

In vitro activity of Tigecycline and Comparators Against Global Isolates of Multidrug Resistant *Acinetobacter* Species (2004 - 2008)

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M. Renteria¹, J. Johnson¹, R. Badal¹, S. Hawser¹, M. Hackel¹, S. Bouchillon¹, B. Johnson¹, D. Hoban¹, M. Dowzicky²

¹International Health Management Associates, Inc., Schaumburg, IL, USA
²Wyeth Pharmaceuticals, Collegeville, PA, USA



IHMA, Inc.
 2122 Palmer Dr.
 Schaumburg, IL
 60173
 Tel: 847.303.5003
 Fax: 847.303.5601

Revised Abstract

Objectives: Tigecycline is a glycolcycline, a new generation of tetracyclines significantly different to be classified as a separate antimicrobial class. Tigecycline is better tolerated and is more active than tetracyclines against wide varieties of Gram-positive and Gram-negative bacteria including *Acinetobacter* spp. The T.E.S.T. program determined the in vitro activity of TIG against *Acinetobacter* resistant to one or more of piperacillin/tazobactam (PT), levofloxacin (LVX), ceftriaxone (CAX), cefepime (CPE), amikacin (AK), minocycline (MIN), ceftazidime (CAZ) and imipenem (IMP). **Methods:** A total of 1,889 clinical isolates of multidrug resistant *Acinetobacter* spp. were identified to species level from participating sites and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines, with tigecycline susceptible breakpoint defined as ≤ 2 $\mu\text{g/ml}$. **Results:** TIG inhibited 95.5% of *Acinetobacter* resistant to 4 or more drug classes (CLSI) and inhibited 377/394 (95.7%) and 71/84 (84.5%) or imipenem- and minocycline-resistant strains, respectively. Resistance rates for comparator drugs against all multidrug resistant *Acinetobacter* were CAX 0%, CAZ 2.6%, LVX 1.5%, CPE 1.7%, PT 0.4%, AK 26.5%, IMP 27%, and MIN 76.3%. Only one strain had an MIC of 8 mcg/ml against TIG. The modal TIG MIC for strains resistant to 4 or more drug classes was 1 $\mu\text{g/ml}$ compared to 0.12 $\mu\text{g/ml}$ for strains with no resistant parameters, indicating an 8-fold diminishment of activity. **Conclusions:** It has been seen in some species that existing multi-drug efflux pumps may also pump TIG. In spite of this, TIG remained effective and inhibited most *Acinetobacter* strains resistant to four or more other drugs in this study, although the higher TIG MICs seen for these strains suggests some linkage to resistance mechanisms for other drugs. TIG remained effective in inhibiting multidrug resistant *Acinetobacter* spp., further broadening its wide spectrum of activity vs. drug-resistant bacteria.

Introduction

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycolcyclines, that are active against multiple antimicrobial resistant mechanisms. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, it has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10^{-9} [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. The MIC₉₀ values for *Pseudomonas* isolates are generally elevated, in the range of 8-16 $\mu\text{g/ml}$ due to synergism between outer membrane impermeability and efflux mechanisms [10]. However, tigecycline has been shown to be active in vitro against multidrug resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections [5].

This study prospectively compared the activity of tigecycline with comparative antimicrobial agents against multiple drug resistant clinical isolates of *Acinetobacter* spp. from global sources.

Materials & Methods

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted. Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory.
- Clinical isolates were collected and tested between January 2004 and September 2008 from 1016 study centers worldwide.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, West Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in $\mu\text{g/ml}$): piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute where applicable [12]. Tigecycline breakpoints against *Acinetobacter* spp have not been determined but are conservatively defined as susceptible ≤ 2 $\mu\text{g/ml}$ in this publication for comparative purposes only.
- Multidrug resistance is defined as the in vitro resistance to 4 or more drug classes.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922.
- The collection, transportation, and confirmation of identification of organisms, as well as construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL).

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Results

Table 1. In vitro activity of tigecycline and comparative agents against 1,889 isolates of multidrug-resistant *Acinetobacter* spp.

Drug	Mode	MIC ($\mu\text{g/ml}$)				%Sus ^a
		MIC ₅₀	MIC ₉₀	Range	Breakpoints	
Tigecycline	1	1	2	≤ 0.008 ->16	≤ 2 - ≥ 8	93.2
Ceftazidime	>32	>32	>32	≤ 8 ->32	≤ 8 - ≥ 32	2.9
Ceftriaxone	>64	>64	>64	16->64	≤ 8 - ≥ 64	0.3
Cefepime	>32	>32	>32	8->32	≤ 8 - ≥ 32	3.7
PipTazo	>128	>128	>128	4->128	≤ 16 - ≥ 128	0.8
Imipenem	>16	>16	>16	0.25->16	≤ 4 - ≥ 16	22.4
Levofloxacin	>8	>8	>8	2->8	≤ 2 - ≥ 8	2.0
Amikacin	>64	64	>64	2->64	≤ 16 - ≥ 64	17.7
Minocycline	≤ 0.5	1	16	≤ 0.5 ->16	≤ 4 - ≥ 16	75.3

^aBreakpoints as defined by CLSI where available (M100-S16), 2008. Breakpoints for tigecycline and *Acinetobacter* spp have not been established. A breakpoint of ≤ 2 $\mu\text{g/ml}$ for Enterobacteriaceae from the US FDA is applied as a conservative measure of tigecycline activity for this species and is presented here for comparative purposes only. Multidrug resistance is defined as in vitro resistance to 4 or more classes of antibiotics.

