

# Global Susceptibility Trends and Extended Spectrum Beta-lactamase (ESBL) Rates Among *Proteus mirabilis*: Results of the SMART 2010-2014 Analysis

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## Revised Abstract

**Background:** *P. mirabilis* plays a significant role in both intra-abdominal (IAI) and urinary tract infections (UTI). Treatment options are increasingly limited due to increased resistance among various enteric species. This study focused on resistance patterns associated specifically with *P. mirabilis* and evaluated the *in vitro* activity of ertapenem and comparators against *P. mirabilis*, including ESBL-positive populations. **Methods:** From 2010-2014, 4,849 *P. mirabilis* isolates were obtained from patients with IAI and UTI. The patients were from SMART surveillance program sites distributed globally. MICs were determined by the central reference laboratory using supplied microdilution panels and interpreted according to CLSI guidelines. **Results:** % susceptibility of ertapenem and comparators and ESBL rates are shown in the table below.

	% (IAI, ESBL+, ESBL-)			
	2010	2011	2012	2013
N (all, ESBL+, -)	86152/809	91998/821	1041103/938	1041118/923
% ESBL	6.0	10.7	9.9	11.3
Amikacin	98.3/86.5/99.0	96.9/83.7/98.4	96.5/84.5/97.9	95.7/79.7/97.7
Amp-Sulbactam	73.9/15.4/77.6	70.7/23.5/76.4	70.6/21.4/76.0	71.3/25.4/77.1
Cefepime	94.2/17.3/99.1	83.6/20.4/91.1	88.8/15.5/96.8	88.5/20.3/97.2
Cefoxitin	94.5/8.9/94.9	94.3/8.7/95.1	93.5/8.8/94.0	92.3/8.2/93.6
Ceftriaxone	87.8/9.6/92.8	85.4/18.4/93.4	85.6/8.7/94.0	85.8/18.6/94.4
Ciprofloxacin	73.6/21.2/77.0	70.4/29.6/75.3	70.2/25.2/75.2	71.2/18.6/77.9
Ertapenem	99.9/100/99.9	99.5/99.0/99.5	99.9/99.0/100	99.9/99.2/100
Imipenem*	28.2/34.6/27.8	19.0/19.4/19.0	16.9/14.6/17.2	27.0/20.3/27.8
Levofloxacin	82.9/34.6/86.0	81.4/44.9/85.8	78.9/37.9/83.4	80.6/32.2/86.8
Pip-Tazo	99.0/96.2/99.1	94.6/89.8/95.1	98.3/94.2/98.7	98.9/96.6/99.2

**Conclusion:** Over the 5 year study period ertapenem exhibited consistent (>99% susceptible) activity against both ESBL-positive and -negative *P. mirabilis*. Amikacin and piperacillin-tazobactam were active against ESBL negative isolates, but exhibited diminished activity against ESBL phenotypes. ESBL rates affect antimicrobial activity of many antimicrobials used to treat IAI and UTI where *P. mirabilis* is a causative pathogen.

