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Antimicrobial susceptibility of Enterobacteriaceae, including molecular characterization of extended-spectrum beta-lactamase–producing species, in urinary tract isolates from hospitalized patients in North America and Europe: results from the SMART study 2009–2010☆,☆☆,★,★★

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ABSTRACT

In 2009–2010, 3646 urinary tract isolates of *Enterobacteriaceae* spp. were isolated from hospitalized patients in North America and Europe. Extended-spectrum beta-lactamase (ESBL) production was detected in 8.5% and 8.8% of *Escherichia coli* and *Klebsiella pneumoniae*, respectively, in North America and in 17.6% and 38.9% for Europe, respectively. The carbapenems (ertapenem and imipenem) were the most active agents in vitro, with ampicillin–sulbactam the least active. Molecular characterization of about 50% of ESBL-positive isolates identified the presence of bla_{CTX-M} genes in over 90% of *Escherichia coli* from both continents. bla_{KPC} was more common in North American isolates of *K. pneumoniae* than in European isolates (21.4% versus 6.9%). bla_{TEM} and AmpC genes were infrequent. *Enterobacteriaceae* spp. isolated from hospitalized patients with urinary tract infections in both North America and Europe are often resistant to commonly used antimicrobials with bla_{CTX-M} genes common in both *Escherichia coli* and *K. pneumoniae*.

1. Introduction

Urinary tract infection (UTI) is a common cause for hospitalization and is also frequently acquired by patients hospitalized for other indications (Wagenlehner et al., 2008, 2011). Enterobacteriaceae are the family most commonly implicated including *Escherichia coli, Klebsiella pneumoniae/oxytoca*, and *Proteus mirabilis* (Alhambra et al., 2004; Mathai et al., 2001; Zhanel et al., 2010). Empirical antimicrobial therapy is guided by knowledge of the bacterial spectrum of UTI pathogens and the prevalence of antimicrobial resistance (Bader et al., 2010). Antimicrobial resistance varies by institution, country, and continent. Globally, resistance to commonly used oral and parenteral antimicrobials including aminoglycosides, third-generation cephalosporins, carbapenems, and beta-lactam/beta-lactamase inhibitor combinations is increasing (Meier et al., 2011; Perez et al., 2007). Over the past 10 years, the prevalence of extended-spectrum beta-lactamase (ESBL)–positive Enterobacteriaceae, as well as those now demonstrating carbapenem resistance, has increased dramatically (Hoban et al., 2010a, 2010b). The Study for Monitoring Antimicrobial Resistance Trends (SMART) is an ongoing, multinational surveillance program that has monitored the susceptibilities of Gram-negative bacilli from intra-abdominal infections since 2002. SMART also began monitoring the susceptibilities of Gram-negative bacilli from hospitalized patients with UTIs in late 2009. This report describes the in vitro susceptibility of selected Enterobacteriaceae from UTI and the molecular characterization of a subgroup of ESBL-positive isolates from North America and Europe from 2009 to 2010.

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2. Materials and methods

2.1. Collection centers

Up to 50 Gram-negative bacilli per site from hospitalized patients with UTIs were obtained from hospitals in North America (2009: 29 sites; 2010: 31 sites) and Europe (2009: 39 sites; 2010: 43 sites).

2.2. Bacterial isolates

Each study site was requested to submit consecutive Gram-negative bacilli isolated from in-patients with UTIs. All isolates were deemed to be clinically significant ($>10^5$ CFU/mL) by the participating site. Only 1 isolate per species per patient was accepted. Isolate inclusion was independent of antimicrobial usage. The only patient-specific data collected were age and gender. No identifiable patient-specific information including symptoms or catheterization status was recorded. Institutional review board approval was obtained at the local institutional level as needed. Isolates were identified to the species level at each participating site and submitted to the central reference study center (Laboratories International for Microbiology Studies, a subsidiary of International Health Management Associates, Schaumburg, IL, USA) for isolate identification confirmation and susceptibility testing. In 2009–2010, 4004 Gram-negative bacilli were collected, including 3646 Enterobacteriaceae of which 2241, 604, 107, and 239 were *Escherichia coli, K. pneumoniae, K. oxytoca*, and *Proteus mirabilis*, respectively.

