C1024 In Vitro Activity of Minocycline Against *Acinetobacter baumannii, Stenotrophomonas maltophilia* and *Burkholderia cepacia* Isolated During 2013 from a Global Surveillance Program

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Abstract

Background

Minocycline (MIN) is a second generation tetracycline (TET) which is one of a few agents approved by the USA-FDA for treatment of *Acinetobacter* infections. In this study, the activity of MIN and comparators was evaluated against *Acinetobacter baumannii-calcoaceticus* species complex (AB), *Stenotrophomonas maltophilia* (SM), and *Burkholderia cepacia* species complex (BC) from patients at medical centers (2013).

Methods

AB, SM, and BC from 171 medical centers in 46 countries were susceptibility (S) tested against MIN and comparator agents. One isolate per infected patient episode was included. Local identifications were confirmed by the monitoring laboratory. S testing followed CLSI methods and quality control guidelines. CLSI and EUCAST interpretations were applied, where available. MDR were classified based on published recommendations using CLSI interpretive criteria (Magiorakos et. al.).

Results

MIN was among the most active agents tested against AB (72.3% S, $MIC_{50/90}$, 2/>8 µg/mL). S to MIN was 18.9, 23.1 and 24.3% greater than doxycycline (DOX) against all AB, MDR and XDR, respectively and 45.2, 54.2 and 55.8% greater than TET. MIN was the most active agent tested against SM (99.1% S, MIC_{90}, 2 µg/mL). After MIN, trimethoprim-sulfamethoxazole (SMX, $MIC_{50/90}$,≤0.5/>4 µg/mL; 89.7% S) and levofloxacin (LEV, 74.0% S; $MIC_{50/90}$,1/>4 µg/mL) were the next most active agents against SM. Against BC, SMX was the most active agent ($MIC_{50/90}$, ≤0.5/2 µg/mL; 100.0% S) followed by MIN (93.3% S, MIC_{90}, 4 µg/mL), ceftazidime (CAZ, 93.1% S; MIC_{90}, 4µg/mL), and meropenem (MEM, 89.7% S; MIC_{90}, 8 µg/mL).

Conclusions

MIN was among the most active agents against AB, and also exhibited a high level of activity for SM and BC. As an FDA-approved agent for treatment of infections due to *Acinetobacter* sp., MIN shows high activity in vitro, including MDR/XDR isolates. Clinical studies in infections due to SM and BC are warranted.

Organism (no. tested)	$MIC_{50/90}$ in µg/mL (% S by CLSI):								
	MIN	DOX	TET	COL	LEV	MEM	CAZ	AMK	SMX
Acinetobacter *baumannii* (1,312)	2/>8 (72.3)	2/>8 (53.4)	>32/>32 (27.1)	1/2 (96.4)	>4/>4 (19.8)	>8/>8 (23.5)	>32/>32 (19.7)	>32/>32 (31.5)	>4/>4 (29.5)
MDR (1070)	4/>8 (66.2)	>8/>8 (43.1)	>32/>32 (12.0)	1/2 (95.9)	>4/>4 (2.2)	>8/>8 (6.4)	>32/>32 (3.0)	>32/>32 (16.3)	>4/>4 (14.1)
XDR (943)	4/>8 (62.9)	>8/>8 (38.6)	>32/>32 (7.1)	1/2 (95.6)	>4/>4 (0.1)	>8/>8 (2.2)	>32/>32 (0.5%)	>32/>32 (12.3)	>4/>4 (9.2)
Burkholderia *cepacia* (30)	2/4 (93.3)	4/8 (--)	>32/>32 (--)	>8/>8 (--)	2/4 (86.2)	2/8 (89.7)-	2/4 (93.1%)	>32/>32 (--)	≤0.5/2 (100.0)
Stenotrophomonas maltophila (464)	0.25/2 (99.1)	2/4 (--)	16/32 (--)	4/>8 (--)	1/>4 (74.0)	>8/>8 (--)	32/>32 (35.2)	>32/>32 (--)	≤0.5/>4 (89.7)

MDR = non-susceptible to ≥1 agent in ≥3 antimicrobial categories; XDR= non-susceptible to ≥1 agent in all but ≤2 antimicrobial classes; --, not available

Introduction

The tetracyclines were one of the early discovered broad-spectrum antimicrobial classes which were found in the 1940s, with activity against Gram-positive and -negative bacteria. Development of enhanced compounds, second- and third-generation semisynthetic compounds, has improved the range of coverage and/or improved oral bioavailability. One of the tetracyclines, minocycline, is among a few agents available which have been FDA-approved for treatment of infections due to *Acinetobacter* spp. The intravenous formulation of minocycline was recently granted status as a Qualified Infectious Disease Product (QIDP) by the US FDA for treatment of infections in patients with cystic fibrosis and chronic granulomatous disease (CGD) due to *Stenotrophomonas maltophilia* and *Burkholderia cepacia.*

Acinetobacter spp. is one of the ESKAPE pathogens for which there are limited treatment choices available. *Acinetobacter spp*. are frequently multidrug-resistant (MDR), so there are very few choices of antimicrobial treatments which are active against this bacterium. The usefulness of carbapenems against these organisms has diminished with the widespread occurrence of carbapenamase-mediated resistance. Polymyxins may be used, although there are questions about appropriate dosing, resistance development and toxicity.