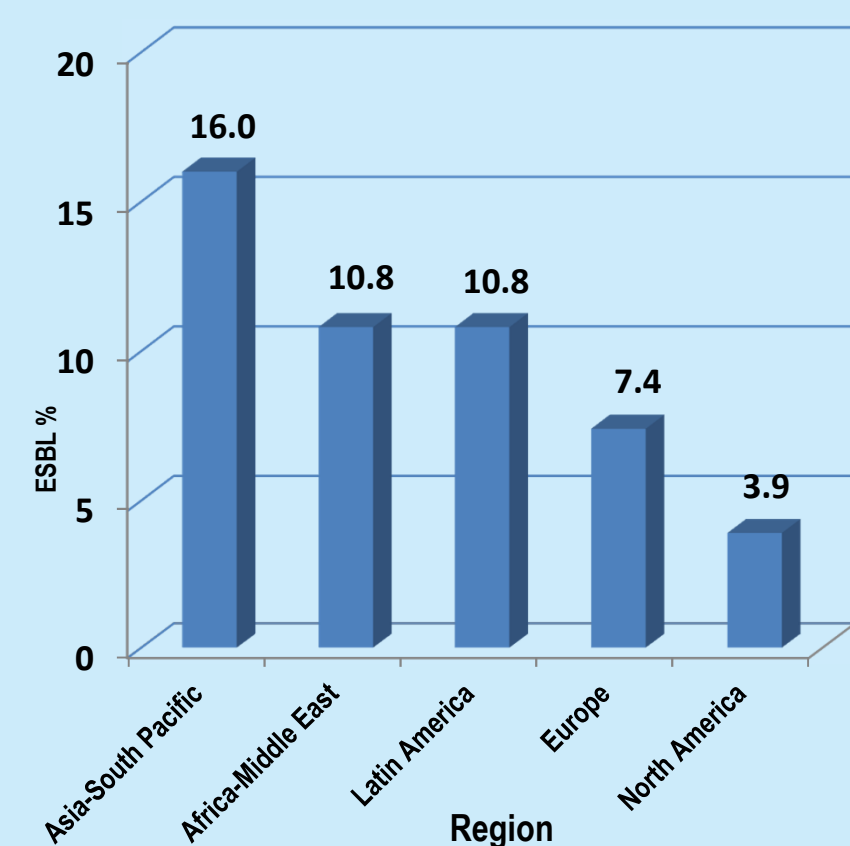
## Introduction

*P. mirabilis* is a significant pathogen causing both intra-abdominal (IAI) and urinary tract infections (UTI). Treatment options are increasingly limited due to increased resistance among various enteric species. This study focused on resistance patterns associated specifically with *P. mirabilis* and evaluated the *in vitro* activity of ertapenem and comparators against *P. mirabilis*, including ESBL-positive populations.

## Materials & Methods

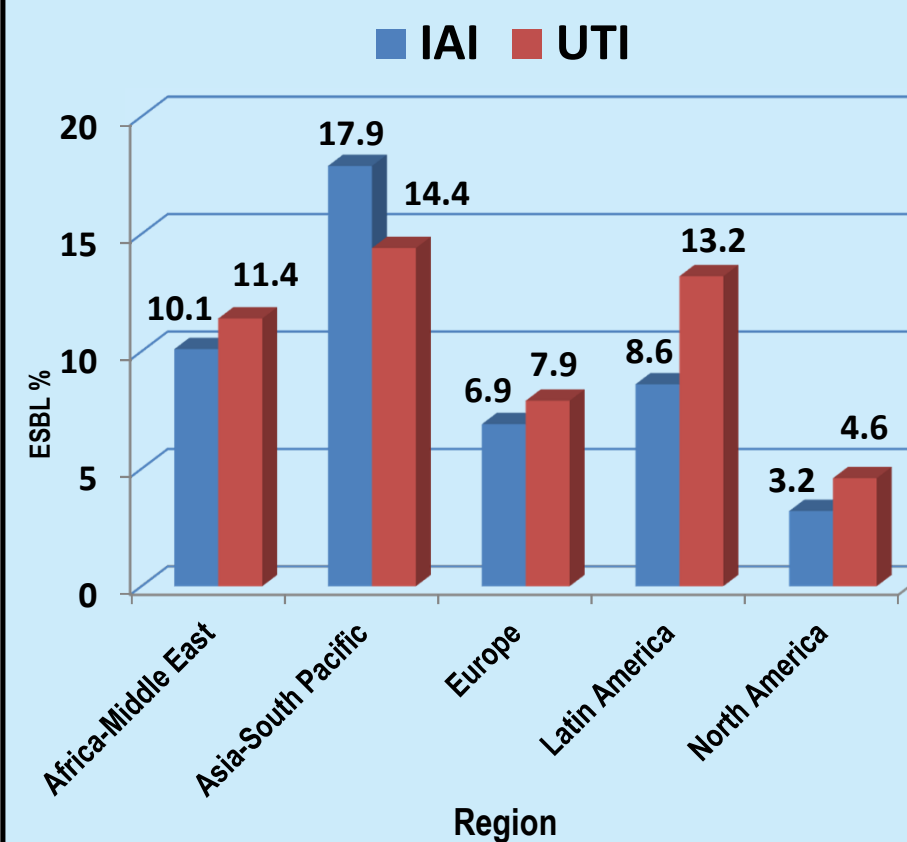
- From 2010 to 2014 a total of 4,849 *P. mirabilis* isolates were obtained from patients with IAI and UTI. The single patient isolates were sent to the central reference laboratory (IHMA, Inc., Schaumburg, IL) where the identification was confirmed and susceptibility testing, using broth microdilution according to CLSI guidelines, was conducted (1).
- Patient isolates were collected from the SMART surveillance program sites distributed globally. MIC values were determined at the central reference laboratory (IHMA, Inc.) using supplied microdilution panels and interpreted according to CLSI guidelines.
- ESBL phenotypes were determined using CLSI definitions and interpretive criteria (1,2).

