SUPPLEMENT ARTICLE

Update on *Acinetobacter* Species: Mechanisms of Antimicrobial Resistance and Contemporary In Vitro Activity of Minocycline and Other Treatment Options

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Among *Acinetobacter* species, *A. baumannii* and other closely related species are commonly implicated in nosocomial infections. These organisms are usually multidrug resistant (MDR), and therapeutic options to treat *A. baumannii* infections are very limited. Clinicians have been resorting to older antimicrobial agents to treat infections caused by MDR *A. baumannii*, and some of these agents have documented toxicity and/or are not optimized for the infection type to be treated. Recent clinical experience supported by antimicrobial susceptibility data suggests that minocycline has greater activity than other tetracyclines and glycylcyclines against various MDR pathogens that have limited therapeutic options available, including *Acinetobacter* species. An intravenous formulation of minocycline has recently become available for clinical use, and in contrast to most older tetracyclines, minocycline has high activity against *Acinetobacter* species. In this report, we summarized some of the characteristics of the tetracycline class, and quantified the minocycline activity against contemporary (2007–2011) isolates and its potential therapeutic role against a collection of 5477 *A. baumannii* and other relevant gram-negative organisms when compared directly with tetracycline, doxycycline, and other broad-spectrum antimicrobial agents. *Acinetobacter baumannii* strains were highly resistant to all agents tested, with the exception of minocycline (79.1% susceptible) and colistin (98.8% susceptible). Minocycline (minimum inhibitory concentration that inhibits 50% and 90% of the isolates [$MIC_{50/90}$]: 1/8 μg/mL) displayed greater activity than doxycycline ($MIC_{50/90}$: 2/>8 μg/mL) and tetracycline hydrochloride (HCL) (only 30.2% susceptible) against *A. baumannii* isolates, and was significantly more active than other tetracyclines against *Burkholderia cepacia*, *Escherichia coli*, *Serratia marcescens*, and *Stenotrophomonas maltophilia* isolates. In vitro susceptibility testing using tetracycline HCL as a surrogate for the susceptibility other tetracyclines fails to detect minocycline-susceptible isolates and the potential utility of minocycline for the treatment of many MDR *A. baumannii* infections and other difficult-to-treat species, where there are often limited choices of antimicrobials.

Keywords. *Acinetobacter* spp; minocycline; surrogate testing.

The tetracyclines in the 1940s became the first broad-spectrum antimicrobial class to be described [1]. These compounds were derived from *Streptomyces* species (*S. rimosus* and *S. aureofaciens*), and this class was expanded by semisynthetic processes to include tetracycline hydrochloride (HCL) and the more lipophilic agents doxycycline and minocycline. Their mode of action targeted the bacterial ribosome, resulting in the inhibition of protein synthesis [2]. Tetracycline HCL is considered short-acting, and doxycycline and minocycline are long-acting, each having extended serum half-lives [1, 3, 4]. Long-lasting tetracyclines possess more potent spectrums against some bacterial species, particularly the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), *Staphylococcus aureus*

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Clinical Infectious Diseases® 2014;59(S6):S367–73

DOI: 10.1093/cid/ciu706

(including methicillin-resistant *S. aureus* [MRSA]), and nonfermentative gram-negative bacilli such as *Acinetobacter* species (including multidrug-resistant [MDR] strains) [3, 5].

The tetracycline molecule is formed by 4 linear tetracyclic rings, the hydronaphthacene nucleus, and a carboximide at the position C-2, which are essential to antibacterial activity [1, 3, 6]. In comparison with the tetracycline molecule, minocycline possesses a-dimethylamino in position C-7 and no substituent in position C-6, whereas doxycycline is formed through the removal of a hydroxyl group at C-6 and an addition of a hydroxyl in position C-7 [1, 6]. These alterations increase the molecule lipophilic properties facilitating tissue penetration and improving antibacterial activity [3]. Minocycline is the most lipophilic of all tetracyclines, and this compound has been recognized as the most potent agent in this class, followed by doxycycline [6]. Furthermore, minocycline and doxycycline have the capability to overcome many tetracycline resistance mechanisms [3].

