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In Vitro Activity of Minocycline against U.S. Isolates of *Acinetobacter baumannii-Acinetobacter calcoaceticus* Species Complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* Complex: Results from the SENTRY Antimicrobial Surveillance Program, 2014 to 2018

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ABSTRACT We evaluated the activity of minocycline and comparator agents against a large number of *Stenotrophomonas maltophilia* ($n = 1,289$), *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex ($n = 1,081$), and *Burkholderia cepacia* complex ($n = 101$) isolates collected from 2014 to 2018 from 87 U.S. medical centers spanning all 9 census divisions. The isolates were collected primarily from hospitalized patients with pneumonia (1,632 isolates; 66.0% overall), skin and skin structure infections (354 isolates; 14.3% overall), bloodstream infections (266 isolates; 10.8% overall), urinary tract infections (126 isolates; 5.1% overall), intra-abdominal infections (61 isolates; 2.5% overall), and other infections (32 isolates; 1.3% overall). Against the *A. baumannii-A. calcoaceticus* species complex, colistin was the most active agent, exhibiting $MIC_{50/90}$ values at ≤0.5/2 μg/ml and 92.4% susceptibility. Minocycline ranked second in activity, with $MIC_{50/90}$ values at 0.25/8 μg/ml and susceptibility at 85.7%. Activity for these two agents was reduced against extensively drug-resistant and multidrug-resistant isolates of the *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex. Only two agents showed high levels of activity (susceptibility, >90%) against *S. maltophilia*, minocycline ($MIC_{50/90}$, 0.5/2 μg/ml; 99.5% susceptible) and trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/1 μg/ml; 94.6% susceptible). Minocycline was active against 92.8% (MIC_{90}, 4 μg/ml) of trimethoprim-sulfamethoxazole-resistant *S. maltophilia* isolates. Various agents exhibited susceptibility rates of nearly 90% against the *B. cepacia* complex isolates; these were trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/2 μg/ml; 93.1% susceptible), ceftazidime ($MIC_{50/90}$, 2/8 μg/ml; 91.0% susceptible), meropenem ($MIC_{50/90}$, 2/8 μg/ml; 89.1% susceptible), and minocycline ($MIC_{50/90}$, 2/8 μg/ml; 88.1% susceptible). These results indicate that minocycline is among the most active agents for these three problematic potential pathogen groups when tested against U.S. isolates.

KEYWORDS *Acinetobacter*, minocycline, surveillance

Stenotrophomonas maltophilia, the *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex, and the *Burkholderia cepacia* complex are nonfermentative Gram-negative bacteria that are typically resistant to many antimicrobials (1–8). Infections from *S. maltophilia* and the *A. baumannii-A. calcoaceticus* species complex often occur in intensive care units and in immunocompromised patients. These organisms are associated with a variety of infections, but most commonly, bloodstream infections and pneumonia in hospitalized patients (7, 9–11). The multidrug-resistant (MDR; resis-

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TABLE 1 Antimicrobial activity of minocycline tested against the main organisms and organism groups

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (μg/ml) of:									MIC_{50}	MIC_{90}
	≤0.06	0.12	0.25	0.5	1	2	4[a]	8	>[b]		
A. baumannii-A. calcoaceticus complex (1,081)	136	250	170	82	105	119	64	66	89	0.25	8
	12.6	35.7	51.4	59.0	68.7	79.7	85.7	91.8	100.0		
MDR *A. baumannii-A. calcoaceticus* complex (539)	4	21	35	53	98	112	61	66	89	2	>8
	0.7	4.6	11.1	21.0	39.1	59.9	71.2	83.5	100.0		
XDR *A. baumannii-A. calcoaceticus* complex (401)	1	5	12	35	77	89	51	55	76	2	>8
	0.2	1.5	4.5	13.2	32.4	54.6	67.3	81.0	100.0		
S. maltophilia (1,289)	3	72	296	480	265	126	41	3	3	0.5	2
	0.2	5.8	28.8	66.0	86.6	96.4	99.5	99.8	100.0		
S. maltophilia (trimethoprim-sulfamethoxazole resistant, 69)	0	1	7	15	20	15	6	3	2	1	4
	0.0	1.4	11.6	33.3	62.3	84.1	92.8	97.1	100.0		
B. cepacia complex (101)	1	0	1	4	30	43	10	7	5	2	8
	1.0	1.0	2.0	5.9	35.6	78.2	88.1	95.0	100.0		