**Figure 1. Regional ESBL Percentages Among *P. mirabilis* Collected from IAI and UTI (2010-2014).\***



\* Number of isolates in each region: Asia-South Pacific (1,071), Africa-Middle East (418), Latin America (851), Europe (1,668), North America (841).

**Figure 2. Regional ESBL Percentages Observed Among *P. mirabilis* According to Specimen Source (2010-2014).\***



\* Number of isolates in each region (IAI/UTI): Asia-South Pacific (846/585), Africa-Middle East (199/219), Latin America (443/408), Europe (897/771), North America (408/433).

## Results

**Table 1. MIC Values and Susceptibility Percentages for Antimicrobial Agents Against 2,213 ESBL-Negative *P. mirabilis* Causing IAI From Five Regions.**

Region (n)	Drug	% Susceptible	% Resistant	MIC <sub>50</sub>
Africa-Middle East (179)	Amikacin	97.8	2.2	8
	Ampicillin-sulbactam	68.2	21.2	> 16
	Cefepime	100	0.0	≤ 0.5
	Cefoxitin	93.9	1.1	8
	Ceftriaxone	91.1	6.2	≤ 1
	Ciprofloxacin	77.7	19.0	> 2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	21.8	20.1	4
	Levofloxacin	83.2	10.6	> 4
	Piperacillin-tazobactam	100	0.0	≤ 2
Asia-South Pacific (399)	Amikacin	99.8	0.0	8
	Ampicillin-sulbactam	81.0	9.5	16
	Cefepime	98.5	0.5	≤ 0.5
	Cefoxitin	97.5	1.0	8
	Ceftriaxone	95.0	3.3	≤ 1
	Ciprofloxacin	79.7	13.8	> 2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	21.8	32.1	4
	Levofloxacin	90.2	5.5	2
	Piperacillin-tazobactam	98.8	0.5	≤ 2
Europe (835)	Amikacin	98.1	1.8	8
	Ampicillin-sulbactam	75.9	15.9	> 16
	Cefepime	97.5	1.3	≤ 0.5
	Cefoxitin	93.3	2.9	8
	Ceftriaxone	92.6	6.0	≤ 1
	Ciprofloxacin	76.5	15.7	> 2
	Ertapenem	99.8	0.0	≤ 0.03
	Imipenem*	22.5	25.6	4
	Levofloxacin	88.5	9.1	4
	Piperacillin-tazobactam	98.6	0.6	≤ 2
Latin America (405)	Amikacin	99.3	0.5	8
	Ampicillin-sulbactam	82.5	8.2	16
	Cefepime	95.6	2.5	≤ 0.5
	Cefoxitin	96.1	1.7	8
	Ceftriaxone	95.1	3.5	≤ 1
	Ciprofloxacin	78.3	16.3	> 2
	Ertapenem	99.8	0.3	≤ 0.03
	Imipenem*	23.5	31.1	4
	Levofloxacin	86.2	6.7	4
	Piperacillin Tazobactam	97.5	1.5	≤ 2
North America (395)	Amikacin	99.8	0.0	8
	Ampicillin-sulbactam	86.8	5.1	16
	Cefepime	95.2	1.3	≤ 0.5
	Cefoxitin	96.5	1.5	8
	Ceftriaxone	96.2	2.3	≤ 1
	Ciprofloxacin	82.3	15.4	> 2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	22.8	33.7	4
	Levofloxacin	87.1	9.9	4
	Piperacillin-tazobactam	98.5	0.5	≤ 2