Tetracyclines enter the bacteria through an energy-dependent process [1, 7], using outer membrane protein channels in gram-negative organisms [2]. Once in the cell, these compounds bind to the 30S unit of the ribosome blocking the entry of aminoacyl transfer RNA into the site A of the ribosome, which prevents the incorporation of amino acids into elongation peptide chain. The binding is reversible, and this most likely provides bacteriostatic activity to these compounds [7]. Additionally, interactions with the cytoplasmic membrane enhance the activity of many tetracyclines, including minocycline, providing bactericidal properties to these compounds [1].

Spectrum of Activity and Susceptibility Testing

Tetracyclines exhibit activity against most aerobic and anaerobic gram-positive and -negative organisms, atypical bacteria (including chlamydiae and mycoplasma), rickettsiae, and protozoan parasites [7]. Elevated minimum inhibitory concentration (MIC) values for these agents are observed among *Pseudomonas* species (MIC that inhibits 50% and 90% of the isolates [$MIC_{50/90}$]: 8/32 μg/mL for *P. aeruginosa*) and various aerobic gram-negative organisms, including species of *Proteus*, *Providencia*, *Salmonella*, and *Shigella* (MIC_{50}: ≥8, >8, 2, and 2 μg/mL, respectively) [1].

It was previously stated that all tetracyclines have similar spectrum of activity against all gram-negative organisms [7]; however, differences among the tetracyclines have been documented, and minocycline has been described to be more potent than tetracycline against *Acinetobacter* species [1, 3], *Burkholderia cepacia*, and *Stenotrophomonas maltophilia* [1]. Minocycline is also active against *Nocardia* species, whereas other members of this class have limited activity against this pathogen; similarly, doxycycline can be more active than other tetracyclines against *Neisseria gonorrhoeae* [1, 7].

Guidelines for susceptibility testing of tetracyclines have dated from the earliest years of standardized methods development, with breakpoints appearing in the initial interpretive tables of the Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [8]). More than 3 decades ago, all tetracyclines were interpreted by a MIC breakpoint of ≤4 μg/mL for susceptibility and ≥16 μg/mL for resistance using correlate disk diffusion interpretive criteria with application to all pathogens tested [6]. Today, the published criteria vary widely by the pathogen tested and the published international guidelines utilized, but tetracycline HCL testing has long been recommended as a surrogate to predict susceptibility to other compounds from the same class.

Resistance Mechanisms

The tetracyclines have been used in human and animals, which has consequently resulted in strong selective pressure and emergence of resistant organisms. There are several genes currently known to confer resistance to tetracyclines among gram-negative organisms. The most common tetracycline resistance mechanisms are due to efflux pump– and ribosomal protection–encoding genes [1]. Other and less common resistance mechanisms include chemical molecule modification and target site modifications [3].

There are currently 29 efflux pump–encoding genes that encode resistance to tetracyclines [9]. These genes encode for proteins that belong to the major facilitator superfamily. These proteins are located in the cytoplasmic membrane and decrease the tetracycline intracellular concentration by exchanging a proton for the tetracycline-cation complex [10]. A total of 26 efflux pump–encoding genes have been detected among gram-negative organisms [9]. These encoded proteins are effective in transporting out tetracycline and doxycycline, except for *tet*(B), which also exports the synthetic derivative minocycline [10]. Newer-generation tetracycline molecules, such as tigecycline, were designed to overcome the efflux pump systems or ribosomal protection mechanisms [11]. Six efflux pump–encoding genes have been reported in *Acinetobacter* species, including *tet*(A), *tet*(B), *tet*(G), *tet*(H), *tet*(L), and *tet*(39) [9].