2.3. Susceptibility testing

Minimum inhibitory concentrations (MICs) for amikacin, ampicillin–sulbactam, cefepime, cefotaxime, cefotaxime–clavulanic acid, cefoxitin, ceftazidime, ceftazidime–clavulanic acid, ceftriaxone, ciprofloxacin, ertapenem, imipenem, levofloxacin, and piperacillin–tazobactam were determined at the central reference study center using MicroScan® custom-manufactured dehydrated microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA), using the Clinical and Laboratory Standards Institute interpretive criteria (CLSI, 2012) breakpoints.

2.4. Extended-spectrum beta-lactamase confirmation

Isolates were classified as ESBL producers when there was at least an 8-fold reduction of the MICs for ceftazidime and/or cefotaxime tested in combination with clavulanic acid compared with the MICs when tested alone (CLSI, 2012).

2.5. Quality control

Quality control (QC) was performed on each day of testing using the CLSI-recommended QC strains: *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *K. pneumoniae* ATCC 700603 (positive ESBL control). Results were included in the data analysis only when corresponding QC values were within the acceptable range as specified by CLSI (2012).

2.6. Extended-spectrum beta-lactamase characterization

Approximately 50% (244) of the ESBL-positive Enterobacteriaceae were randomly chosen to undergo ESBL molecular characterization. *Escherichia coli*: North America (39), Europe (116); *K. pneumoniae*: North America (14), Europe (58); *K. oxytoca*: North America (4), Europe (4); and *Proteus mirabilis*: North America (1), Europe (8).

2.6.1. DNA Isolation

Whole genomic DNA was extracted from overnight colonies grown on blood agar (Remel, Lenexa, KS, USA) using the QIAamp DNA Mini Kit and the QIAcube instrument (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions.

2.6.2. Check-MDR 101 array

The Check-Points microarray Check-MDR CT101, previously evaluated (Bogaerts et al., 2011), was used as a first step for detection of the ESBL (bla_{TEM}, bla_{SHV}, bla_{CTX-M}), AmpC (bla_{CMY}, bla_{DHA}, bla_{FOX}, bla_{MOX}, bla_{ACC}, bla_{MIR}, and bla_{ACT}), and carbapenemase (bla_{KPC} and bla_{NDM}) genes according to the manufacturer's instructions (Check-Points, Wageningen, The Netherlands, http://www.check-points.com).

2.6.3. Amplification and DNA sequencing of the ESBL and KPC genes

Polymerase chain reaction (PCR) was performed on the bla_{ESBL} and bla_{KPC} genes identified by the Check-Points method on an ABI 9700 thermocycler (Applied Biosystems, Carlsbad, CA, USA). Extended spectrum *bla* genes of the TEM, SHV, CTX-M, and KPC types were amplified as previously described (Lascols et al., 2011; Mena et al., 2006; Mulvey et al., 2004; Nuesch-Inderbinen et al., 1996; Speldooren et al., 1998; Woodford et al., 2006; Yigit et al., 2001). PCR was carried out with the Fast Cycling PCR Kit (Qiagen). Purification of the PCR products was performed using Exo-SAP-IT® (USB, Cleveland, OH, USA). PCR amplified fragments were sequenced using the ABI 3730XL DNA analyzer (Applied Biosystems). Nucleotide sequences were analyzed with SeqScape v. 7.0 (Applied Biosystems) and compared to sequences available at the National Center for Biotechnology Information website (http://www.ncbi.nlm.nih.gov).

