

Activity of the novel antibiotic RG6006 against *Acinetobacter* spp. and exploration of the susceptibility testing method

Introduction

RG6006 is the first representative of a novel class of tethered macrocyclic peptide antibiotics active against *Acinetobacter* spp., including carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (ABC) organisms. In this study, the susceptibility testing of RG6006 was carried out against a panel of 166 *Acinetobacter* spp. isolates randomly selected (115 *A. baumannii* & 51 non-*A. baumannii*) representing a wide geography and susceptibility profile (62% of which were multi-drug resistant [MDR]) from 2019 collection. The assay was performed under varying conditions to optimize the minimum inhibitory concentration (MIC) reading endpoints.

Methods

MICs were performed using the Clinical Laboratory Standards Institute (CLSI) broth dilution method in cation-adjusted Mueller Hinton broth (CA-MHB) and also in the presence of 20% of human serum (HS) or 20% of horse serum (HoS). The readings were done at 100% and 80% inhibition in CA-MHB and at complete inhibition in the presence of sera (100%).

Results Summary

Summary data are shown in Table 1. For a fraction of isolates (circa 25%), MIC determination of RG6006 was affected by ambiguous readings (not clear endpoint readings: trailing, multiple skipped wells) in CA-MHB. This effect complicated routine susceptibility testing hence the use of reading at 80% of inhibition. In addition, supplementation of serum allowed for accurate MIC determinations though no major variation in MIC distribution between the different conditions. Indeed, RG6006 was active against all *Acinetobacter* spp., with an MIC_{50/90} of 0.12/0.5 mg/L in CA-MHB supplemented with serum and an MIC_{50/90} of 0.12/1 mg/L in CA-MHB when read at 80% inhibition.

Conclusions

RG6006 works as an antibacterial agent with a potent *in vitro* activity against *Acinetobacter* isolates. These data support the continued clinical development of RG6006 for infections caused by *Acinetobacter baumannii-calcoaceticus* complex (ABC) isolates, including difficult to treat carbapenem-resistant isolates. Varying testing conditions such as CA-MHB supplementation with serum improved MIC readings with this novel agent. Further optimization of the MIC method with RG6006 is ongoing.

Acknowledgements

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References

- Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eleventh Edition*. CLSI document M07-Ed11. 2018. CLSI, Wayne, PA.
- Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing – 32nd ed.* CLSI Supplement M100. 2022. CLSI, Wayne, PA.