There are currently 12 ribosomal protection proteins described in the microbiology literature [9]. Although these genes possess a G + C content similar to that of gram-positive organisms, they have been detected among both gram-positive and -negative genera. However, *tetB*(P), *otr*(A), and *tet* have been observed among environmental isolates only [9, 12]. These genes encode for cytoplasmic proteins, which prevent tetracycline, doxycycline, and minocycline from binding to the ribosome, causing in vivo and in vitro resistance [2]. These protection proteins interact with the base of h34 protein within the ribosome, causing disruption of the primary tetracycline binding site. Consequently, the tetracycline molecule binding is reduced or released from the ribosome,

which maintains or returns to a conformational state that allows protein synthesis [12].

There are only 3 genes currently associated with the enzymatic inactivation of tetracyclines. These genes are *tet*(X), *tet*(34), and *tet*(37) [9]. These genes encode for cytoplasmic proteins (oxidoreductase) that adds a hydroxyl group to the C-11a position of tetracyclines in the presence of nicotinamide adenine dinucleotide phosphate and oxygen, except for *tet*(34), which is more similar to the xanthine-guanine phosphoribosyl transferase [10, 12]. These proteins modify the first and second generation of tetracyclines, and also recognize tigecycline as a substrate [13]. *tet*(X) has been detected among several species of gram-negative isolates, including clinical isolates of *Acinetobacter* species, *Enterobacter cloacae*, *Comamonas testosteroni*, *Escherichia coli*, *K. pneumoniae*, *Delftia acidovorans*, *Enterobacter* species, and other members of Enterobacteriaceae and Pseudomonadaceae [13, 14]. The *tet*(34) gene has been observed among *Pseudomonas* species, *Serratia* species, and *Vibrio* species [10].

Other mechanisms include *tet*(U) and *otr*(C), which have been detected exclusively in anaerobes. *tet*(U) encodes for a small protein that confers low-level tetracycline resistance [10]. In addition, chromosomal mutations have been rarely associated with tetracycline resistance in *N. gonorrhoeae* [3]. However, more recently, several efflux pump systems belonging to the resistance/nodulation/division family present in Enterobacteriaceae (AcrAB) and *A. baumannii* (AdeABC, AdeIJK, AdeFGH, AbeM, and AdeDE) have been reported to extrude numerous antimicrobial agents, including older tetracyclines and tigecycline when mutations cause overexpression of these systems [14, 15].

Acinetobacter species represent a worldwide challenge for antimicrobial therapy [16], and isolates belonging to the *Acinetobacter calcoaceticus-baumannii* complex (herein named *A. baumannii*), the most clinically relevant group among this genus [3, 17], are often MDR. These organisms have become a more frequent cause of nosocomial infections [16]. This recent increase in difficult-to-treat MDR organisms, including *Acinetobacter* species and carbapenem-resistant Enterobacteriaceae, motivated clinicians to use established but older agents that are often toxic or not recommended for the indication to be treated. In this study, we assessed the contemporary activity of minocycline and other antimicrobial agents against *A. baumannii* and other non-*Pseudomonas* gram-negative pathogens. We queried the large organism resistance surveillance collection of the SENTRY Antimicrobial Surveillance Program (2007–2011) for >5000 *A. baumannii* and other organisms, including 57 493 Enterobacteriaceae, 1706 *S. maltophilia*, and 191 *B. cepacia* isolates.

Contemporary Spectrum Analyses

A total of 64 867 isolates were collected between 2007 and 2011 from medical centers located worldwide (United States, Europe, Latin America, and the Asia-Pacific) and submitted for reference identification and susceptibility testing. Local identifications were confirmed by the monitoring laboratory using biochemical algorithms and Vitek 2 under Good Laboratory Practice/Clinical Laboratory Improvement Amendments–certified conditions (JMI Laboratories, North Liberty, Iowa).

