

Revised Abstract

Background: Multi-drug resistance (MDR) presents an increasing challenge for antimicrobial treatment of infections caused by gram-negative organisms, especially ESKAPE pathogens. MDR rates have been shown to vary widely across global regions seriously limiting therapeutic options in some areas. Using isolates from intra-abdominal infections (IAI) and urinary tract infections (UTI) from the Study for Monitoring Antimicrobial Resistance Trends (SMART), this report assessed antimicrobial susceptibility and MDR of selected species in the Middle East, and placed MDR rates into a regional context by comparing to rates in Eastern Europe (Croatia, Czech Republic, Estonia, Greece, Hungary, Latvia, Lithuania, Romania, Serbia, Slovenia, Turkey) and Western Europe (France, Germany, Italy, Portugal, Spain, United Kingdom).

Materials/Methods: Participating sites collected up to 100 consecutive gram-negative isolates from IAI and 50 from UTI each year 2012-2014. 12 hospitals participated in the Middle East (Georgia [1 site], Israel [3], Jordan [2], Lebanon [2], Saudi Arabia [2]), and the United Arab Emirates [UAE, 2]. Susceptibility was determined using CLSI broth microdilution guidelines and EUCAST interpretive breakpoints. MDR was defined as resistance to at least one drug in three or more of the tested drug classes (aminoglycosides, β -lactam/ β -lactamase inhibitor combinations, cepheems, carbapenems, and quinolones).

Results: Susceptibility to selected agents of the three most common *Enterobacteriaceae* species and two most common non-fermenters from the Middle East are shown below (with values $\geq 90\%$ shaded).

	n	% Susceptible									
		ETP	IPM	FEP	CRO	CAZ	SAM	TZP	CIP	LVX	AMK
<i>E. coli</i>	1663	98.5	99.2	61.0	58.5	60.2	33.8	86.4	53.4	94.6	
<i>K. pneumoniae</i>	633	89.7	92.1	50.1	49.1	48.7	38.9	66.8	53.1	87.2	
<i>E. cloacae</i>	137	86.9	98.5	65.0	51.8	49.6	16.1	71.5	70.1	95.6	
<i>P. aeruginosa</i>	314	NA	75.8	72.0	NA	71.7	NA	72.6	65.9	79.0	
<i>A. baumannii</i>	100	NA	10.0	NA	NA	NA	NA	NA	6.0	13.0	
MDR <i>E. coli</i>	460	95.2	97.8	5.7	2.4	4.6	0.0	67.8	1.1	85.0	
MDR <i>K. pneumoniae</i>	250	75.6	82.4	2.0	1.6	1.6	0.0	32.4	2.8	68.0	
MDR <i>E. cloacae</i>	35	68.6	94.3	14.3	8.6	2.9	0.0	45.7	8.6	85.7	
MDR <i>P. aeruginosa</i>	73	NA	20.6	4.1	NA	11.0	NA	5.5	15.1	38.4	
MDR <i>A. baumannii</i>	69	NA	0.0	NA	NA	NA	NA	NA	0.0	0.0	

ETP, ertapenem; IPM, imipenem; FEP, cefepime; CRO, ceftriaxone; CAZ, ceftazidime; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; CIP, ciprofloxacin; AMK, amikacin; NA, no breakpoint available.

MDR rates for *E. coli* were 27.7% in Middle East compared to 12.1% in Eastern Europe and 8.6% in Western Europe; for *K. pneumoniae* 39.5%, 44.7%, and 23.0%, respectively; for *E. cloacae* 25.5%, 26.2%, and 11.4%; for *P. aeruginosa* 23.2%, 24.3%, and 17.4%; and for *A. baumannii* 69.0%, 64.0, and 59.8%, respectively. The two most common species had large enough sample sizes in all studied Middle East countries to allow comparison of national rates: MDR rates for *E. coli* ranged from 12.1% in Saudi Arabia to 48.7% in UAE and for *K. pneumoniae* from 24.8% in Saudi Arabia to 53.8% in Jordan.

Conclusions:

- In vitro* susceptibility of the studied gram-negative pathogens was low in the Middle East with only the carbapenems and amikacin highly active against the studied *Enterobacteriaceae* and none of the tested agents exceeding 80% susceptibility for the non-fermenters.
- MDR rates varied somewhat across countries but were overall high in the Middle East, not only for the studied ESKAPE pathogens but also for *E. coli*. MDR rates demonstrated an East-West gradient, with MDR rates in the Middle East generally higher or similar to Eastern Europe and much higher than Western Europe.
- Physicians in Western Europe may need to take the high resistance levels in the Middle East into account when making empiric IAI and UTI treatment decision for patients from this region.