Results

Figure 1. The Chemical Structure of RG6006, a Tethered Macrocyclic Peptide

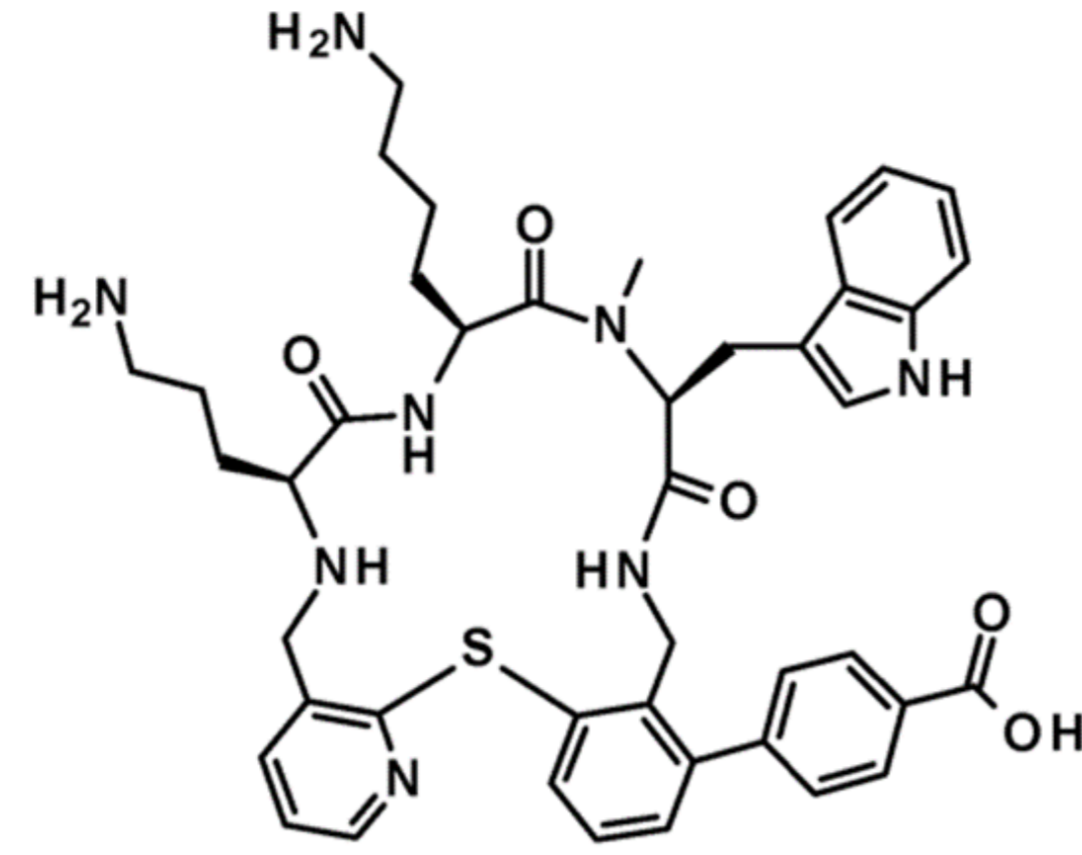
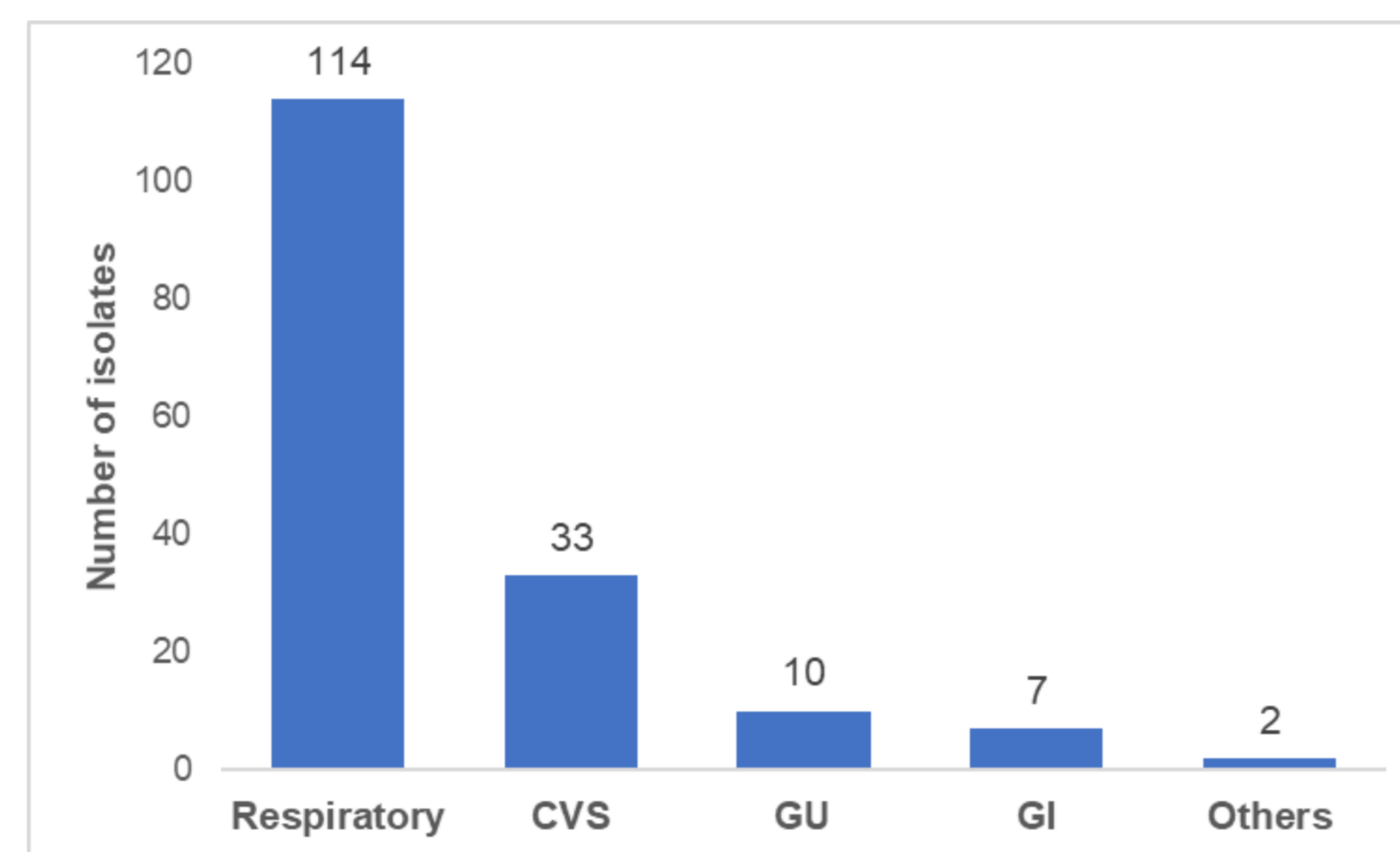