These organisms included *A. baumannii* (5478), *S. maltophilia* (1706 strains), *B. cepacia* (191 strains), and 57 493 Enterobacteriaceae. Among the latter group, the major species groups were *E. coli* (23 977), *Klebsiella* species (14 808), *Enterobacter* species (7441), *Serratia* species (3525), *Proteus mirabilis* (2662), *Citrobacter* species (2001), indole-positive Proteae (1958), and another 1121 isolates representing other species.

These selected gram-negative bacilli were tested for susceptibility to the tetracyclines by reference broth microdilution methods [18]. The validated broth microdilution panels were produced under Good Manufacturing Practices conditions at ThermoFisher Scientific (Cleveland, Ohio). Interpretations of all MIC results applied current CLSI and European Committee on Antimicrobial Susceptibility Testing breakpoints [19, 20]. Quality control (QC) was assured by using CLSI-recommended strains: *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *P. aeruginosa* ATCC 27853. All QC results were observed to be within published QC ranges [19].

Analyses were applied to determine (1) spectrums of activity (percentage susceptible) for each drug according to established CLSI breakpoint criteria, (2) cross-susceptibility accuracy using tetracycline HCL results to predict minocycline (or doxycycline) susceptibility, and (3) cross-susceptibility and -resistance for all categories for the tetracyclines.

RESULTS AND DISCUSSION

Acinetobacter baumannii isolates generally displayed elevated MIC values for most antimicrobial agents tested that are listed in the current CLSI interpretive tables (Table 1) [19]. Minocycline was the second most active (79.1% susceptible) agent, only exceeded by colistin (98.8% susceptibility using current breakpoints of ≤2 μg/mL). All other classes of agents had susceptibility rates of less than 41.9% (tobramycin; Table 1).

A direct comparison of the activity of minocycline with other tetracyclines was performed for *A. baumannii* and selected gram-negative organisms (Table 2). Minocycline potency against *A. baumannii* (MIC_{50}: 1 μg/mL) was 2- and ≥8-fold greater than doxycycline and tetracycline HCL, respectively. Against Enterobacteriaceae, minocycline displayed 2-fold greater potency than doxycycline agents against *E. coli* (MIC_{50}: 1 and 2 μg/mL, respectively; Table 2), but the MIC_{50} activity of these 2 molecules was similar for all other organisms analyzed. As expected, these 2 agents were more potent than tetracycline HCL

Table 1. Minocycline Activity Compared With Selected Comparator Agents Tested Against 5478 *Acinetobacter baumannii* Clinical Isolates (2007–2011)

	MIC, μg/mL		% Susceptible by	
Antimicrobial Agent	50%	90%	CLSI	EUCAST[a]
Minocycline	1	8	79.1[b,c]	. . .
Doxycycline	2	>8	59.6	. . .
Tetracycline HCL	>8	>8	30.2	. . .
Piperacillin/tazobactam	>64/4	>64/4	17.7	. . .
Ampicillin/sulbactam	>16/4	>16/4	25.9	. . .
Cefepime	>16	>16	21.9	. . .
Ceftazidime	>16	>16	20.8	. . .
Ceftriaxone	>8	>8	7.2	. . .
Imipenem	>8	>8	37.4	34.3
Meropenem	>8	>8	36.4	32.8
Amikacin	>32	>32	34.4	31.7
Gentamicin	>8	>8	29.5	29.5
Tobramycin	>16	>16	41.9	41.9
Ciprofloxacin	>4	>4	20.5	20.5
Levofloxacin	>4	>4	21.8	21.0
Trimethoprim/sulfamethoxazole	>2/38	>2/38	28.5	28.5
Colistin	≤0.5	1	98.8[b]	98.8[b]

Interpretations were made using CLSI and EUCAST criteria [19, 20].

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HCL, hydrochloride; MIC, minimum inhibitory concentration.

[a] ". . ." indicates no published breakpoint criteria.

[b] Most active agents are underlined.

