Lack of Ertapenem "MIC Creep" in *Enterobacter cloacae*: Data from SMART 2002-2009

#E-828

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Revised Abstract

Background: The Study for Monitoring Antimicrobial Resistance Trends (SMART) has tracked susceptibility of intra-abdominal infection (IAI) pathogens since 2002. As ertapenem is often used in IAI against a wide range of *Enterobacteriaceae*, monitoring its activity over time is important. This report analyzes ertapenem susceptibility trends of clinical isolates of *E. cloacae* over 8 years for evidence of diminished activity or "MIC creep".
Methods: A total of 3,247 isolates of *E. cloacae* from IAIs were collected from 678 cumulative sites from 44 countries from 2002–2009. Broth microdilution susceptibility testing was done following CLSI and plate manufacturer guidelines. MIC_{50}, MIC_{80}, MIC_{90}, and geometric mean MICs for each year were calculated. Percent susceptibility was determined using CLSI breakpoints.
Results: Data from eight years collection of *E. cloacae* are summarized below:

Year	N	MIC_{50}	MIC_{80}	MIC_{90}	Geo Mean[a]	% S[b]
2002	169	0.06	1	2	0.137	97.0
2003	340	0.06	0.5	1	0.122	95.9
2004	386	0.06	0.5	1	0.111	97.7
2005	329	0.12	0.5	2	0.143	95.1
2006	401	0.12	1	2	0.160	92.0
2007	435	0.12	1	2	0.157	94.9
2008	506	0.06	0.5	1	0.121	98.8
2009	681	0.06	0.5	1	0.127	96.9

[a]Geo Mean: geometric mean MIC; [b]% S/I/R based on CLSI breakpoints.

Conclusions:
Ertapenem exhibited relatively consistent *in vitro* activity against *E. cloacae* from 2002–2009 with a maximum one dilution variation of MIC_{50}, MIC_{80}, MIC_{90}, and geometric mean MICs.
Global susceptibility of *E. cloacae* to ertapenem remained essentially constant from 97% in 2002 to 96.9% in 2009 (*P*>.05).
Overall, these data show that many years after its launch, there has been no "MIC creep" with ertapenem against clinical isolates of *E. cloacae* from IAIs.

Introduction

Ertapenem is indicated for use in the United States for the treatment of several infections (1) that include:

- complicated intra-abdominal infections (IAI)
- complicated skin and skin structure infections
- community-acquired pneumonia
- complicated urinary tract infections, including pyelonephritis
- acute pelvic infections including postpartum endomyometritis, septic abortion, and postsurgical gynecologic infections
- prophylaxis of surgical site infection following elective colorectal surgery

The agent is widely used in clinical practice and the monitoring of susceptibility trends with respect to multiple target pathogens is required. The Study for Monitoring Antimicrobial Resistance Trends (SMART) monitors the susceptibility of GNB from IAI to ertapenem and comparators, and has been ongoing since 2002. The present report investigates the susceptibility trends of ertapenem with respect to *Enterobacter cloacae*, an important nosocomial causative pathogen of complicated IAI, to determine if there has been any significant diminishment of ertapenem activity over the past eight years.

Materials & Methods

Clinical isolates: All isolates were derived from IAI. Only one isolate per species per patient was accepted into the study. *E. cloacae* isolates from each participating hospital were cultured from specimens from IAI body sites (e.g. appendix, peritoneum, colon, bile, pelvis, and pancreas). The majority of IAI specimens were obtained during surgery, though some paracentesis specimens were also accepted. Isolates from blood, urine, and perirectal abscesses were excluded. All isolates were from the period 2002 - 2009 and originated from Africa, Asia/Pacific, Europe, Latin America, Middle East, and North America. Isolates were identified to the species level and tested for antimicrobial susceptibility at each site from 2002-2007, but starting in 2008 were sent to a central laboratory (Laboratories International for Microbiology Studies, a subsidiary of International Health Management Associates, Inc., Schaumburg, Illinois, USA) for confirmation of identification and antimicrobial susceptibility testing. Development of a centralized database of study results was managed by International Health Management Associates, Inc. located in Schaumburg, IL, USA. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of antimicrobic use, age, or gender. Statistical significance was determined by Fisher's Exact Test, two-tailed.

Susceptibility testing: Minimum inhibitory concentrations (MICs) were determined using MicroScan dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA), following the manufacturer's and Clinical and Laboratory Standards Institute (CLSI) guidelines (2). Susceptibility was determined using clinical breakpoints published by the CLSI (3).

References

1. Invanz™ package insert and prescribing information. www.invanz.com.
2. Clinical and Laboratory Standards Institute, Methods for Dilution Antimicrobial *Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition*, in *Document M7-A7*. 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
3. Clinical and Laboratory Standards Institute, *Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement*, in CLSI document M100-S20. 2010: CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.

Acknowledgements

The authors gratefully acknowledge the contributions to this work of all the SMART investigators around the world.

The SMART program is funded by a grant from Merck & Co., Inc.

Results

Table 1. Susceptibility of *E. cloacae* to ertapenem: global susceptibility data.