[a]CLSI M100 (29) susceptible breakpoint indicated by shaded column.
[b]Greater than the highest concentration tested.

tant to three or more classes of agents) nature of these organisms makes them serious treatment challenges (3, 9–12).

MDR *Acinetobacter* pathogens are included in the 2013 CDC list of pathogens posing a serious health risk and the 2017 WHO list of bacteria for which new antibiotics are a critical priority (13, 14). *S. maltophilia* has occurred in numerous hospital outbreaks, increasingly causing ventilator-associated pneumonia (7, 9, 12). *S. maltophilia* was among the 10 most common bacterial pathogens causing pneumonia in hospitalized patients from Europe, China, and the United States (15). The *B. cepacia* complex is a serious problem for cystic fibrosis patients and is increasingly occurring in hospital outbreaks in intensive care settings (5, 16–18).

Tetracycline agents have historically exhibited broad-spectrum antibacterial activity (19, 20). These agents were expanded from the original class representative, tetracycline, to later-generation agents with expanded activity, either oral or intravenous, and with improved safety (19–22). Doxycycline, minocycline, omadacycline, eravacycline, and tigecycline are examples of later-generation tetracyclines (23–27). Of these agents, minocycline has been shown to have the best activity against *S. maltophilia*, the *A. baumannii-A. calcoaceticus* species complex, and the *B. cepacia* complex (28).

The aim of this study was to evaluate the *in vitro* activity of minocycline and comparator agents against a large collection of contemporary U.S. isolates consisting of *S. maltophilia*, the *A. baumannii-A. calcoaceticus* species complex, and the *Burkholderia cepacia* complex. These isolates were collected from 2014 to 2018 from 87 U.S. medical centers spanning all nine census divisions.

RESULTS

A total of 1,081 isolates of the *Acinetobacter baumannii-A. calcoaceticus* species complex, 1,289 isolates of *Stenotrophomonas maltophilia*, and 101 isolates of the *Burkholderia cepacia* complex from the SENTRY Antimicrobial Surveillance Program collection were evaluated, representing 87 medical centers in the 9 U.S. census divisions from 2014 to 2018 (Table 1). The isolates were collected primarily from specimens from pneumonia in hospitalized patients (1,632 isolates; 66.0% overall), skin and skin structure infections (354 isolates; 14.3% overall), bloodstream infections (266 isolates; 10.8% overall), urinary tract infections (126 isolates; 5.1% overall), intra-abdominal infections (61 isolates; 2.5% overall), and other infections (32 isolates; 1.3% overall).

Table 1 shows the MIC distributions for these organisms, including a breakdown of the distributions for MDR and extensively drug resistant (XDR) *A. baumannii-A. cal-*

coaceticus species complex isolates. Susceptibility profiles for minocycline and comparator agents are presented in Table 2.

Activity against the *Acinetobacter baumannii-A. calcoaceticus* species complex. Colistin was the most active agent against the *A. baumannii-A. calcoaceticus* species complex, exhibiting $MIC_{50/90}$ values at ≤0.5/2 μg/ml (Table 2) with 92.4% of isolates susceptible (Table 2). Colistin activity was slightly decreased for MDR and XDR isolates with an MIC_{90} value of 4 μg/ml for each resistance phenotype (Table 2). Minocycline ranked second in activity against all *A. baumannii-A. calcoaceticus* species complex isolates with $MIC_{50/90}$ results at 0.25/8 μg/ml and susceptibility at 85.7% (Table 2). Against MDR and XDR isolates, susceptibility was reduced to 71.2% and 67.3%, respectively, for minocycline (Table 2). Activity for the carbapenems, third- and fourth-generation cephalosporins, and the β-lactam/β-lactamase inhibitor combinations piperacillin-tazobactam and ampicillin-sulbactam ranged from 50.2% to 62.4% for all *A. baumannii-A. calcoaceticus* species complex isolates and was much lower for MDR (7.1% to 25.8% susceptible) and XDR (0.2% to 11.2% susceptible) isolates. Susceptibility for amikacin was at 79.2% for all isolates and at 58.7% and 48.9% for MDR and XDR isolates, respectively (Table 2).