[c] A statistically significant greater susceptibility rate for minocycline compared with peer tetracyclines ($P < .05$) was noted (see underline).

against Enterobacteriaceae isolates. For *B. cepacia* and *S. maltophilia*, minocycline potency (MIC_{50}: 2 and 0.5 μg/mL, respectively) was 2- and 4-fold greater than doxycycline and ≥8-fold greater than tetracycline HCL, respectively. At CLSI susceptibility breakpoints, minocycline coverage for *A. baumannii* (79.1% susceptible) was 29.5% more than doxycycline (59.6%), and 58.9% more than tetracycline HCL (Table 2). In contrast, minocycline, doxycycline, and tetracycline have similar rates of susceptibility using CLSI current breakpoints when tested against *Klebsiella* species (73.6%–75.7%), *Enterobacter* species (81.1%–81.4%), and *Citrobacter* species (81.7%–84.8%). However, a significantly wider spectrum/rate of susceptibility was observed for minocycline vs *E. coli* (78.8% vs 57.9%–61.0%), *Serratia* species (77.7% vs 8.6%–52.8%), and Enterobacteriaceae (73.7% vs 60.3%–64.2%) overall (Table 2).

Table 3 compares the differing rates of minocycline susceptibility and potencies across the 4 sampled geographic regions. Across all regions, minocycline was the most active tetracycline against *A. baumannii*, with activity highest in Latin America (MIC_{50}: 0.5 μg/mL; 91.7% susceptible) and lowest against strains isolated in Europe (MIC_{50}: 2 μg/mL; 72.5% susceptible). Minocycline was most active against Enterobacteriaceae in the United States and Europe and only slightly less active against isolates from Latin America and the Asia-Pacific regions (Table 3). Minocycline susceptibility among *S. maltophilia* (≤4 μg/mL) was similar across regions and exceeded 97.0% across all geographic regions. Additionally, for *B. cepacia*, minocycline was most active against US isolates (88.2% susceptible to ≤4 μg/mL).

As recommended in CLSI documents only until recently, tetracycline HCL breakpoints were used to predict minocycline or doxycycline susceptibilities in the 5477 *A. baumannii* isolates. When this analysis was performed in these contemporary isolates (Table 4), only 1654 isolates were susceptible to tetracycline HCL, but 2684 isolates were minocycline susceptible, with an additional 639 strains having an intermediate result (MICs: at 8 μg/mL) for minocycline (11.7%; Table 4). The number of *A. baumannii* strains resistant (MICs: >8 μg/mL) was markedly different among minocycline (500 isolates), tetracycline HCL (3135), and doxycycline (2119).

Acinetobacter species, in particular species belonging to the *A. calcoaceticus-baumannii* complex that includes *A. baumannii*, *A. calcoaceticus*, *A. nosocomialis* (previously *Acinetobacter* genospecies 13TU), and *A. pitti* (previously *Acinetobacter* genospecies 3) [17], are clinically important nosocomial pathogens. These organisms are a common cause of bloodstream infections, hospital-acquired pneumonia, and wound and other surgical site infections, and MDR *A. baumannii* has emerged as one of the most challenging organisms for appropriate antimicrobial therapy [21]. Among antimicrobials tested and considered as candidate regimens for *A. baumannii*, minocycline and colistin were the only 2 agents that had susceptibility rates (per CLSI criteria) exceeding 50% (79.1% and 98.8%, respectively) in this study [19], confirming that very few options are available for therapy. Additionally, against the *A. baumannii* isolates tested, the rank order of potency among tetracyclines was minocycline, followed by doxycycline and tetracycline HCL with the lowest activity (79.1%, 59.6%, and 30.2% susceptible at CLSI current breakpoints, respectively).