Figure 3. Distribution by Infection Source



CVS, cardio-vascular; GU, genito-urinary; GI, gastro-intestinal

Figure 2. Distribution by Geographical Location

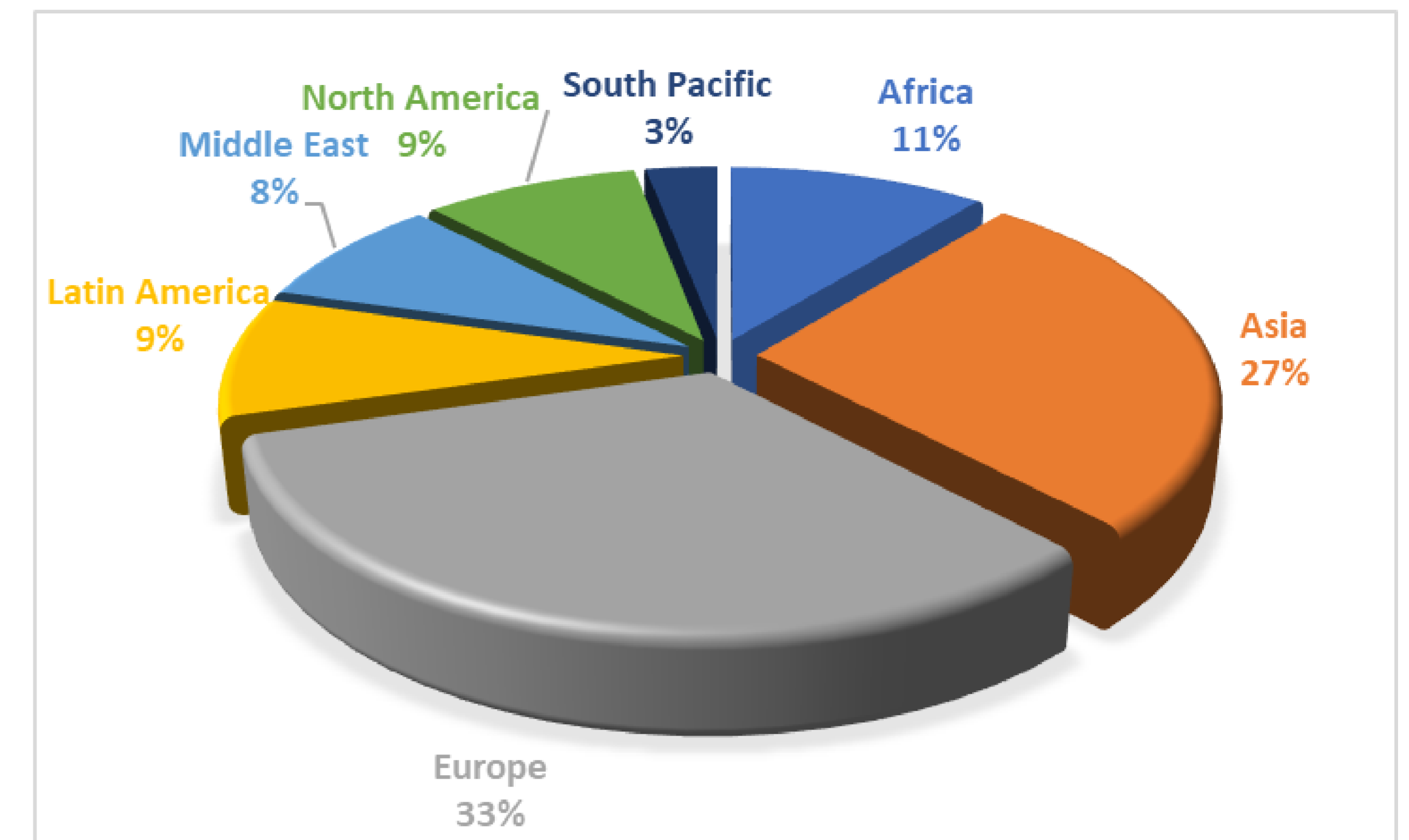


Figure 4. RG6006 MIC Readings Against Clinical Isolates and NCTC Strains

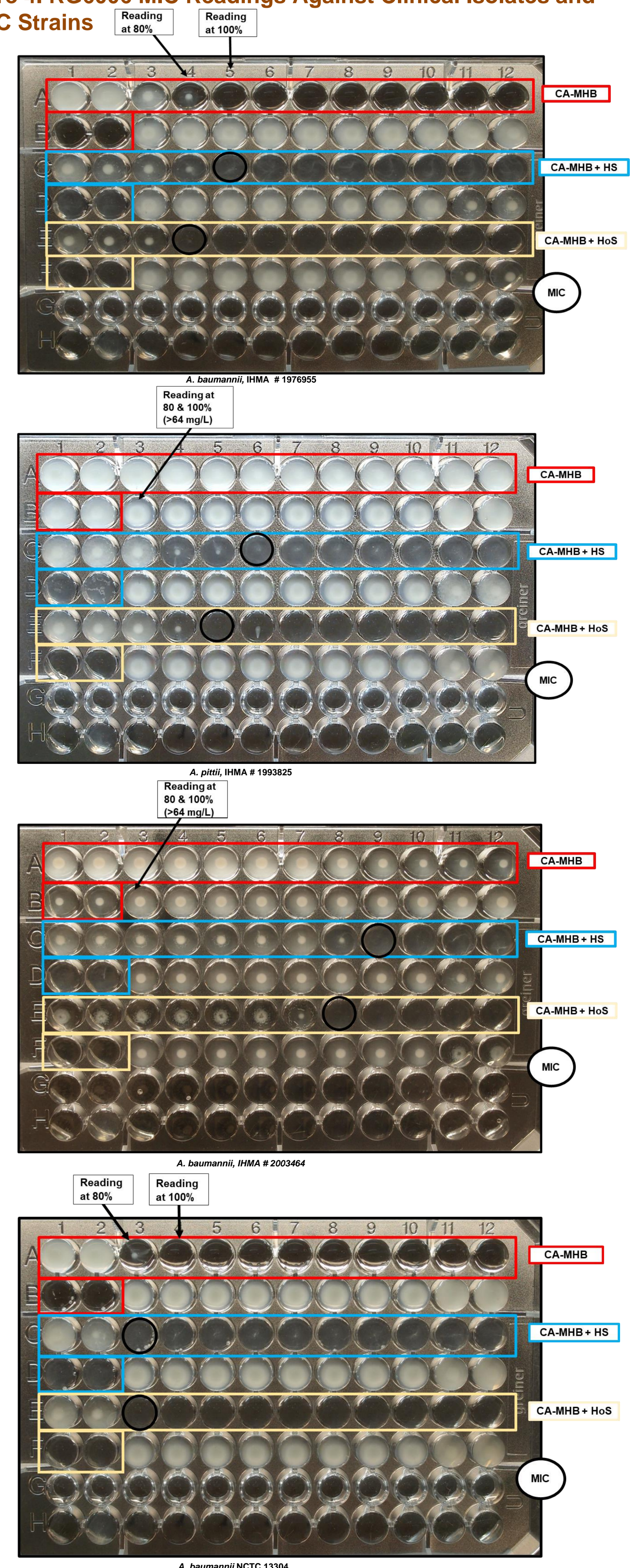


Table 1. Antimicrobial Activity of RG6006 and Meropenem in Various Media Tested Against *Acinetobacter* spp. Isolates

Drug	MIC (mg/L)			
	MIC ₅₀	MIC ₉₀	MIN	MAX
All Isolates (n = 166)				
RG6006 (CA-MHB, read 100%)	>64	>64	0.03	>64
RG6006 (CA-MHB, read 80%)	0.12	1	0.016	>64
RG6006 (CA-MHB+20%HS*)	0.12	0.5	≤0.008	8
RG6006 (CA-MHB+20%HoS*)	0.12	0.5	≤0.008	4
Meropenem	32	>32	0.06	>32
<i>A. baumannii</i> (n = 115)				