Activity against *Stenotrophomonas maltophilia*. Only seven agents (ticarcillin-clavulanate, ceftazidime, cefidericol, minocycline, levofloxacin, trimethoprim-sulfamethoxazole, and chloramphenicol) have susceptibility interpretive criteria for *Stenotrophomonas maltophilia* in CLSI M100 (2019), four of which (ceftazidime, minocycline, levofloxacin, and trimethoprim-sulfamethoxazole) are included in this study (29). Among the agents not tested, cefiderocol is still in clinical development and has not yet been approved for marketing in the United States, ticarcillin-clavulanate was discontinued by the manufacturer in the United States in 2015, and chloramphenicol has markedly poor activity against this organism. Two of the tested agents showed high levels of activity (susceptibility, >90%). The highest susceptibility rate was minocycline (99.5%) with $MIC_{50/90}$ values at 0.5/2 μg/ml (Table 2). Trimethoprim-sulfamethoxazole activity was 94.6% susceptible with $MIC_{50/90}$ values at ≤0.5/1 μg/ml (Table 2). Levofloxacin (75.8% susceptible) showed moderate activity, and ceftazidime exhibited poor activity (26.8% susceptible; Table 2). Minocycline was active against 92.8% (MIC_{90}, 4 μg/ml) of trimethoprim-sulfamethoxazole-resistant isolates (Tables 1 and 2). The three other agents with published interpretive criteria against this species, ticarcillin-clavulanate, cefiderocol, and chloramphenicol, were not tested.

Activity against *Burkholderia cepacia*. As with *S. maltophilia*, only seven agents (ticarcillin-clavulanate, ceftazidime, meropenem, minocycline, levofloxacin, trimethoprim-sulfamethoxazole, and chloramphenicol) have interpretive criteria for *Burkholderia cepacia* in CLSI M100 (2019), five of which (ceftazidime, levofloxacin, meropenem, minocycline, and trimethoprim-sulfamethoxazole) were tested in the present study (29). A total of 88.1% of isolate MIC values for minocycline were ≤4 μg/ml ($MIC_{50/90}$ at 2/8 μg/ml; 88.1% susceptible; Tables 1 and 2). Other active agents included trimethoprim-sulfamethoxazole (93.1% susceptible), ceftazidime (91.0%), and meropenem (89.1%) (Table 2). Susceptibility to levofloxacin was 71.3% (Table 2). Ticarcillin-clavulanate and chloramphenicol were not tested.

DISCUSSION

The only agent that demonstrated a high level of susceptibility against all three organism groups of *S. maltophilia*, the *A. baumannii-A. calcoaceticus* species complex, and the *B. cepacia* complex was minocycline. Colistin was the most active agent against the *A. baumannii-A. calcoaceticus* species complex (92.4% susceptible, MIC_{90}, 2 μg/ml), and minocycline was the next most active agent (85.7% susceptible, MIC_{90}, 8 μg/ml).

Although we have identified 22 different species of *Acinetobacter* in the course of the SENTRY Program (7), we do not routinely go beyond complex for the *Acinetobacter baumannii-A. calcoaceticus* species complex. In general, *A. baumannii sensu stricto* was less susceptible to the agents tested than the other members of the *Acinetobacter baumannii-A. calcoaceticus* species complex (data not shown).