Minocycline also displayed good activity against other nonfermentative organisms tested that included *B. cepacia* ($MIC_{50/90}$: 2/8 μg/mL; 83.3% susceptible to ≤4 μg/mL) and *S. maltophilia* ($MIC_{50/90}$: 0.5/2 μg/mL; 98.9% susceptible to ≤4 μg/mL) and certain Enterobacteriaceae species. This tetracycline had markedly greater activity against *E. coli* and *S. marcescens* (ESKAPE pathogens) that might also display MDR phenotypes and challenge available therapeutic options.

More than 99.0% of isolates susceptible to tetracycline HCL were also susceptible to minocycline; however, this long-lasting tetracycline was active at ≤4 μg/mL against an additional 49.0% of *A. baumannii* isolates that were nonsusceptible to

Table 2. Comparative Activity of Minocycline and Other Tetracyclines Tested Against *Acinetobacter baumannii* and Other Gram-Negative Strains From a Worldwide Surveillance Program (2007–2011)

Species (No. Tested) and Antimicrobial Agent	Cumulative % Inhibited at MIC, µg/mL							MIC, µg/mL	
	≤0.12	0.25	0.5	1	2	4[a]	8	50%	90%
Acinetobacter baumannii (5477)[b]									
Minocycline	19.1	29.5	45.9	59.2	64.3	79.1[b,c]	90.9	1	8
Doxycycline	17.7	24.6	38.1	48.4	56.4	59.6[c]	61.3	2	>8
Tetracycline	. . .	0.1	0.8	4.1	20.5	30.2[c]	42.8	>8	>8
Burkholderia cepacia (191)									
Minocycline	2.1	3.1	10.5	31.4	54.2	83.3[c]	92.2	2	8
Doxycycline	2.1	7.3	12.6	21.5	37.7	64.9	81.2	4	>8
Tetracycline	. . .	0.0	1.1	1.8	10.0	15.8	16.8	>8	>8
Stenotrophomonas maltophilia (1706)									
Minocycline	7.6	33.7	67.5	87.3	96.0	98.9[c]	99.9	0.5	2
Doxycycline	0.1	0.8	5.1	31.1	75.5	94.7	98.5	2	4
Tetracycline	. . .	<0.1	<0.1	0.1	0.5	3.1	22.0	>8	>8
Enterobacteriaceae (57 493)									
Minocycline	0.1	1.3	11.5	31.7	58.1	73.7[c]	83.0	2	>8
Doxycycline	0.1	0.4	5.6	30.0	54.8	64.2	73.4	2	>8
Tetracycline	. . .	. . .	. . .	. . .	55.2	60.3	63.8	≤2	>8
Escherichia coli (23 977)									
Minocycline	0.2	2.7	24.8	53.2	70.3	78.8[c]	87.4	1	>8
Doxycycline	<0.1	0.4	8.5	41.2	56.6	61.0	72.0	2	>8
Tetracycline	. . .	. . .	. . .	. . .	56.1	57.9	58.2	≤2	>8
Serratia species (3525)									
Minocycline	0.1	0.1	0.2	3.8	30.9	77.7[c]	94.4	4	>8
Doxycycline	<0.1	0.1	0.2	2.6	19.9	52.8	85.2	4	>8
Tetracycline	. . .	. . .	. . .	. . .	1.2	8.6	34.1	>8	>8
Klebsiella species (14 808)									
Minocycline	0.1	0.3	1.5	21.7	59.9	75.7	84.6	2	>8
Doxycycline	0.1	0.3	7.1	34.3	65.4	73.6	78.9	2	>8
Tetracycline	. . .	. . .	. . .	. . .	65.3	74.4	78.1	≤2	>8
Enterobacter species (7441)									
Minocycline	0.1	0.2	0.9	12.2	54.2	81.4	88.6	2	>8
Doxycycline	0.1	0.1	0.6	12.2	63.2	81.4	87.8	2	>8
Tetracycline	. . .	. . .	. . .	. . .	71.7	81.1	85.2	≤2	>8
Citrobacter species (2001)									
Minocycline	0.1	0.8	12.6	37.5	71.9	84.8	90.5	2	>8
Doxycycline	<0.1	0.1	4.4	30.8	71.4	81.7	87.1	2	>8
Tetracycline	. . .	. . .	. . .	. . .	79.6	84.2	86.8	≤2	>8

Abbreviations: *B. cepacia, Burkholderia cepacia*; HCL, hydrochloride; MIC, minimum inhibitory concentration; *S. maltophilia, Stenotrophomonas maltophilia*.