Year	N	MIC_{50}	MIC_{80}	MIC_{90}	Geo. Mean	% S*	%I	%R
2002	169	0.06	1	2	0.137	97.04	2.37	0.59
2003	340	0.06	0.5	1	0.122	95.88	2.94	1.18
2004	386	0.06	0.5	1	0.111	97.67	1.81	0.52
2005	329	0.12	0.5	2	0.143	95.14	3.34	1.52
2006	401	0.12	1	2	0.160	92.02	4.74	3.24
2007	435	0.12	1	2	0.157	94.94	3.45	1.61
2008	506	0.06	0.5	1	0.121	98.81	0.2	0.99
2009	681	0.06	0.5	1	0.127	96.92	0.73	2.35

*% percent of isolates susceptible (S), intermediate (I) or resistant (R) to ertapenem, based on CLSI M100-S20 (January 2010).

Figure 1. Total number of *E. cloacae* isolates (n=3,247) by geographical region.

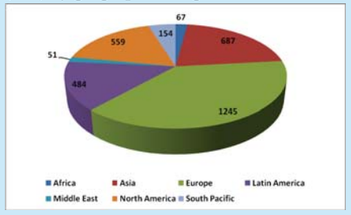


Figure 2. Annual number of *E. cloacae* isolates by geographical region.

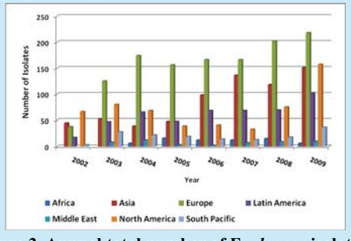


Figure 3. Annual total number of E. *cloacae* isolates.

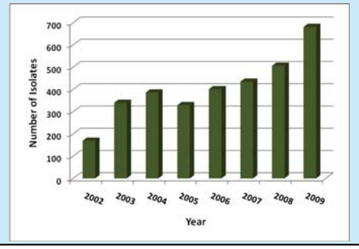
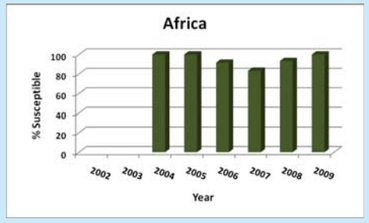
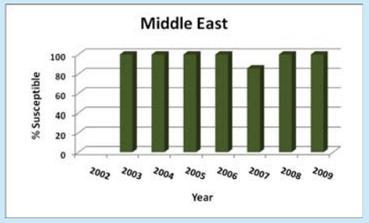
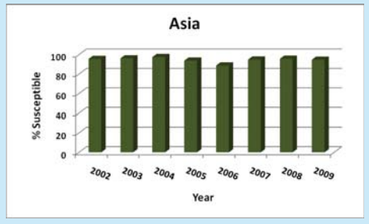
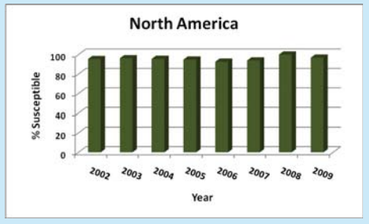


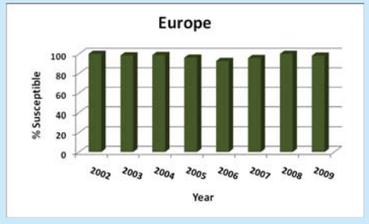
Figure 4. Annual susceptibility of E. *cloacae* to ertapenem: global and regional susceptibility.

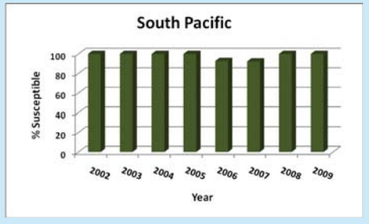


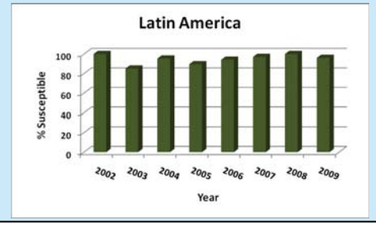












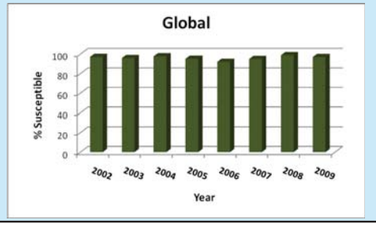
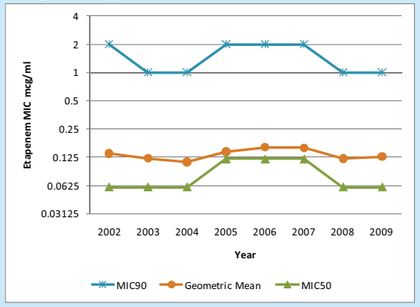


Figure 5. Trends in susceptibility of *E. cloacae* to ertapenem – global data 2002-2009.



Conclusions

- Ertapenem exhibited relatively consistent *in vitro* activity against *E. cloacae* from 2002–2009 with a maximum of +/- one doubling dilution variation of MIC_{50}, MIC_{80}, MIC_{90}, and geometric mean MICs.
- Global susceptibility of *E. cloacae* to ertapenem remained essentially constant from 97% in 2002 to 96.9% in 2009 (p>.05).
- Overall, these data show that many years after its launch, there has been no "MIC creep" of ertapenem against isolates of *E. cloacae* from IAIs.