TABLE 2 Activity of minocycline and comparators when tested against *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* complex isolates from the United States (2014 to 2018)

Organism/organism group (no. of isolates) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	CLSI[a] %S	%I	%R
A. baumannii-A. calcoaceticus complex (1,081)						
Amikacin	4	>32	≤0.25–>32	79.2	2.6	18.2
Ampicillin-sulbactam	4	>32	0.5–32	62.4	12.9	24.7
Cefepime	8	>16	≤0.5–>16	50.8	11.5	37.7
Ceftazidime	8	>32	0.5–>32	56.0	6.2	37.8
Colistin	≤0.5	2	≤0.5–>8	92.4		7.6
Gentamicin	≤1	>8	≤1–>8	64.0	5.1	30.9
Imipenem	0.25	>8	≤0.12–>8	61.5	3.2	35.2
Levofloxacin	0.5	>4	≤0.12–>4	55.2	1.9	42.9
Meropenem	1	>32	0.06–>32	58.8	1.9	39.4
Minocycline	0.25	8	≤0.06–>8	85.7	6.1	8.2
Piperacillin-tazobactam	16	>64	≤0.5–>64	50.2	7.6	42.1
Tetracycline[b]	4	>8	≤0.5–>8	51.8	6.1	42.1
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5–>4	59.6		40.4
MDR *A. baumannii-A. calcoaceticus* complex (539)[c]						
Amikacin	8	>32	0.5–>32	58.7	5.0	36.3
Ampicillin-sulbactam	16	>32	1–>32	25.8	24.9	49.4
Cefepime	>16	>16	2–>16	7.8	18.4	73.8
Ceftazidime	>32	>32	2–>32	16.5	9.8	73.7
Colistin	≤0.5	4	≤0.5–>8	87.9		12.1
Gentamicin	>8	>8	≤1–>8	30.1	9.3	60.7
Imipenem	>8	>8	≤0.12–>8	22.8	6.5	70.7
Levofloxacin	>4	>4	≤0.12–>4	11.3	3.3	85.3
Meropenem	32	>32	0.12–>32	18.0	3.2	78.8
Minocycline	2	>8	≤0.06–>8	71.2	12.2	16.5
Piperacillin-tazobactam	>64	>64	≤0.5–>64	7.1	12.8	80.1
Tetracycline[b]	>8	>8	≤0.25–>8	10.2	8.2	81.6
Trimethoprim-sulfamethoxazole	>4	>4	≤0.5–>4	25.0		75.0
XDR *A. baumannii-A. calcoaceticus* (401)[c]						
Amikacin	32	>32	0.5–>32	48.9	6.0	45.1
Ampicillin-sulbactam	32	>32	2–>32	11.2	28.7	60.1
Cefepime	>16	>16	4–>16	2.5	15.2	82.3
Ceftazidime	>32	>32	2–>32	11.0	8.0	81.0
Colistin	≤0.5	4	≤0.5–>8	86.5		13.5
Gentamicin	>8	>8	≤1–>8	18.0	9.5	72.6
Imipenem	>8	>8	0.25– >8	6.7	5.2	88.0
Levofloxacin	>4	>4	0.5–>4	1.2	3.0	95.8
Meropenem	>32	>32	1–>32	2.5	3.5	94.0
Minocycline	2	>8	0.06–>8	67.3	13.7	19.0
Piperacillin-tazobactam	>64	>64	8–>64	0.2	6.2	93.5
Tetracycline[b]	>8	>8	1–>8	3.4	6.2	90.5
Trimethoprim-sulfamethoxazole	>4	>4	≤0.5–>4	14.2		85.8
S. maltophilia (1,289)						
Amikacin	>32	>32	1–>32			
Ampicillin-sulbactam	>32	>32	2>32			
Cefepime	>16	>16	≤0.5–>16			
Ceftazidime	32	>32	0.5–>32	26.8	9.9	63.3
Colistin	4	>8	≤0.5–>8			
Gentamicin	>8	>8	≤1–>8			
Imipenem	>8	>8	0.5–>8			
Levofloxacin	1	>4	≤0.12–>4	75.8	9.7	14.5
Meropenem	>32	>32	0.03–>32			
Minocycline	0.5	2	≤0.06–>8	99.5	0.2	0.2
Piperacillin-tazobactam	>64	>64	2–>64			
Tetracycline[b]	>8	>8	0.5–>8			
Trimethoprim-sulfamethoxazole	≤0.5	1	≤0.5–>4	94.6		5.4
Trimethoprim-sulfamethoxazole-resistant *S. maltophilia* (69)						
Ceftazidime	>32	>32	1–>32	20.3	4.3	75.4
Levofloxacin	>4	>4	0.5–>4	21.7	15.9	62.3
Minocycline	1	4	0.12–>8	92.8	4.3	2.9