3. Results

In 2009–2010, 4004 Gram-negative bacilli were collected in the SMART program from hospitalized patients in North America and Europe with UTIs. Enterobacteriaceae comprised 3646 (91.1%) of these isolates. *Escherichia coli* (2,241, 61.5%), *K. pneumoniae* (604, 16.6%), *K. oxytoca* (107, 2.9%), and *Proteus mirabilis* (239, 6.6%) were the most common Enterobacteriaceae species. *P. aeruginosa* and *Acinetobacter* spp. represented 8.6% of the Gram-negative bacilli. The antimicrobial susceptibility profiles of the Enterobacteriaceae species with $n > 10$ per continent are shown in Table 1.

In North America, 8.5%, 8.8%, 13.0%, and 1.1% of *Escherichia coli, K. pneumoniae, K. oxytoca*, and *Proteus mirabilis*, respectively, were ESBL positive. Carbapenems (ertapenem and imipenem) had the highest susceptibility levels for most Enterobacteriaceae species, with >98% susceptible to ertapenem for 6/10 of the top species and >98% to imipenem for 4/10 of the top species. ESBL-positive *Klebsiella* spp. displayed a lower percent susceptible to all antimicrobials tested. Piperacillin–tazobactam and amikacin also showed good activity against most species including ESBL-positive isolates. Amikacin was generally more active (96–100%) than piperacillin–tazobactam (76-100%) against *Citrobacter freundii, Enterobacter* spp., and *Serratia marcescens*. The cephalosporins, as expected, demonstrated reduced activity against beta-lactamase–positive strains. Both fluoroquinolones tested (ciprofloxacin and levofloxacin) were less active against ESBL-positive isolates (7–33% susceptible), but retained varying degrees of susceptibility (58–100%) against other Enterobacteriaceae species. Ampicillin–sulbactam was the least active antimicrobial studied with susceptibility only exceeding 80% for ESBL-negative *Proteus mirabilis* and *Citrobacter koseri*.

European isolates of Enterobacteriaceae, with the exception of *K. oxytoca*, exhibited higher ESBL-positive rates than North American isolates, with rates for *Escherichia coli, K. pneumoniae, K. oxytoca*, and

Table 1
In vitro susceptibility of Enterobacteriaceae species from complicated UTI in North America (NA) and Europe (EU), 2009–2010.

