated as follows: (number of false-resistant results ÷ number of susceptible isolates) × 100.

^d Calculated as follows: (number of S to I, I to S, R to I, or I to R results ÷ total number of isolates tested) × 100, where S is susceptible, I is intermediate, and R is resistant.

^e The interpretations of vancomycin susceptibilities by disk diffusion with NCCLS staphylococcal and enterococcal breakpoints are compared.

errors and approximately 50% minor errors with each of these techniques compared with the results obtained by broth microdilution. One major error was also noted.

DISCUSSION

Since the original characterization of *Flavobacterium* species in 1959, several taxonomic modifications and methods for differentiating species within this genus have been proposed. Most recently, ribotyping and DNA hybridization techniques led to the creation of two new genera, *Chryseobacterium* and *Myroides* (26, 27). Some formerly designated *Flavobacterium* species have been placed into the genera *Sphingobacterium*, *Weeksella*, and *Empedobacter* and unnamed Centers for Disease Control and Prevention groups. These organisms do not have the antimicrobial resistance characteristics for which chryseobacteria and *M. odoratum* are notable.

Clinicians from time to time are faced with the challenge of treating opportunistic infections caused by chryseobacteria and other former *Flavobacterium* species. Because infections with *Chryseobacterium* and *Myroides* species are being reported more frequently (4, 10, 13, 14, 17, 23, 25), we thought it was an opportune time to look at new and older antimicrobial agents and their in vitro effectiveness against a number of clinical isolates. The literature provides some contradictory information about drugs which may be used for empirical therapy and about the in vitro susceptibilities of previously isolated strains.

In many reports, susceptibility testing was performed by disk diffusion, which has previously been shown to be inaccurate for these organisms (1, 8, 28). An automated dilution method of susceptibility testing (Vitek) was shown to be less accurate than was disk susceptibility testing (7, 23). Furthermore, early studies frequently tested antibiotics which are not currently considered to be effective against gram-negative bacteria and varied interpretive (disk diffusion) and breakpoint (MIC) criteria were used for assigning isolates to susceptible and resistant categories (1, 2, 22) or those criteria were not listed (11, 20, 21).

Our findings demonstrated poor correlation between disk diffusion and microdilution results when vancomycin was tested and very poor correlation between disk, E-test, or agar dilution results and microdilution results with piperacillin-tazobactam. The reasons for the discrepant results are unclear, but there may be discrepancies because the broth dilution technique does not require the diffusion of drugs through agar.

We also noted the unusual appearance of growth in many of the piperacillin-tazobactam wells, suggesting partial inhibition. This effect may not have been apparent in reading disk, agar diffusion, and E-test results.

The most effective drugs that we tested were minocycline, the newer fluoroquinolones, and rifampin. Twenty percent of isolates showed intermediate susceptibilities to vancomycin, but the remainder were resistant (according to the published criteria of NCCLS for gram-positive organisms). Our MIC results for vancomycin, erythromycin, clindamycin, lincomycin, quinupristin-dalfopristin, and two investigational oxazolidinone agents (linezolid and eperzolid) designed to treat infections caused by gram-positive bacteria do not support previous observations that *C. meningosepticum* is susceptible to antimicrobial agents that have traditionally been reserved for treating infections caused by gram-positive bacteria.

In this study, we did not attempt to correlate our in vitro results with clinical efficacy. In vitro data may not always predict clinical outcome when infections with chryseobacteria are encountered; therefore, MICs may be no more valid than are E-test or disk results in testing these bacteria. However, infections caused by *C. meningosepticum* are often lethal, and broth dilution testing is often considered to be the reference method of choice in the United States for antimicrobial susceptibility testing. Our data indicate that with these organisms, differences may exist between the results determined by broth- and agar-based tests. We cannot determine from our results the source of this discrepancy. Future studies may compare methodologies for those compounds with lower MICs and provide additional clinical reports of in vitro results compared with in vivo efficacy.

Some published reports have documented the successful use of vancomycin to treat patients with infections caused by *C. meningosepticum* (11, 23), and at least one reference recommends vancomycin as the therapy of choice (24). However, George et al. also described several clinical failures when vancomycin was employed (11). Several reports (1, 2, 6, 8, 23) have documented the susceptibility of *C. meningosepticum* isolates to rifampin and its successful use in treating neonatal meningitis caused by this organism (18, 25). In a few cases, ciprofloxacin has been used successfully to treat infections caused by *M. odoratum* and *Chryseobacterium* species. The use of minocycline has previously been reported for only two cases (6), even though multiple studies have documented its activities

against these organisms in vitro (13, 15, 23, 29). Although cephalosporins and other β -lactam antibiotics have occasionally been used to treat infections caused by chryseobacteria, their in vitro activities are poor compared with those of the most effective drugs in our study and earlier studies.

Both *M. odoratum* and *C. meningosepticum* produce a chromosomally mediated noninducible metallo- β -lactamase which is capable of hydrolyzing cephamycins, penicillins, cephalosporins, aztreonam, imipenem, and meropenem (5). Despite their low levels of virulence, these bacteria are resistant to many antimicrobial agents, which may favor nosocomial infections or infections in immunocompromised individuals due to the selection of strains by using broad-spectrum antibiotics. *C. meningosepticum* has previously been documented to acquire resistance during therapy with drugs to which it was originally susceptible in vitro (6, 18). Earlier studies (3, 8, 15, 16) reported higher susceptibilities of chryseobacteria to ciprofloxacin and ofloxacin than have more recent studies (6, 7, 13, 23), suggesting that as fluoroquinolone use has increased, so has selection pressure to develop resistance.

When significant infections with chryseobacteria or *Myroides* strains are encountered, susceptibility testing should be performed by a broth microdilution technique and therapy should be guided by those results.

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