(Continued on following page)

TABLE 2 (Continued)

Organism/organism group (no. of isolates) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	CLSI[a]		
				%S	%I	%R
B. cepacia complex (101)						
Amikacin	>32	>32	≤0.25–>32			
Ampicillin-sulbactam	>32	>32	1–>32			
Cefepime	16	>16	≤0.5–>16			
Ceftazidime	2	8	0.5–>32	91.0	4.0	5.0
Colistin	>8	>8	≤0.5–8			
Gentamicin	>8	>8	≤0.5–>8			
Imipenem	4	>8	≤0.12–>8			
Levofloxacin	2	>4	≤0.12–>4	71.3	9.9	18.8
Meropenem	2	8	0.06–>32	89.1	5.0	5.9
Minocycline	2	8	≤0.06–>8	88.1	6.9	5.0
Piperacillin-tazobactam	4	64	≤0.5–>64			
Tetracycline[b]	>8	>8	2–>8			
Trimethoprim-sulfamethoxazole	≤0.5	2	≤0.5–>4	93.1		6.9

[a]Clinical and Laboratory Standards Institute (2019). S, susceptible; I, intermediate; R, resistant.
[b]Not tested in 2015.
[c]Multidrug-resistant and extensively drug-resistant as described in references 7 and 28.

Colistin showed significant *in vitro* activity; however, concerns exist about its safety and efficacy due to its narrow therapeutic window and the suboptimal and uncertain pharmacokinetics (11, 30). In addition, there are concerns about the development of resistance (11, 30). Colistin has been used in combination treatment; however, optimization of dosing regimens and whether those will prevent the emergence of resistance is still a question (31, 32). In contrast, minocycline has been shown to have few adverse events (AE; primarily central nervous system [dizziness, lightheadedness, and vertigo] and gastrointestinal [nausea and diarrhea]), favorable pharmacokinetic (PK)/pharmacodynamic (PD) profiles (oral and parenteral formulations, dosing flexibility, low protein binding, good tissue distribution, and long half-life), and stability to many tetracycline resistance mechanisms (18–22). Although the combinations of minocycline and several other agents have been studied, there is no consensus as to the optimal combination and its clinical utility (7, 31).

Typically, trimethoprim-sulfamethoxazole is very active against *S. maltophilia* (3, 7, 28). Minocycline has also been shown to be one of the more active agents (3, 7, 28). In our study, minocycline was the most active agent in terms of susceptibility (99.5% susceptible), followed closely by trimethoprim-sulfamethoxazole (94.6%). Due to problems in maintaining a supply of intravenous trimethoprim-sulfamethoxazole, Hand et al. conducted a retrospective chart review and concluded that treatment failure did not differ among patients taking monotherapy with trimethoprim-sulfamethoxazole or minocycline for *S. maltophilia* infections (4).

Agents that might be considered for use in treatment of *B. cepacia* complex infections in the lung include trimethoprim-sulfamethoxazole, meropenem, ciprofloxacin or levofloxacin, minocycline, or chloramphenicol (33). In this study, high levels of susceptibility occurred with trimethoprim-sulfamethoxazole (93.1% susceptible), ceftazidime (91.0% susceptible), meropenem (89.1% susceptible), and minocycline (88.1% susceptible).