Organism	No. of NA/EU	Drug (NA/EU) % susceptible[a]											
		AK	A/S	CPE	CFT	CFX	CAZ	CAX	CP	ETP	IMP	LVX	P/T
Escherichia coli (all)	859/1382	98.5/97.8	51.5/42.8	92.8/86.1	87.9/80.7	88.4/94.5	91.3/87.0	88.6/80.5	64.1/67.0	99.8/99.4	99.7/99.8	64.5/67.9	95.5/92.5
Escherichia coli ESBL−	786/1139	99.2/99.7	55.3/50.9	99.8/99.9	95.8/97.8	89.8/96.2	96.2/98.2	96.4/97.5	69.5/77.1	99.9/99.9	99.6/99.7	69.9/77.7	96.6/95.4
Escherichia coli ESBL+	73/243	90.4/89.3	9.6/4.9	17.8/21.4	2.7/0.4	72.6/86.4	31.5/34.2	4.1/0.8	6.9/19.8	98.6/97.1	100/100	6.9/21.8	83.6/78.6
%ESBL+	8.5/17.6												
Klebsiella pneumoniae (all)	249/355	95.6/93.5	72.7/36.9	92.8/64.8	91.6/56.6	85.9/82.3	92.0/61.4	91.6/55.5	90.4/57.2	96.4/91.3	96.0/94.1	91.6/62.0	91.2/65.4
Klebsiella pneumoniae ESBL−	227/217	98.7/97.7	78.9/58.5	99.1/94.0	98.7/89.9	89.9/84.8	98.7/90.3	98.7/89.9	97.4/78.3	99.1/94.9	99.2/94.9	99.2/80.7	96.5/79.7
Klebsiella pneumoniae ESBL+	22/138	63.6/87.0	9.1/2.9	27.3/18.8	18.2/4.4	45.5/78.3	22.7/15.9	18.2/1.5	18.2/23.9	68.2/85.5	72.7/92.8	22.7/32.6	36.4/42.8
%ESBL+	8.8/38.9												
Klebsiella oxytoca (all)	46/61	100/95.1	60.9/49.2	93.5/85.3	76.1/82.0	91.3/91.8	87.0/91.8	73.9/78.7	82.6/85.3	97.8/98.4	100/98.4	84.8/90.2	89.1/80.3
Klebsiella oxytoca ESBL−	40/55	100/98.2	65.0/54.6	97.5/92.7	87.5/90.9	95.0/92.7	97.5/100	85.0/87.3	92.5/90.9	100/100	100/98.2	92.5/92.7	87.5/85.5
Klebsiella oxytoca ESBL+	6/6	100/66.7	33.3/0	66.7/16.7	0/0	66.7/83.3	16.7/16.7	0/0	16.7/33.3	83.3/83.3	100/100	33.3/66.7	100/33.3
%ESBL+	13.0/9.8												
Proteus mirabilis (all)	94/145	98.9/97.9	83.0/67.6	97.9/93.1	95.7/82.1	94.7/89.7	96.8/91.0	95.7/82.8	64.9/67.6	98.9/100	29.8/20.0	74.5/82.8	100/95.2
Proteus mirabilis ESBL−	93/132	98.9/98.5	83.9/72.7	98.9/97.7	95.7/88.6	94.6/89.4	97.9/92.4	95.7/89.4	65.6/72.0	98.9/100	29.0/18.9	74.2/85.6	100/94.7
Proteus mirabilis ESBL+	1/13	−/92.3	−/15.4	−/46.2	−/15.4	−/92.3	−/76.9	−/15.4	−/23.1	−/100	−/30.8	−/53.9	−/100
%ESBL+	1.1/9.0												
Citrobacter freundii	33/28	100/100	39.4/46.4	97.0/92.9	69.7/60.7	6.1/19.7	69.7/60.7	66.7/60.7	84.9/78.6	100/100	100/82.1	84.9/82.1	87.9/85.7
Citrobacter koseri	18/24	100/100	94.4/100	100/100	100/100	88.9/95.8	100/100	94.4/100	100/100	100/100	100/100	100/100	100/100
Enterobacter aerogenes	32/27	100/100	25.0/48.2	100/100	56.3/74.1	12.5/14.8	65.6/85.2	62.5/74.1	96.9/92.6	93.8/96.3	87.5/85.2	100/92.6	78.1/88.9
Enterobacter cloacae	67/77	98.5/96.1	13.4/26.0	94.0/85.7	58.2/54.6	11.9/11.7	70.2/59.7	56.7/54.6	82.1/71.4	82.1/79.2	97.0/97.4	88.1/77.9	76.1/70.1
Morganella morganii	19/26	100/100	−/3.9	94.7/92.3	63.2/61.5	84.2/84.6	84.2/80.8	79.0/84.6	57.9/84.6	100/100	21.1/3.9	68.4/88.5	100/100
Serratia marcescens	30/23	96.7/95.7	−/8.7	96.7/78.3	80.0/60.9	53.3/30.4	93.3/82.6	83.3/60.9	96.7/73.9	96.7/100	93.3/100	96.7/87.0	90.0/73.9

NA = North America; EU = Europe; AK = amikacin; A/S = ampicillin–sulbactam; CPE = cefepime; CFT = cefotaxime; CFX = cefoxitin; CAZ = ceftazidime; CAX = ceftriaxone; CP = ciprofloxacin; ETP = ertapenem; IMP = imipenem; LVX = levofloxacin; P/T = piperacillin–tazobactam.
% S ≥90% (shaded).
Other Enterobacteriaceae species not included in the table: *Citrobacter amalonaticus* (1), *C. brakki* (1), *C. diversus* (3), *Enterobacter asburiae* (4), *Enterobacter sakazakii* (1), *Klebsiella ornithinolytica* (1), *K. planticola* (1), *Proteus vulgaris* (12), *Providencia rettgeri* (5), *Providencia rustigianii* (1), *Providencia stuartii* (13), *Salmonella* sp. (1), *Serratia odorifera* (5), *Serratia rubidaea* (1).
[a] Results only shown for species with n >10 per continent.