Introduction

Multi-drug resistance (MDR) presents an increasing challenge for antimicrobial treatment of infections caused by gram-negative organisms, especially ESKAPE pathogens. MDR rates have been shown to vary widely across global regions seriously limiting therapeutic options in some areas. Using isolates from intra-abdominal infections (IAI) and urinary tract infections (UTI) from the Study for Monitoring Antimicrobial Resistance Trends (SMART), this report assessed antimicrobial susceptibility and MDR of selected species in the Middle East, and placed MDR rates into a regional context by comparing to rates in Eastern Europe (Croatia, Czech Republic, Estonia, Greece, Hungary, Latvia, Lithuania, Romania, Serbia, Slovenia, Turkey) and Western Europe (France, Germany, Italy, Portugal, Spain, United Kingdom).

Materials & Methods

Participating sites collected up to 100 consecutive gram-negative isolates from IAI and 50 from UTI each year 2012-2014. 12 hospitals participated in the Middle East (Georgia [1 site], Israel [3], Jordan [2], Lebanon [2], Saudi Arabia [2]), and the United Arab Emirates [UAE, 2]. Susceptibility was determined using CLSI broth microdilution guidelines and EUCAST interpretive breakpoints [1-3]. MDR was defined as resistance to at least one drug in three or more of the tested drug classes (aminoglycosides, β -lactam/ β -lactamase inhibitor combinations, cepheems, carbapenems, and quinolones). An infection was defined as hospital- or community-associated if the length of stay at time of specimen collection was ≥ 48 hours or < 48 hours post-admission, respectively.

Results

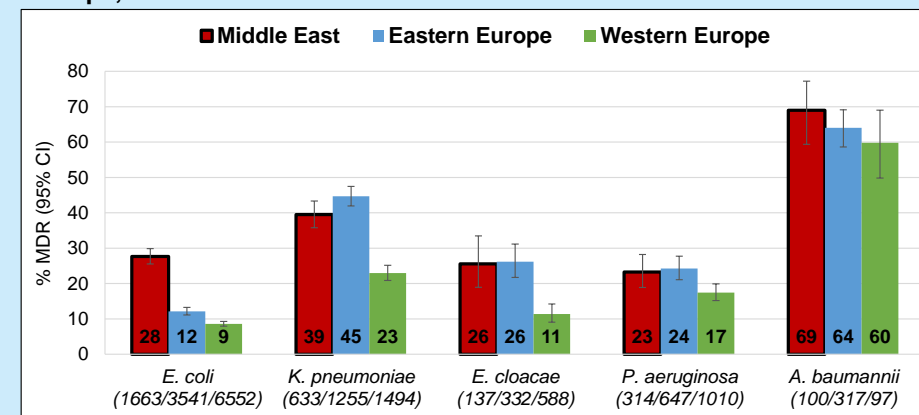
Table 1. Susceptibility to ertapenem and comparators in the Middle East, 2012-2014.

	n	% Susceptible ^a										
		ETP	IPM	FEP	CRO	CTX	CAZ	SAM	TZP	CIP	LVX	AMK
<i>E. coli</i>	1663	98.5	99.2	61.0	58.5	58.6	60.2	33.8	86.4	53.4	94.6	
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<i>E. coli</i> MDR	460	95.2	97.8	5.7	2.4	1.5	4.6	0.0	67.8	1.1	85.0	
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<i>A. baumannii</i> MDR	69	NA	0.0	NA	NA	NA	NA	NA	0.0	0.0	0.0	

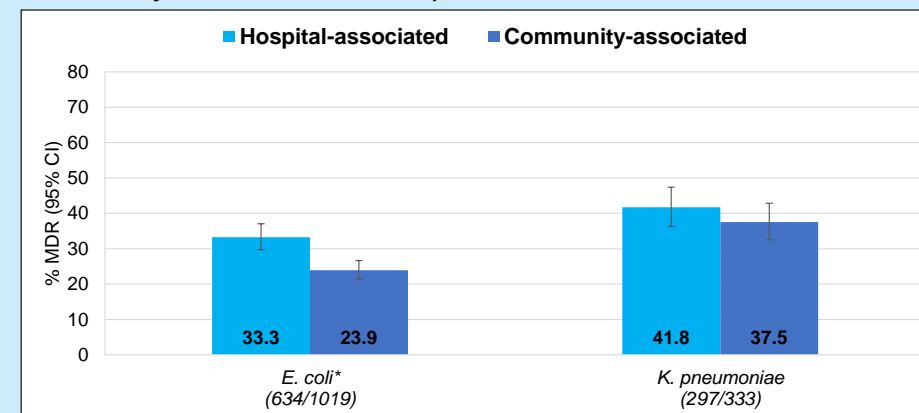
^a Values $\geq 90\%$ are shaded green.

ETP, ertapenem; IPM, imipenem; FEP, cefepime; CRO, ceftriaxone; CTX, cefotaxime; CAZ, ceftazidime; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; MDR, multi-drug resistant; NA, no breakpoint available.