More than 20 testable agents have CLSI susceptibility interpretive criteria for the *A. baumannii-A. calcoaceticus* species complex (29). Unfortunately, due to the large number of resistance mechanisms that include efflux pumps, which may provide resistance across multiple classes of antibiotics, the actual number of antimicrobials that might test as susceptible may be very limited. For example, in this study, 37.1% of *A. baumannii-A. calcoaceticus* species complex isolates were an XDR phenotype and 49.9% were an MDR phenotype.

The number of antimicrobial agents that laboratories can test and provide antimicrobial susceptibility category results for *S. maltophilia* or the *B. cepacia* complex is quite limited (29). Notably, two of the testable agents for these organism groups are

chloramphenicol and ticarcillin-clavulanate (discontinued by the manufacturer in the United States in 2015), neither of which represent an optimal choice.

Given the limited number of agents available with robust activity against *S. maltophilia*, the *A. baumannii-A. calcoaceticus* species complex, and the *Burkholderia cepacia* complex, developing new antimicrobials with activity against these organisms, as well as gaining a better understanding of the role and optimization of combinations of agents, is needed. In this study, four agents tested (ceftazidime, levofloxacin, minocycline, and trimethoprim-sulfamethoxazole) have established CLSI interpretive criteria against all *S. maltophilia*, *A. baumannii-A. calcoaceticus* species complex, and *Burkholderia cepacia* species complex isolates. Of the four agents, minocycline exhibited the best overall susceptibility at 99.5%, 85.7%, and 88.1%, respectively.

MATERIALS AND METHODS

Isolate collection. A total of 2,471 isolates were selected from a collection of isolates recovered from documented infections from the nine U.S. census divisions from 2014 to 2018. The isolates chosen consisted of the *A. baumannii-A. calcoaceticus* species complex (for the purpose of this study, isolates identified as *A. baumannii*, *A. calcoaceticus*, *A. nosocomialis*, *A. pittii*, and the *A. baumannii-A. calcoaceticus* complex were collectively designated *A. baumannii-A. calcoaceticus* complex isolates), *S. maltophilia*, and the *B. cepacia* complex. Isolates were from a variety of infection types that included bloodstream, skin and skin structure, pneumonia in hospitalized patients, urinary tract, intra-abdominal, and others. Bacterial species were identified by the submitting laboratories and confirmed by JMI Laboratories using standard microbiology methods and matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing. Broth microdilution methods for antimicrobial susceptibility were performed and interpreted following CLSI guidelines (29). CLSI interpretive criteria for minocycline are as follows: susceptible, $\leq$4 μg/ml; intermediate, 8 μg/ml; resistant, $\geq$16 μg/ml (29). JMI Laboratories produced the frozen-form 96-well panels used to test minocycline and the comparator agents. The testing medium was cation-adjusted Mueller-Hinton broth. Amikacin, ampicillin, cefepime, ceftazidime, gentamicin, imipenem, levofloxacin, meropenem, minocycline, sulbactam, tazobactam, tetracycline, and trimethoprim were obtained from United States Pharmacopeia (North Bethesda, MD, USA). Colistin, piperacillin, and sulfamethoxazole were obtained from Sigma-Aldrich (St. Louis, MO, USA).

Resistance phenotype definitions. The *A. baumannii-A. calcoaceticus* species complex isolates were defined as MDR if organisms were nonsusceptible to three or more drug classes and as XDR if all but two or fewer drug classes had a nonsusceptible drug (7, 28). The drug classes used were extended-spectrum cephalosporins (ceftazidime and cefepime), carbapenems (imipenem and meropenem), antipseudomonal penicillins plus a β-lactamase inhibitor (piperacillin-tazobactam), fluoroquinolones (levofloxacin), aminoglycosides (amikacin and gentamicin), polymyxins (colistin), tetracyclines (tetracycline and minocycline), and penicillins plus β-lactamase inhibitors (ampicillin-sulbactam).