RG6006 (CA-MHB, read 100%)	>64	>64	0.03	>64
RG6006 (CA-MHB, read 80%)	0.12	0.25	0.016	>64
RG6006 (CA-MHB+20%HS)	0.12	0.25	≤0.008	8
RG6006 (CA-MHB+20%HoS)	0.12	0.25	0.016	1
Meropenem	>32	>32	0.06	>32
Other <i>Acinetobacter</i> spp. (n = 51)				
RG6006 (CA-MHB, read 100%)	>64	>64	0.03	>64
RG6006 (CA-MHB, read 80%)	0.12	>64	0.03	>64
RG6006 (CA-MHB+20%HS)	0.12	1	0.016	4
RG6006 (CA-MHB+20%HoS)	0.06	1	≤0.008	4
Meropenem	0.25	32	0.06	>32
MDR-<i>Acinetobacter</i> spp. (n = 103)				
RG6006 (CA-MHB, read 100%)	>64	>64	0.06	>64
RG6006 (CA-MHB, read 80%)	0.12	0.5	0.03	>64
RG6006 (CA-MHB+20%HS)	0.12	0.25	≤0.008	8
RG6006 (CA-MHB+20%HoS)	0.12	0.5	0.03	2
Meropenem	>32	>32	1	>32

*HS: human serum; HoS: horse serum