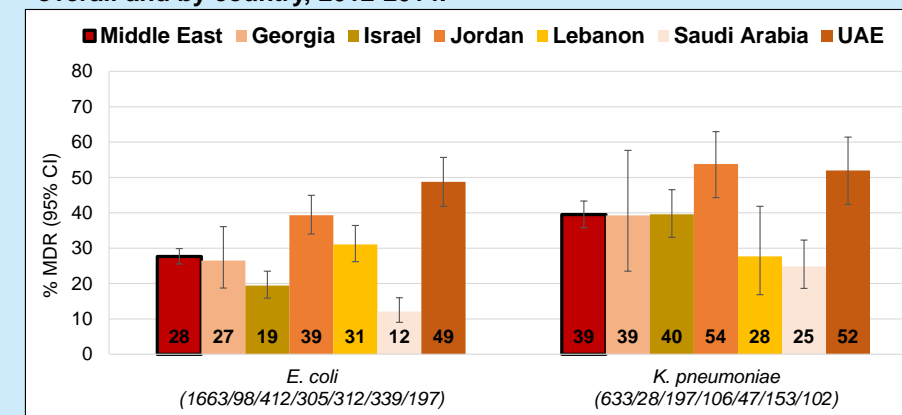
Figure 1. MDR rates in the Middle East compared to Eastern and Western Europe, 2012-2014.



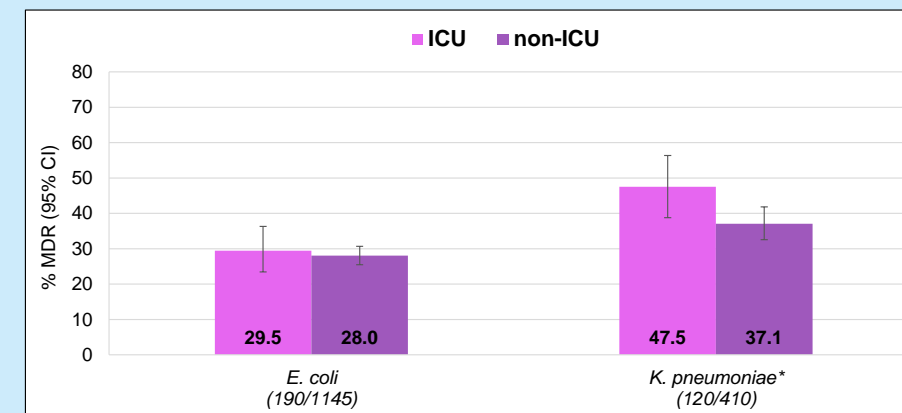
Sample sizes per region are shown in the axis labels.

Figure 3. MDR rates of *E. coli* and *K. pneumoniae* in the Middle East, by length of stay at time of specimen collection (hospital- versus community-associated infections), 2012-2014.

* Statistically significant difference between isolates from hospital- and community-associated infections ($p < 0.05$). Sample sizes for hospital- and community-associated subsets are shown in the axis labels.

Figure 2. MDR rates of *E. coli* and *K. pneumoniae* in the Middle East, overall and by country, 2012-2014.

Sample sizes per country are shown in the axis labels.

Figure 4. MDR rates of *E. coli* and *K. pneumoniae* in the Middle East, by type of ward, 2012-2014.

* Statistically significant difference between isolates from ICU and non-ICU wards ($p < 0.05$). Sample sizes for ICU and non-ICU subsets are shown in the axis labels.

Results Summary

- Susceptibility was low in the Middle East with only the carbapenems and amikacin highly active against the studied *Enterobacteriaceae* and none of the tested agents exceeding 80% susceptibility for the non-fermenters (Table 1).
- MDR rates demonstrated an East-West gradient, with rates in the Middle East generally higher or similar to Eastern Europe and much higher than Western Europe (Figure 1).
- Among Middle East isolates, sample sizes for *E. coli* and *K. pneumoniae* were large enough to allow subset analyses:
 - MDR rates for both species were highest in Jordan and UAE (Figure 2).
 - E. coli* MDR rates were significantly higher in hospital- than community-associated infections (Figure 3).
 - K. pneumoniae* MDR rates were significantly higher in isolates from ICU than non-ICU wards (Figure 4).

Conclusions

- Antimicrobial susceptibility was low and MDR rates were high in the Middle East, not only for the studied ESKAPE pathogens but also for *E. coli*.
- These results suggest that empiric IAI and UTI treatment decisions in the Middle East should take into account national resistance rates, the ward type, and whether the infection was hospital- or community-associated.
- Physicians in Western Europe may need to consider the high resistance levels in the Middle East when making empiric therapy decision for patients who came from this region.

References and Acknowledgments:

- Clinical and Laboratory Standards Institute. 2015. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 10th ed. Approved standards M7-A10. Clinical and Laboratory Standards Institute, Wayne, PA.
- Clinical and Laboratory Standards Institute. 2015. Performance standards for antimicrobial susceptibility testing; twenty-fifth informational supplement. CLSI document M100-S25. Clinical and Laboratory Standards Institute, Wayne, PA.
- European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters, version 5.0, 2015 <http://www.eucastr.org>.

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