Proteus mirabilis of 17.6%, 38.9%, 9.8%, and 9.0%, respectively. As observed with North American *Escherichia coli, K. pneumoniae, K. oxytoca,* and *Proteus mirabilis*, ertapenem and imipenem were the most in vitro active agents with percent susceptible for ESBL-negative isolates >95% with the exception of *Proteus mirabilis*, among which <20% were susceptible. Both carbapenems maintained good activity against ESBL-positive isolates of *Escherichia coli* (>97% susceptible) but had reduced activity against *Klebsiella* spp. and intrinsically less susceptible *Proteus mirabilis*. Ertapenem, in particular, was less active than imipenem against ESBL-positive *Klebsiella* spp., while imipenem was less active than ertapenem against *Proteus mirabilis*. Among the noncarbapenem antimicrobials, amikacin was the most active agent with overall susceptibilities of >97% for ESBL-positive *Escherichia coli* and >90% of *Klebsiella* spp. susceptible. Piperacillin–tazobactam susceptibility exceeded 90% only for ESBL-negative *Escherichia coli, Proteus mirabilis, C. koseri*, and *Morganella morganii*. The activity of cephalosporins and fluoroquinolones was highly dependent upon the presence of ESBLs and the particular species of Enterobacteriaceae. Similarly to the North American isolates, ampicillin–sulbactam was the least active agent studied.

Overall, for both North American and European strains, the most active agents against UTI Enterobacteriaceae were ertapenem/imipenem > amikacin > piperacillin–tazobactam > cephalosporins > fluoroquinolones > ampicillin–sulbactam.

Check-Points Array analysis of ESBL-positive Enterobacteriaceae (Table 2) displayed a wide variety of genes present, along with limited plasmidic bla_{AmpC} resistance genes. *Escherichia coli* tested positive for the presence of bla_{CTX-M} genes in 37/39 (94.9%) North American and in 112/116 (96.6%) European isolates. Of the bla_{CTX-M}-positive isolates, 73% (North America) and 75% (Europe) were $bla_{CTX-M-15}$. Neither bla_{SHV} nor bla_{KPC} genes were found in North American *Escherichia coli*, while 2 isolates contained bla_{TEM}. bla_{SHV} was found in 4 *Escherichia coli* isolates from Europe, but no bla_{KPC} or bla_{TEM} genes were detected. *K. pneumoniae* also commonly contained bla_{CTX-M} genes with 5/14 (35.7%) and 38/58 (65.5%) of North American and European isolates containing bla_{CTX-M} genes, respectively. Of the bla_{CTX-M}-positive isolates, 80% (North America) and 76.3% (Europe) were $bla_{CTX-M-15}$. bla_{SHV} and bla_{KPC} genes were also detected in North American and European isolates of *K. pneumoniae*. bla_{TEM} was found in a single isolate from Europe, while 3 isolates were found to contain bla_{AmpC} genes. Among the *K. oxytoca* isolates, bla_{CTX-M} , $bla_{SHV,}$ bla_{KPC}, and bla_{TEM} were detected in 0, 2, 1, and 1 isolate each from North America and were detected in 3, 1, 0, and 0 isolates from Europe, respectively. No isolates of *K. oxytoca* contained bla_{AmpC} genes. A single isolate of *Proteus mirabilis* from North America contained bla_{TEM}, while 6 European isolates contained bla_{CTX-M} and 2 bla_{TEM}. No isolates from either continent contained bla_{NDM}.

4. Discussion

The spectrum of bacteria isolated from UTIs in hospitalized patients is very broad and includes both Gram-positive and Gram-

Table 2
Check-points array/PCR resistance profile analysis.