\* Due to intrinsic resistance (non-susceptible) of this species, many isolates had intermediate MIC values.

**Table 2. MIC Values and Susceptibility Percentages for Antimicrobial Agents Against 220 ESBL-Positive *P. mirabilis* Causing IAI From Five Regions.**

Region (n)	Drug	% Susceptible	% Resistant	MIC <sub>50</sub>
Africa-Middle East (20)	Amikacin	80.0	20.0	> 32
	Ampicillin-sulbactam	20.0	50.0	> 16
	Cefepime	10.0	80.0	> 32
	Cefoxitin	85.0	10.0	16
	Ceftriaxone	15.0	85.0	> 32
	Ciprofloxacin	25.0	70.0	> 2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	20.0	45.0	4
	Levofloxacin	45.0	50.0	> 4
	Piperacillin-tazobactam	95.0	0.0	≤ 2
Asia-South Pacific (87)	Amikacin	87.4	9.2	32
	Ampicillin-sulbactam	20.7	46.0	> 16
	Cefepime	19.5	63.2	> 32
	Cefoxitin	86.2	8.1	16
	Ceftriaxone	9.2	86.2	> 32
	Ciprofloxacin	25.3	66.7	> 2
	Ertapenem	97.7	1.2	0.12
	Imipenem*	16.1	43.7	4
	Levofloxacin	39.1	50.6	> 4
	Piperacillin-tazobactam	89.7	2.3	32
Europe (62)	Amikacin	83.9	11.3	> 32
	Ampicillin-sulbactam	38.7	41.9	> 16
	Cefepime	19.4	66.1	> 32
	Cefoxitin	82.3	11.3	> 16
	Ceftriaxone	16.1	83.9	> 32
	Ciprofloxacin	35.5	58.1	> 2
	Ertapenem	98.4	1.6	0.06
	Imipenem*	22.6	25.8	4
	Levofloxacin	46.8	45.2	> 4
	Piperacillin-tazobactam	98.4	0.0	4
Latin America (38)	Amikacin	73.7	7.9	32
	Ampicillin-sulbactam	18.4	57.9	> 16
	Cefepime	2.6	79.0	> 32
	Cefoxitin	94.7	2.6	8
	Ceftriaxone	13.2	86.8	> 32
	Ciprofloxacin	21.1	73.7	> 2
	Ertapenem	100	0.0	0.12
	Imipenem*	18.4	29.0	4
	Levofloxacin	26.3	57.9	> 4
	Piperacillin-tazobactam	89.5	7.9	64
North America (13)	Amikacin	100	0.0	16
	Ampicillin-sulbactam	30.8	23.1	> 16
	Cefepime	53.9	46.1	> 32
	Cefoxitin	100	0.0	8
	Ceftriaxone	61.5	38.5	> 32
	Ciprofloxacin	30.8	61.5	> 2
	Ertapenem	100	0.0	0.12
	Imipenem*	7.7	76.9	4
	Levofloxacin	38.5	53.9	> 4
	Piperacillin-tazobactam	100	0.0	≤ 2

\* Due to intrinsic resistance (non-susceptible) of this species, many isolates had intermediate MIC values.