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Ltd., SinSa Labs, Spero Therapeutics, Summit Pharmaceuticals International Corp., Synlogic, T2 Biosystems, Inc., Taisho Pharmaceutical Co., Ltd., TenNor Therapeutics Ltd., Tetraphase Pharmaceuticals, The Medicines Company, Theravance Biopharma, University of Colorado, University of Southern California-San Diego, University of North Texas Health Science Center, VenatoRx Pharmaceuticals, Inc., Vyome Therapeutics, Inc., Wockhardt, Yukon Pharmaceuticals, Inc., Zai Lab, Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

REFERENCES

1. Carroll KC, Pfaller MA, Landry ML, McAdam AJ, Patel R, Richter SS, Warnock DW. 2019. Manual of clinical microbiology, 12th ed ASM Press, Washington, DC.
2. Tewari R, Chopra D, Wazahat R, Dhingra S, Dudeja M. 2018. Antimicrobial susceptibility patterns of an emerging multidrug resistant nosocomial pathogen: *Acinetobacter baumannii*. Malays J Med Sci 25:129–134. https://doi.org/10.21315/mjms2018.25.3.13.
3. Sader HS, Castanheira M, Mendes RE, Flamm RK. 2018. Frequency and antimicrobial susceptibility of Gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015–17). J Antimicrob Chemother 73:3053–3059. https://doi.org/10.1093/jac/dky279.
4. Hand E, Davis H, Kim T, Duhon B. 2016. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. J Antimicrob Chemother 71:1071–1075. https://doi.org/10.1093/jac/dkv456.
5. El Chakhtoura NG, Saade E, Wilson BM, Perez F, Papp-Wallace KM, Bonomo RA. 2017. A 17-year nationwide study of *Burkholderia cepacia* complex bloodstream infections among patients in the United States Veterans Health Administration. Clin Infect Dis 65:1253–1259. https://doi.org/10.1093/cid/cix559.
6. Bhavana MV, Joshi S, Adhikary R, Beena HB. 2017. Antibiotic susceptibility pattern of *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia*: a 5-year analysis. Indian J Med Microbiol 35:318–319.
7. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. 2019. Antimicrobial susceptibility of *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex and *Stenotrophomonas maltophilia* clinical isolates: results from the SENTRY Antimicrobial Surveillance Program (1997–2016). Open Forum Infect Dis 6:S34–S46. https://doi.org/10.1093/ofid/ofy293.
8. Peeters E, Nelis HJ, Coenye T. 2009. *In vitro* activity of ceftazidime, ciprofloxacin, meropenem, minocycline, tobramycin and trimethoprim/sulfamethoxazole against planktonic and sessile *Burkholderia cepacia* complex bacteria. J Antimicrob Chemother 64:801–809. https://doi.org/10.1093/jac/dkp253.
9. Chang YT, Lin CY, Chen YH, Hsueh PR. 2015. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. Front Microbiol 6:893. https://doi.org/10.3389/fmicb.2015.00893.
10. Peleg AY, Seifert H, Paterson DL. 2008. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 21:538–582. https://doi.org/10.1128/CMR.00058-07.
11. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. 2017. Clinical and pathophysiological overview of *Acinetobacter* infections: a century of challenges. Clin Microbiol Rev 30:409–447. https://doi.org/10.1128/CMR.00058-16.
12. Looney WJ, Narita M, Muhlemann K. 2009. *Stenotrophomonas maltophilia:* an emerging opportunist human pathogen. Lancet Infect Dis 9:312–323. https://doi.org/10.1016/S1473-3099(09)70083-0.
13. CDC. 2013. Antibiotic resistance threats in the United States, 2013. http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed May 2019.
14. WHO. 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf. Accessed May 2019.