This study evaluated the contemporary activity of minocycline tested against a collection of *A. baumannii* complex (hereafter referred to as *A. baumannii), Stenotrophomonas maltophilia* and *Burkholderia cepacia* species complex from patients at medical centers (2013) in North America, Europe and the Mediterranean region, Latin America and the Asia-Pacific.

Materials and Methods

Organisms: Isolates of *A. baumannii* (1,312), *S. maltophila* (464), and *B. cepacia* spp. complex (30) were selected from 171 medical centers in 46 countries including North America, Europe and the Mediterranean region (EU), Latin America, and the Asia Pacific. Only one isolate per infected patient episode was included and local organism identifications were confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using biochemical methods, the VITEK 2 System (bioMerieux, Hazelwood, Missouri, USA) and MALDI-TOF (Bruker Daltonics, Bellerica, Massachusetts, USA), as necessary.

Susceptibility Testing: Isolates were susceptibility tested using the reference broth microdilution method as described by the Clinical Laboratory and Standards Institute (CLSI). MDR and extensively drug-resistant (XDR) *A. baumannii* were classified as such per recently recommended guidelines (Magiorakos et. a;. 2012), using the following antimicrobial class representative agents and CLSI non-susceptible interpretive criteria for *A. baumannii*: ceftazidime (≥16 µg/mL), meropenem (≥4 µg/mL), piperacillin/tazobactam (≥32/4 µg/mL), levofloxacin (≥4 µg/mL), gentamicin (≥8 µg/mL), colistin (≥4 µg/mL), trimethoprim/sulfamethoxazole (≥4/76 µg/mL) and tetracycline (≥8 µg/mL). Classifications were based on the following recommended parameters: MDR = non-susceptible to ≥ one agent in ≥ three antimicrobial classes; XDR = non-susceptible to all but ≤ two antimicrobial classes.

Results

Acinetobacter baumannii

A total of 81.6% of *A. baumannii* and were MDR (Table 1). The percentages of MDR varied by region from 61.7% in North America to 92.8% in EU (data not shown). XDR ranged from 51.2% in North America to 80.2% in Europe. Colistin was the most active agent tested against all *A. baumannii* with a MIC_{50} value of 2 µg/mL (96.4% susceptible; Table 2). *A. baumannii* susceptibilities to other agents were less than 50% except for minocycline (MIC_{50} value of 2 µg/mL; 72.3% susceptible) and doxycycline (53.4% susceptible). Figure 1 shows the cumulative MIC frequency distributions for all *A. baumannii* for minocycline and a number of comparative agents. Among the MDR *A. baumannii*, colistin was the most active agent exhibiting a MIC_{90} value of 2 µg/mL (95.9% susceptible; Table 2). Minocycline was the next most active agent exhibiting 66.2% susceptibility. Poorer susceptibility was noted with doxycycline (43.1%) and tetracycline (12.0%). Against XDR, colistin was the most active agent (MIC_{90}, 2 µg/mL; 95.6% susceptible; Table 2), followed by minocycline (62.9%) and doxycycline (38.6%). Susceptibility to other agents was less than 30% (Table 2).

Stenotrophomonas maltophilia and *Burkholderia cepacia* complex

There were only three antimicrobials that demonstrated potent activity against *S. maltophilia* (Table 3). Minocycline was the most active agent (MIC_{90}, 2 µg/mL; 99.1% susceptible; Table 3). Doxycycline was slightly less active (MIC_{90}, 4 µg/mL) and trimethoprim-sulfamethoxazole showed a MIC_{90} of 4 µg/mL (89.7-91.7% [CLSI and EUCAST interpretive criteria]; Table 3). Minocycline activity ranged from 98.3% susceptible (Latin America) to 100.0% susceptible (Asia-Pacific) and trimethoprim-sulfamethoxazole susceptibility was 87.2% (Asia-Pacific) to 92.4% (North America; data not shown).

There were only 30 *Burkholderia cepacia* complex isolates evaluated (Table 3). Trimethoprim-sulfamethoxazole was the most active agent (MIC_{90}, 2 µg/mL; 100.0% susceptible; Table 3). Two other antimicrobials exhibited >90% susceptibility rates, and these were ceftazidime (MIC_{90}, 4 µg/mL; 93.1% susceptible) and minocycline (MIC_{90}, 4 µg/mL; 93.3% susceptible; Table 3). Susceptibility to meropenem was 89.7% (MIC_{90}, 8 µg/mL; Table 3).

