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Trends in susceptibility of Enterobacteriaceae to ertapenem in five global regions, SMART 2011-2015

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Background: Antimicrobial resistance among *Enterobacteriaceae* has been increasing, especially due to extended-spectrum β-lactamases (ESBLs), but also as a result of the emergence of carbapenemases which threaten even last-resort agents like ertapenem. Increased resistance, especially among hospital-associated infections, has been seen worldwide but not equally in all regions. This analysis examines trends in susceptibility of ertapenem and comparators against *Enterobacteriaceae* isolates from intra-abdominal infections (IAI) and urinary tract infections (UTI) from 5 global regions collected as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2011 to 2015.

Material/methods: Only countries that participated in SMART in all 5 years were included. 179 hospital laboratories in 47 countries collected 100 consecutive aerobic and facultative gram-negative bacilli from IAI and 50 from UTI for a total of 100,194 isolates. *Enterobacteriaceae* represented 88% of all collected isolates (n=87,817). Susceptibility and ESBL phenotype were determined using CLSI broth microdilution and CLSI breakpoints. An infection was defined as hospital-associated if cultured ≥48 hours post-admission.

Results: The 5 most common *Enterobacteriaceae* species in all regions were *Escherichia coli* (with the proportion among *Enterobacteriaceae* isolates ranging from 51% in North America to 59% in Latin America and Middle East/Africa), *Klebsiella pneumoniae* (15% to 21%), *Enterobacter cloacae* (5% to

7%), *Proteus mirabilis* (4% to 6%), and *K. oxytoca* (2% to 4%). The table below shows the trends in percentage of *Enterobacteriaceae* isolates susceptible to ertapenem:

Region (n per year)	2011	2012	2013	2014	2015
Asia/Pacific (3770|4117|3873|3367|3402)	97.3	97.3	96.5	96.9	96.6*
Europe (5100|5353|5647|5998|6021)	97.1	97.1	96.8	96.9	95.9*
Latin America (3286|3528|3453|3164|3228)	96.3	95.5	94.4	93.5	93.4*
Middle East/Africa (1644|1874|1840|2004|2002)	96.5	96.6	96.4	96.3	96.1
North America (2925|3015|3079|3112|3015)	96.9	97.9	97.4	97.7	97.8

* Statistically significant decrease (Cochran-Armitage test for trend, $p<0.05$).

Ertapenem also maintained excellent activity against the subset of hospital-associated *Enterobacteriaceae* isolates (≥92% susceptible in 2015 in all regions), as well as against >90% of ESBL-positive *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* in all regions except Europe (86% susceptible) and Latin America (89%). Of the comparator agents, only amikacin and imipenem demonstrated activity >90% against *Enterobacteriaceae* in 2015 in all regions, whereas susceptibility to advanced-generation cephalosporins and fluoroquinolones was generally <80%.

Conclusions: Although a statistically significant decreasing trend in susceptibility to ertapenem was seen in three global regions, these decreases were small (between 0.7 and 2.9 percentage points over the 5 study years), and susceptibility of *Enterobacteriaceae* isolates remained ≥93% in 2015 in all studied regions. Ertapenem continues to be an important last-resort agent for the treatment of IAI and UTI in all studied regions, even as ESBLs and other resistance mechanisms limit other therapeutic options.