Table 2. Frequency distribution of tigecycline and comparators against 1,889 isolates of multidrug-resistant *Acinetobacter* spp.

Drug	MIC ($\mu\text{g/ml}$)												
	≤ 0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Tigecycline	24	43	150	483	718	343	108	19		1			
Ceftazidime								54	72	217	1546		
Ceftriaxone	1			1				3	26	49	134	1675	
Cefepime				1			3	66	233	576	1010		
PipTazo	1	1	1	1			3	2	6	9	31	324	1510
Imipenem			2	10	46	43	49	25	126	368			
Levofloxacin	3		2	1	7	25	131	671	1049				
Amikacin				1	4	38	104	94	93	164	409	962	
Minocycline				574	378	245	225	238	179	50			

Figure 1. Comparative in vitro activity of tigecycline and β -lactam antimicrobials against multidrug-resistant *Acinetobacter* spp. (global, n=1,889).

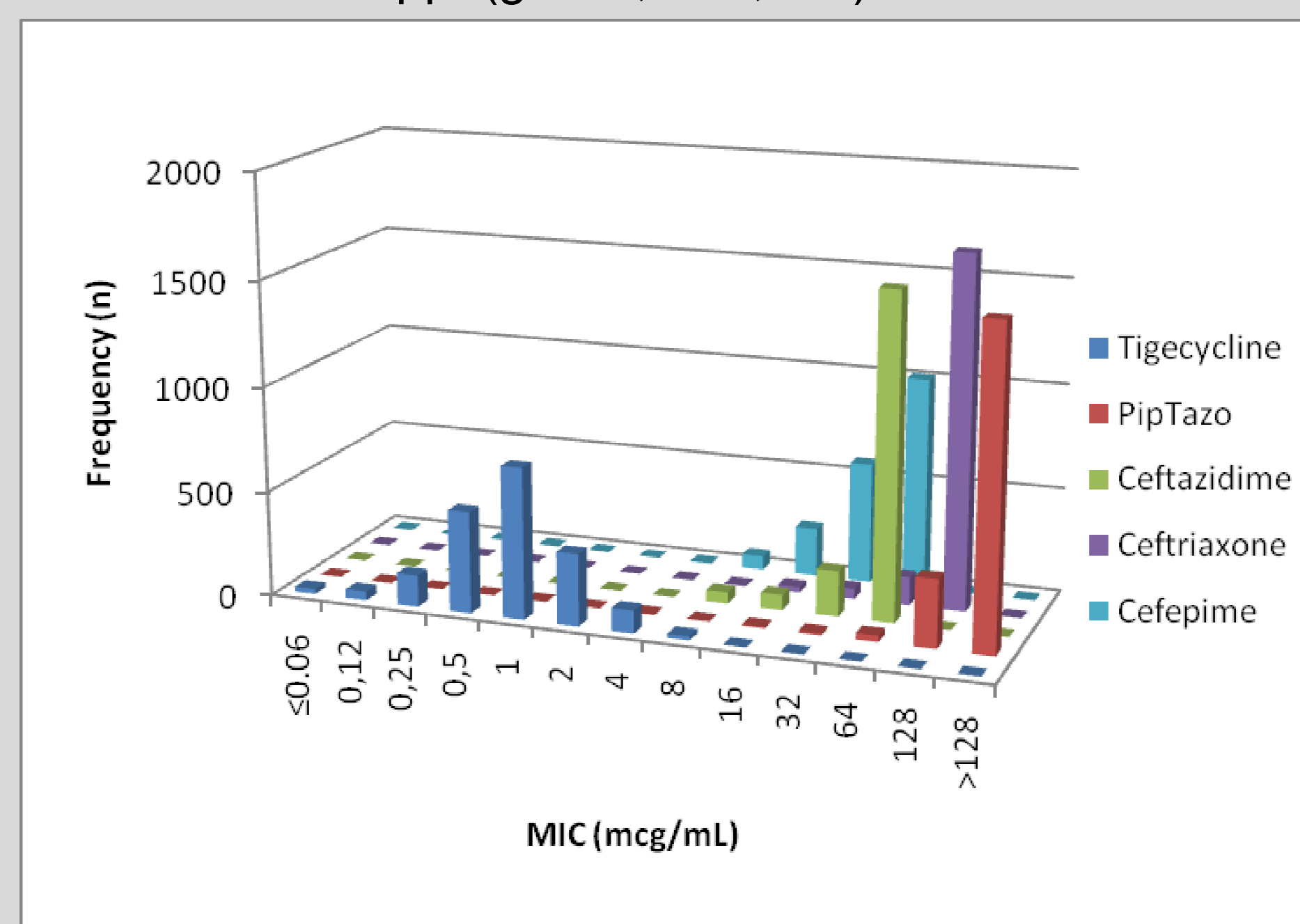
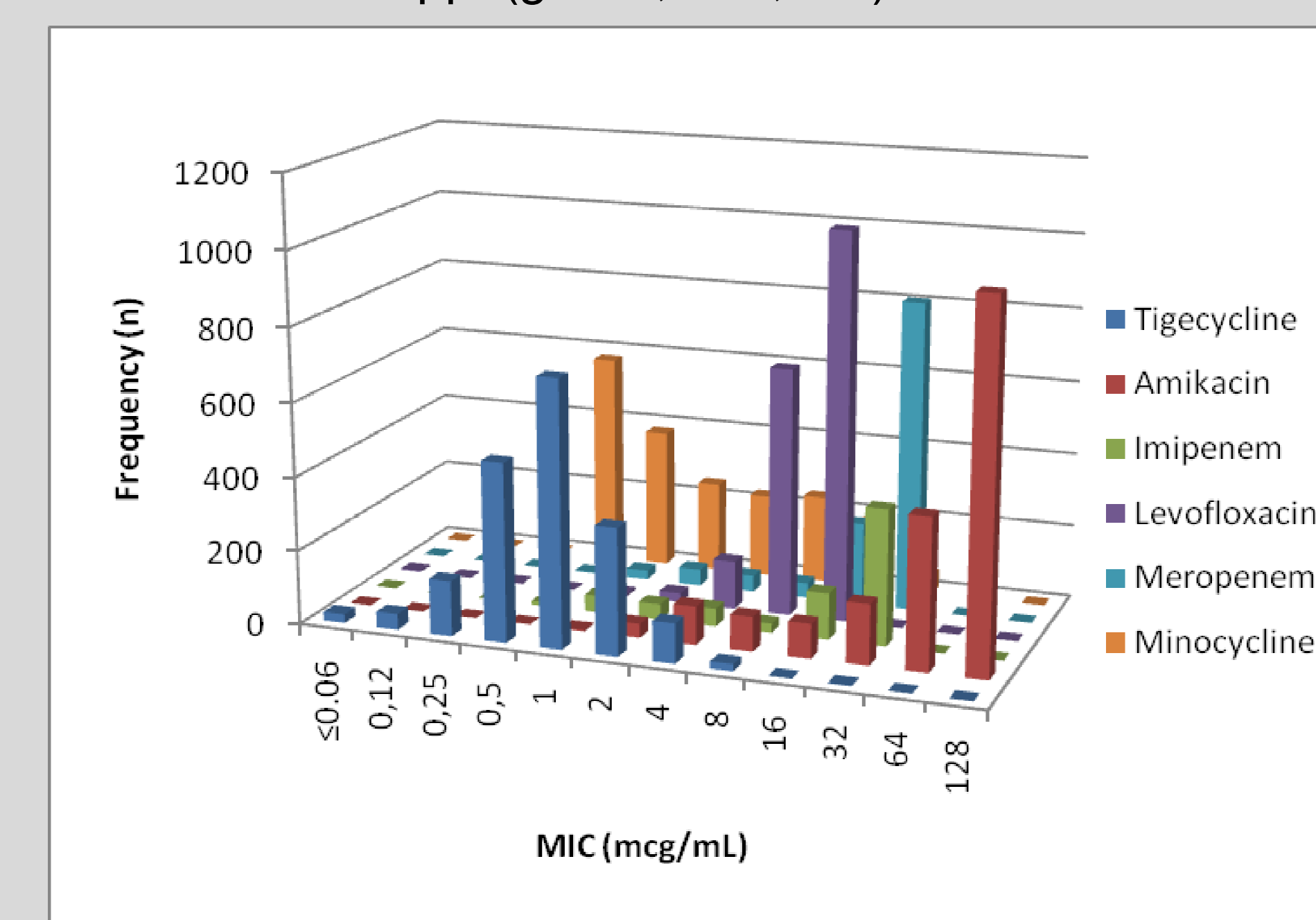


Figure 2. Comparative in vitro activity of tigecycline and other antimicrobials against multidrug-resistant *Acinetobacter* spp. (global, n=1,889).



Conclusions

- Tigecycline inhibited 93.2% of multidrug resistant *Acinetobacter* spp. tested in vitro at an MIC of 2 $\mu\text{g/ml}$.
- Tigecycline's MIC₉₀ of 2 $\mu\text{g/ml}$ against multidrug resistant *Acinetobacter* spp. was the lowest among all the broad spectrum antimicrobials tested.
- All commonly prescribed broad spectrum comparator antimicrobials evaluated in this study had limited activity against multidrug resistant *Acinetobacter* spp. Imipenem, levofloxacin, amikacin and all third and fourth generation cepheims had susceptible percentages less than 25% at their respective breakpoints.
- The in vitro activity of tigecycline in this study suggests that it may be a promising compound for infections caused by difficult to treat multidrug resistant *Acinetobacter* spp.