Table 1. Summary of minocycline activity tested against selected Gram-negative bacteria isolates from global surveillance (2013)

	No. of isolates (cumulative %) inhibited at minocycline MIC (µg/mL) of:										MIC (µg/mL)	
Organism (Number of isolates)	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	> 8	MIC_{50}	MIC_{90}
Acinetobacter baumannii complex (1,312)	6 (0.5)	40 (3.5)	100 (11.1)	109 (19.4)	126 (29.0)	160 (41.2)	109 (49.5)	120 (58.7)	178 (72.3)	199 (87.4)	165 (100.0)	2	> 8
MDR (1,070)	1 (0.1)	4 (0.5)	14 (1.8)	30 (4.6)	98 (13.7)	155 (28.2)	109 (38.4)	119 (49.5)	178 (66.2)	197 (84.6)	165 (100.0)	4	> 8
XDR (943)	--	--	8 (0.8)	12 (2.1)	68 (9.3)	130 (23.1)	100 (33.7)	105 (44.9)	170 (62.9)	191 (83.1)	159 (100.0)	4	> 8
Burkholderia cepacia species complex (30)	--	--	--	--	--	2 (6.7)	9 (36.7)	5 (53.3)	12 (93.3)	2 (100.0)	--	2	4
Stenotrophomonas maltophilia (464)	--	1 (0.2)	4 (1.1)	67 (15.5)	161 (50.2)	116 (75.2)	64 (89.0)	36 (96.8)	11 (99.1)	3 (99.8)	1 (100.0)	0.25	2

Table 2. Activity of minocycline and comparator antimicrobial agents when tested against 1,312 isolates of *Acinetobacter baumannii* (all regions)

Organism/ Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S / %I / %R	EUCAST[a] %S / %I / %R
Acinetobacter baumannii (1,312)				
Minocycline	2	>8	72.3 / 15.1 / 12.6	- / - / -
Doxycycline	2	>8	53.4 / 0.9 / 45.7	- / - / -
Tetracycline	>32	>32	27.1 / 10.8 / 62.1	- / - / -
Piperacillin/tazobactam	>64	>64	16.1 / 3.7 / 80.2	- / - / -
Ceftazidime	>32	>32	19.7 / 2.2 / 78.1	- / - / -
Meropenem	>8	>8	23.5 / 1.3 / 75.2	23.5 / 1.3 / 75.2
Amikacin	>32	>32	31.5 / 4.0 / 64.5	29.5 / 1.9 / 68.6
Gentamicin	>8	>8	25.8 / 6.2 / 68.0	25.8 / 0.0 / 74.2
Tobramycin	>16	>16	43.1 / 1.5 / 55.4	43.1 / 0.0 / 56.9
Levofloxacin	>4	>4	19.8 / 5.3 / 74.9	19.3 / 0.5 / 80.2
Trimethoprim/sulfamethoxazole	>4	>4	29.5 / 0.0 / 70.5	29.5 / 3.1 / 67.4
Colistin	1	2	96.4 / 0.0 / 3.6	96.4 / 0.0 / 3.6
MDR *A. baumannii* (1,070)				
Minocycline	4	>8	66.2 / 18.4 / 15.4	- / - / -
Doxycycline	>8	>8	43.1 / 1.1 / 55.8	- / - / -
Tetracycline	>32	>32	12.0 / 12.6 / 75.4	- / - / -
Piperacillin/tazobactam	>64	>64	0.7 / 2.4 / 96.9	- / - / -
Ceftazidime	>32	>32	3.0 / 1.8 / 95.2	- / - / -
Meropenem	>8	>8	6.4 / 1.7 / 91.9	6.4 / 1.7 / 91.9
Amikacin	>32	>32	16.3 / 4.8 / 78.9	14.2 / 2.1 / 83.7
Gentamicin	>8	>8	10.0 / 7.5 / 82.5	10.0 / 0.0 / 90.0
Tobramycin	>16	>16	30.9 / 1.8 / 67.3	30.9 / 0.0 / 69.1
Levofloxacin	>4	>4	2.2 / 6.3 / 91.5	1.8 / 0.3 / 97.9
Trimethoprim/sulfamethoxazole	>4	>4	14.1 / 0.0 / 85.9	14.1 / 3.6 / 82.3
Colistin	1	2	95.9 / 0.0 / 4.1	95.9 / 0.0 / 4.1
XDR *A. baumannii* (943)				
Minocycline	4	>8	62.9 / 20.2 / 16.9	- / - / -
Doxycycline	>8	>8	38.6 / 1.1 / 60.3	- / - / -
Tetracycline	>32	>32	7.1 / 12.7 / 80.2	- / - / -
Piperacillin/tazobactam	>64	>64	0.0 / 1.3 / 98.7	- / - / -
Ceftazidime	>32	>32	0.5 / 1.4 / 98.1	- / - / -
Meropenem	>8	>8	2.2 / 1.7 / 96.1	2.2 / 1.7 / 96.1
Amikacin	>32	>32	12.3 / 5.1 / 82.6	10.4 / 1.9 / 87.7
Gentamicin	>8	>8	4.4 / 8.1 / 87.5	4.4 / 0.0 / 95.6
Tobramycin	>16	>16	25.8 / 1.7 / 72.5	25.8 / 0.0 / 74.2
Levofloxacin	>4	>4	0.1 / 5.8 / 94.1	0.1 / 0.0 / 99.9
Trimethoprim/sulfamethoxazole	>4	>4	9.2 / 0.0 / 90.8	9.2 / 3.6 / 87.2
Colistin	1	2	95.6 / 0.0 / 4.4	95.6 / 0.0 / 4.4