		Escherichia coli		*Klebsiella pneumoniae*[a]		*Klebsiella oxytoca*[b]		*Proteus mirabilis*[c]	
		NA	EU	NA	EU	NA	EU	NA	EU
Gene	*n*	39	116	14	58	4	4	1	8
bla_{KPC}		0	0	3 (21.4%)	4 (6.9%)	1 (25%)	0	0	0
	KPC-2	0	0	0	4	1	0	0	0
	KPC-3	0	0	2	0	0	0	0	0
	KPC-4	0	0	1	0	0	0	0	0
bla_{CTX-M}		37 (94.9%)	112 (96.6%)	5 (35.7%)	38 (65.5%)	0	3 (75.0%)	0	6 (75.0%)
	CTX-M-1	0	9	0	1	0	0	0	0
	CTX-M-3	0	0	0	1	0	0	0	0
	CTX-M-5	0	0	0	0	0	0	0	2
	CTX-M-9	0	0	0	1	0	0	0	0
	CTX-M-11	0	0	0	0	0	0	0	0
	CTX-M-14	7	14	1	1	0	1	0	1
	CTX-M-15	27	84	4	29	0	2	0	0
	CTX-M-22	0	2	0	4	0	0	0	2
	CTX-M-32	0	2	0	0	0	0	0	0
	CTX-M-27	2	0	0	0	0	0	0	0
	CTX-M-55	0	0	0	0	0	0	0	1
	CTX-M-65	1	0	0	0	0	0	0	0
	CTX-M-92	0	0	0	1	0	0	0	0
	CTX-M-97	0	1	0	0	0	0	0	0
	CTX-M-119	0	0	0	1	0	0	0	0
bla_{SHV}		0	4 (3.4%)	6 (42.9%)	18 (31.0%)	2 (50.0%)	1 (25.0%)	0	0
	SHV-5	0	1	0	7	0	1	0	0
	SHV-12	0	3	6	8	2	0	0	0
	SHV-28	0	0	0	1	0	0	0	0
	SHV-65	0	0	0	1	0	0	0	0
	SHV-90	0	0	0	1	0	0	0	0
bla_{TEM}		2 (5.1%)	0	0	1 (1.7%)	1 (25.0%)	0	1 (100%)	2 (25.0%)
	TEM-10	0	0	0	0	1	0	1	0
	TEM-19	2	0	0	1	0	0	0	0
	TEM-113	0	0	0	0	0	0	0	2
AmpC		0	0	0	3 (5.2%)	0	0	0	1 (12.5%)
	DHA	0	0	0	1	0	0	0	0
	CMY-2	0	0	0	1	0	0	0	1
	ACT/MIR	0	0	0	1	0	0	0	0

[a] *Klebsiella pneumoniae*: 1 isolate with CTX-M-9 + ACT/MIR (Europe), 1 isolate with SHV-5 + ACT/MIR (Europe), 1 isolate with SHV-5 + CMY-2 + KPC-2 (Europe), 3 isolates with SHV-12 + KPC-2 (Europe).
[b] *Klebsiella oxytoca*: 1 isolate with KPC-2 + TEM-10 (North America).
[c] *Proteus mirabilis*: 1 isolate with CTX-M-55 + CMY-2 (Europe).

negative pathogens. In a study examining causative pathogens in both Europe and North America (Gordon and Jones, 2003), typically Gram-negative species account for over 70% and are usually composed of *Escherichia coli, Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Enterobacter* spp., and *Citrobacter* spp. Recently, the epidemiology of complicated UTI pathogens in 7 Asia-Pacific countries documented similar epidemiologic pathogen profiles for Gram-negative species (Hsueh et al., 2011). This report again documents the importance of *Escherichia coli, K. pneumoniae, K. oxytoca, Proteus mirabilis*, and other Enterobacteriaceae species as common causes of UTIs in hospitalized patients in both North America and Europe.