**Table 3. MIC Values and Susceptibility Percentages for Antimicrobial Agents Against 2,172 ESBL-Negative *P. mirabilis* Causing UTI From Five Regions.**

Region (n)	Drug	% Susceptible	% Resistant	MIC <sub>50</sub>
Africa-Middle East (194)	Amikacin	99.0	1.0	8
	Ampicillin-sulbactam	68.0	20.6	> 16
	Cefepime	99.0	0.0	≤ 0.5
	Cefoxitin	95.4	1.0	8
	Ceftriaxone	96.4	2.1	≤ 1
	Ciprofloxacin	68.6	21.7	> 2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	18.0	20.6	4
	Levofloxacin	82.5	12.9	> 4
	Piperacillin-tazobactam	99.5	0.0	≤ 2
Asia-South Pacific (501)	Amikacin	98.6	0.8	16
	Ampicillin-sulbactam	73.1	17.4	> 16
	Cefepime	96.8	1.2	≤ 0.5
	Cefoxitin	94.6	1.4	8
	Ceftriaxone	94.6	3.8	≤ 1
	Ciprofloxacin	75.3	20.6	> 2
	Ertapenem	99.8	0.2	≤ 0.03
	Imipenem*	18.4	32.9	4
	Levofloxacin	83.6	10.0	4
	Piperacillin-tazobactam	99.2	0.6	≤ 2
Europe (710)	Amikacin	96.1	3.7	8
	Ampicillin-sulbactam	68.6	23.2	> 16
	Cefepime	95.4	2.3	1
	Cefoxitin	89.2	4.1	16
	Ceftriaxone	90.4	8.3	≤ 1
	Ciprofloxacin	72.0	19.2	> 2
	Ertapenem	99.7	0.3	≤ 0.03
	Imipenem*	24.1	26.9	4
	Levofloxacin	84.1	12.3	> 4
	Piperacillin-tazobactam	97.3	1.3	≤ 2
Latin America (354)	Amikacin	99.4	0.0	8
	Ampicillin-sulbactam	84.8	6.8	16
	Cefepime	94.4	1.7	≤ 0.5
	Cefoxitin	97.2	1.1	8
	Ceftriaxone	96.1	2.5	≤ 1
	Ciprofloxacin	85.0	9.9	2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	25.4	32.5	4
	Levofloxacin	92.7	6.5	1
	Piperacillin-tazobactam	97.5	1.4	≤ 2
North America (413)	Amikacin	99.5	0.0	8
	Ampicillin-sulbactam	84.0	8.0	16
	Cefepime	98.1	0.5	≤ 0.5
	Cefoxitin	97.3	0.7	8
	Ceftriaxone	97.8	0.7	≤ 1
	Ciprofloxacin	65.4	30.5	> 2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	29.5	23.2	4
	Levofloxacin	73.1	21.6	> 4
	Piperacillin-tazobactam	99.3	0.5	≤ 2

\* Due to intrinsic resistance (non-susceptible) of this species, many isolates had intermediate MIC values.

**Table 4. MIC Values and Susceptibility Percentages for Antimicrobial Agents Against 244 ESBL-Positive *P. mirabilis* Causing UTI From Five Regions.**

Region (n)	Drug	% Susceptible	% Resistant	MIC <sub>50</sub>
Africa-Middle East (25)	Amikacin	76.0	12.0	> 32
	Ampicillin-sulbactam	12.0	68.0	> 16
	Cefepime	8.0	92.0	> 32
	Cefoxitin	100	0.0	8
	Ceftriaxone	8.0	92.0	> 32
	Ciprofloxacin	12.0	80.0	> 2
	Ertapenem	100	0.0	≤ 0.03
	Imipenem*	56.0	8.0	2
	Levofloxacin	32.0	60.0	> 4
	Piperacillin-tazobactam	100	0.0	≤ 2
Asia-South Pacific (84)	Amikacin	86.9	10.7	> 32
	Ampicillin-sulbactam	26.2	52.4	> 16
	Cefepime	11.9	75.0	> 32
	Cefoxitin	91.7	3.6	8
	Ceftriaxone	9.5	89.3	> 32
	Ciprofloxacin	15.5	77.	