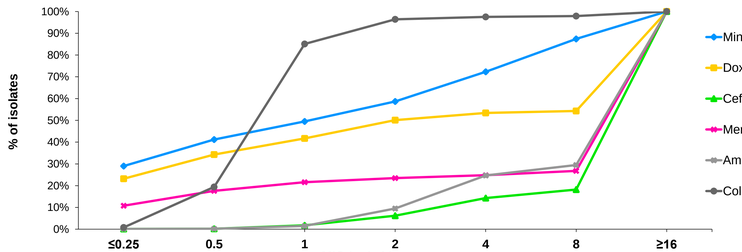
[a] Criteria as published by the CLSI [2015] and EUCAST [2015].

Table 3. Activity of minocycline and comparator agents tested against *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia* (all regions)

Organism/ Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S / %I / %R	EUCAST[a] %S / %I / %R
Burkholderia cepacia species complex (30)				
Minocycline	2	4	93.3 / 6.7 / 0.0	- / - / -
Doxycycline	4	8	- / - / -	- / - / -
Tetracycline	>32	>32	- / - / -	- / - / -
Piperacillin/tazobactam	4	32	- / - / -	- / - / -
Ceftazidime	2	4	93.1 / 6.9 / 0.0	- / - / -
Meropenem	2	8	89.7 / 6.9 / 3.4	- / - / -
Amikacin	>32	>32	- / - / -	- / - / -
Gentamicin	>8	>8	- / - / -	- / - / -
Tobramycin	>16	>16	- / - / -	- / - / -
Levofloxacin	2	4	86.2 / 13.8 / 0.0	- / - / -
Trimethoprim/sulfamethoxazole	≤0.5	2	100.0 / 0.0 / 0.0	- / - / -
Colistin	>8	>8	- / - / -	- / - / -
Stenotrophomonas maltophilia (464)				
Minocycline	0.25	2	99.1 / 0.7 / 0.2	- / - / -
Doxycycline	2	4	- / - / -	- / - / -
Tetracycline	16	32	- / - / -	- / - / -
Piperacillin/tazobactam	>64	>64	- / - / -	- / - / -
Ceftazidime	32	>32	35.2 / 13.3 / 51.5	- / - / -
Meropenem	>8	>8	- / - / -	- / - / -
Amikacin	>32	>32	- / - / -	- / - / -
Gentamicin	>8	>8	- / - / -	- / - / -
Tobramycin	>16	>16	- / - / -	- / - / -
Levofloxacin	1	>4	74.0 / 10.5 / 15.5	- / - / -
Trimethoprim/sulfamethoxazole	≤0.5	4	89.7 / 0.0 / 10.3	91.7 / 0.0 / 8.3
Colistin	4	>8	- / - / -	- / - / -

[a] Criteria as published by the CLSI [2015] and EUCAST [2015], where available.

Figure 1. Cumulative MIC frequency distribution for minocycline and comparator agents against all *A. baumannii*



Conclusions

- Minocycline susceptibility rate against *Acinetobacter baumannii* (81.6% of them MDR) was 72.3%, the second highest after colistin (96.4% susceptible) and significantly higher than doxycycline (53.4%).
- Minocycline was the most potent agent against *S. maltophilia* (99.1% susceptible) closely followed by doxycycline and trimethoprim-sulfamethoxazole.
- Against the small collection of *Burkholderia cepacia* complex isolates (30), minocycline exhibited >93.3% susceptibility rate which was similar to ceftazidime; 100% of these strains were susceptible to trimethoprim-sulfamethoxazole.
- Minocycline, particularly the intravenous formulation, has activity against several ESKAPE pathogens and merits consideration in seriously ill patients where treatment options may be limited due to the presence of MDR and XDR bacteria.

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