15. Flamm RK, Nichols WW, Sader HS, Farrell DJ, Jones RN. 2016. *In vitro* activity of ceftazidime/avibactam against Gram-negative pathogens isolated from pneumonia in hospitalised patients, including ventilated patients. Int J Antimicrob Agents 47:235–242. https://doi.org/10.1016/j.ijantimicag.2016.01.004.
16. Holmes A, Nolan R, Taylor R, Finley R, Riley M, Jiang RZ, Steinbach S, Goldstein R. 1999. An epidemic of *Burkholderia cepacia* transmitted between patients with and without cystic fibrosis. J Infect Dis 179:1197–1205. https://doi.org/10.1086/314699.
17. Ramsay KA, Butler CA, Paynter S, Ware RS, Kidd TJ, Wainwright CE, Bell SC. 2013. Factors influencing acquisition of *Burkholderia cepacia* complex organisms in patients with cystic fibrosis. J Clin Microbiol 51:3975–3980. https://doi.org/10.1128/JCM.01360-13.
18. Speert DP, Henry D, Vandamme P, Corey M, Mahenthiralingam E. 2002. Epidemiology of *Burkholderia cepacia* complex in patients with cystic fibrosis, Canada. Emerg Infect Dis 8:181–187. https://doi.org/10.3201/eid0802.010163.
19. Chopra I, Roberts M. 2001. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev 65:232–260. https://doi.org/10.1128/MMBR.65.2.232-260.2001.
20. Grassi GG. 1993. Tetracyclines: extending the atypical spectrum. Int J Antimicrob Agents 3:S31–S46. https://doi.org/10.1016/0924-8579(93)90033-2.
21. Smith K, Leyden JJ. 2005. Safety of doxycycline and minocycline: a systematic review. Clin Ther 27:1329–1342. https://doi.org/10.1016/j.clinthera.2005.09.005.
22. Shapiro LE, Knowles SR, Shear NH. 1997. Comparative safety of tetracycline, minocycline, and doxycycline. Arch Dermatol 133:1224–1230. https://doi.org/10.1001/archderm.1997.03890460044005.
23. Mylan Pharmaceucticals. 2016. Doxycycline package insert. Mylan Pharmaceucticals, Inc., Morgantown, WV.
24. The Medicines Company. 2015. Minocin package insert. The Medicines Company, Parsippany, NJ.
25. Paratek Pharmaceuticals. 2018. NUZYRA (omadacycline) package insert. Paratek Pharmaceuticals, Inc., Boston, MA.
26. Tetraphase Pharmaceuticals. 2018. XERAVA package insert. Tetraphase Pharmaceuticals, Watertown, MA.
27. Amneal Biosciences. 2018. Tigecycline package insert. Amneal Biosciences LLC, Bridgewater, NJ.
28. Flamm RK, Castanheira M, Streit JM, Jones RN. 2016. Minocycline activity tested against *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* species complex isolates from a global surveillance program (2013). Diagn Microbiol Infect Dis 85:352–355. https://doi.org/10.1016/j.diagmicrobio.2016.03.019.
29. CLSI. 2019. M100Ed29. Performance standards for antimicrobial susceptibility testing; 29th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.
30. Lesho E, Yoon EJ, McGann P, Snesrud E, Kwak Y, Milillo M, Onmus-Leone F, Preston L, St Clair K, Nikolich M, Viscount H, Wortmann G, Zapor M, Grillot-Courvalin C, Courvalin P, Clifford R, Waterman PE. 2013. Emergence of colistin-resistance in extremely drug-resistant *Acinetobacter baumannii* containing a novel *pmrCAB* operon during colistin therapy of wound infections. J Infect Dis 208:1142–1151. https://doi.org/10.1093/infdis/jit293.
31. Viehman JA, Nguyen MH, Doi Y. 2014. Treatment options for carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii* infections. Drugs 74:1315–1333. https://doi.org/10.1007/s40265-014-0267-8.
32. Cai Y, Chai D, Wang R, Liang B, Bai N. 2012. Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother 67:1607–1615. https://doi.org/10.1093/jac/dks084.
33. Antimicrobial Therapy, Inc. 2017. The Sanford guide to antimicrobial therapy 2017, 47th ed. Antimicrobial Therapy, Inc., Sperryville, VA.