[a] Clinical and Laboratory Standards Institute breakpoints [19]; no criteria for doxycycline and tetracycline HCL when testing *B. cepacia* and *S. maltophilia*.

[b] All other agents had very low susceptibility rates at ≤41.9% (includes amikacin [34.4% susceptible], cefepime [21.9%], ceftazidime [20.8%], gentamicin [29.5%], imipenem [37.4%], levofloxacin [21.8%], meropenem [36.4%], piperacillin/tazobactam [17.7%], and tobramycin [41.9%], see Table 2; and tigecycline inhibited 80.7% of strains at ≤1 µg/mL).

[c] A statistically significant greater susceptibility rate for minocycline compared to peer tetracyclines ($P < .05$) was noted (see underline).

tetracycline HCL. Tetracycline-resistant and minocycline-susceptible isolates have been considered a common phenotype [21]; thus, minocycline susceptibility should not be determined using a surrogate class representative approach (tetracycline HCL). Minocycline should be tested directly by CLSI reference methods or validated commercial systems using the appropriate interpretive criteria to guide treatment caused by these nonfermentative species, where there are often limited therapeutic choices. This recommendation is also reflected in the current version of CLSI documents (M-100, 2014).

Table 3. Geographic Variations of Minocycline Activity Directed Against *Acinetobacter baumannii* and Other Gram-Negative Organisms From the SENTRY Antimicrobial Surveillance Program (2007–2011)

Organism/ Parameter	Region			
	United States	Europe	Latin America	Asia-Pacific
Acinetobacter baumannii				
(No. tested)	(760)	(1196)	(1498)	(2024)
MIC, μg/mL				
50%	1	2[a]	0.5[b]	2
90%	>8	>8	4	8
% inhibited				
≤2 μg/mL	66.1	57.3	88.2	50.2
≤4 μg/mL[c]	75.1	72.5[a]	91.7[b]	75.3
≤8 μg/mL	89.6	85.3	95.5	91.2
Enterobacteriaceae				
(No. tested)	(18 507)	(20 430)	(7075)	(11 481)
MIC, μg/mL				
50%	2[b]	2	2	4[a]
90%	>8	>8	>8	>8
% inhibited				
≤2 μg/mL	64.6	61.6	52.4	45.1
≤4 μg/mL[c]	78.2[b]	75.6	68.2	66.3[a]
≤8 μg/mL	85.8	84.3	79.0	78.6
Burkholderia cepacia				
(No. tested)	(34)	(29)	(37)	(91)
MIC, μg/mL				
50%	1[b]	2	2[a]	2
90%	8	5	>8	8
% inhibited				
≤2 μg/mL	70.6	65.5	59.5	52.8
≤4 μg/mL[c]	88.2[b]	82.8	78.4[a]	83.5
≤8 μg/mL	94.1	90.0	86.5	94.5
Stenotrophomonas maltophilia				
(No. tested)	(607)	(479)	(183)	(437)
MIC, μg/mL				
50%	0.5	0.5	0.5[b]	0.5[a]
90%	2	2	1	2
% inhibited				
≤2 μg/mL	96.4	97.1	96.7	93.8
≤4 μg/mL[c]	99.5	99.0	100.0[b]	97.7[a]
≤8 μg/mL	100.0	99.8	100.0	99.8

Abbreviation: MIC, minimum inhibitory concentration.

[a] Lowest activity for minocycline by species among the 4 monitored geographic regions.

[b] Minocycline had greatest activity for this species in this region.

[c] Susceptible breakpoint per Clinical and Laboratory Standards Institute criteria [19].

Table 4. Correlations (Accuracy) of Using Tetracycline Minimum Inhibitory Concentration Results to Predict Minocycline or Doxycycline Susceptibility When Testing *Acinetobacter baumannii* (5477 Strains)[a]

Antimicrobial Agent Predicted	MIC, μg/mL	Tetracycline MIC, μg/mL			
		≤2	4	8	>8
Minocycline	>8			3	497
	8		4	1	638
	4		5[b]	0	806[c]
	2	5[b]	6[b]	7[c]	480[c]
	1	10[b]	36[b]	128[c]	339[c]
	≤0.5	1105[b]	483[b]	549[c]	375[c]
Doxycycline	>8	1	4	1	2113
	8		0	4	90
	4		5[b]	2[c]	166[c]
	2	6[b]	3[b]	16[c]	414[c]
	1	9[b]	27[b]	231[c]	298[c]
	≤0.5	1104[b]	495[b]	433[c]	54[c]

Abbreviation: MIC, minimum inhibitory concentration.

[a] Horizontal and vertical lines show the breakpoint concentrations for each agent (≤4 μg/mL = susceptible; >8 μg/mL = resistant) by Clinical and Laboratory Standards Institute criteria [19].

[b] Number of strains having tetracycline MIC values at ≤4 μg/mL (susceptible) and also susceptible to minocycline (99.76% accuracy) or doxycycline (99.70% accuracy).

[c] False nonsusceptible strains for minocycline (2684 occurrences [49.0%]) and doxycycline (1624 occurrences [29.7%]).

In previous studies, minocycline has been reported to be active against 82.0% of *A. baumannii* isolates collected in 2009 worldwide, and in 76.0% of 3103 meropenem-resistant *A. baumannii* isolates [5]. Similar to the data from the SENTRY database, minocycline was recently shown to be highly active against a worldwide collection of >3500 clinical isolates of *Acinetobacter* species. In that study, >80% of isolates were susceptible to ≤4 μg/mL of minocycline; in the subset of 1660 isolates considered to be MDR, 67.9% were susceptible, compared with ≤22.5% for amikacin, levofloxacin, and various β-lactam antibiotics [22].

Despite the favorable in vitro activity, clinical data are limited for treatment of *A. baumannii* infections, but a few studies demonstrate favorable clinical outcomes in therapies that include minocycline. In 2 studies evaluating the use of minocycline for the treatment of ventilator-associated pneumonia caused by MDR *A. baumannii*, cures were achieved for 80.6%–86.0% of the patients receiving minocycline-based treatments [23, 24]. The number of patient cases was limited in both studies, and most isolates were tetracycline HCL susceptible [23, 24]; however, these 2 independent investigations showed that minocycline or doxycycline might be valuable choices for the treatment of this high-mortality infection when other agents are not active or are inappropriate.

Alternative therapeutic options are needed to treat MDR *Acinetobacter* infections and infections caused by other MDR organisms, with minocycline being a valuable option. In view

of limited choices for the treatment of MDR isolates of *Acinetobacter* and other nonfermentative bacilli, an intravenous formulation of minocycline (Minocin IV) has been reintroduced into the US market. Minocycline is among the few antimicrobial agents with Food and Drug Administration approval for the treatment of *Acinetobacter* species infections. These results and other recent publications describe the clinical use of this agent as treatment for a variety of infections due to *Acinetobacter* species, as there is increasing interest in seeking alternatives to polymyxins in patients infected with MDR isolates.

Notes

Financial support. This analysis of SENTRY Program results for 2007–2011 was supported by an educational/research grant from Rempex Pharmaceuticals.

Supplement sponsorship. This article appears as part of the supplement "Minocycline for the Treatment of Multidrug-Resistant *Acinetobacter baumannii*," sponsored by The Medicines Company.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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