The prevalence of ESBL-positive Enterobacteriaceae varied by species, but ESBL-positive *Escherichia coli* and *K. pneumoniae* were 2 to 3 times more prevalent in Europe than in North America. This observation was previously noted for intra-abdominal isolates from North America and Europe in the SMART surveillance program (Hawser et al., 2010; Hoban et al., 2010a, 2010b). Increasing antimicrobial resistance in urinary tract pathogens from hospitalized patients is well documented including the increasing prevalence of ESBL-positive Enterobacteriaceae and the introduction of carbapenemase-producing isolates (Paterson, 2006).

Surveillance programs such as SMART are designed to assess the prevalence of resistance to commonly used antimicrobials utilized in the treatment of hospitalized patients with UTIs and to discern where possible the enzymatic mechanisms behind increasing resistance. The carbapenems (ertapenem and imipenem) retained the greatest level of activity against ESBL-negative Enterobacteriaceae overall in both North America and Europe. This activity diminishes in ESBL-positive *Klebsiella* spp. but not in ESBL-positive *Escherichia coli*. Piperacillin–tazobactam retained good activity against *Escherichia coli* overall in both continents but exhibited diminished activity in European isolates of *K. pneumoniae* and *K. oxytoca*. The cephalosporins retain adequate levels of activity only against the ESBL-negative isolates. Enterobacteriaceae continue to display resistance to fluoroquinolones, particularly in ESBL-positive isolates. This has been observed before in both UTI and intra-abdominal pathogens (Hoban et al., 2010a, 2010b; 2011).

The Check-Points array (Check-MDR CT101) has previously been shown to be both highly sensitive and specific in detecting bla_{SHV}, bla_{TEM}, $bla_{CTX\text{-}M}$, bla_{KPC}, bla_{NDM}, and bla_{AmpC} genes in Enterobacteriaceae species (Bogaerts et al., 2011), and this study confirms the utility of molecular detection and characterization of resistance genes in pathogens.

This report documents several key observations: 1) *Escherichia coli* remains the predominant pathogen in UTIs in hospitalized patients both in North America and in Europe, followed by *K. pneumoniae*; 2) ESBL phenotypes are more common in European isolates of *Escherichia coli* and *K. pneumoniae* than in North American isolates; 3) the ESBL phenotype dictates a higher level of resistance to commonly used antimicrobials in treatments of UTIs in hospitalized patients; 4) carbapenems (ertapenem and imipenem) continue to maintain a high level of activity against most Enterobacteriaceae with the exception of ESBL-positive *K. pneumoniae*; and 5) molecular detection of the most common resistance genes in ESBL-positive Enterobacteriaceae confirms previous reports that CTX-M beta-lactamases are very common in *Escherichia coli, Klebsiella* spp., and *Proteus mirabilis*. Limitations of this study include the following: 1) no documentation of trends of susceptibility patterns of Enterobacteriaceae as the SMART study only began examining UTI isolates in hospitalized patients in late 2009; 2) lack of ability to characterize all isolates as hospital or community acquired or whether from complicated or uncomplicated UTIs; 3) the low number of ESBL-positive strains for some Enterobacteriaceae introduces uncertainty into the susceptibility results: and 4) the genes responsible for resistance were characterized for only approximately 50% of the ESBL-positive isolates and it is not known whether the results from this subset are generalizable to the full set of strains. The SMART program has documented the patterns and changes in antimicrobial resistance in intra-abdominal infections globally (Hoban et al., 2010a,b). The susceptibility of *Escherichia coli* from a collection of Enterobacteriaceae collected worldwide from urinary tract isolates in hospitalized patients in 2009–2010 has previously documented the patterns of resistance (Hoban et al., 2011). This analysis expands upon that report to include other species of Enterobacteriaceae with details comparing only North America and Europe, as well as describing the genes responsible for resistance among ESBL-positive isolates.

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References

Alhambra A, Cuadros JA, Cacho J, Gómez-Garcés JL, Alós JI. In vitro susceptibility of recent antibiotic-resistant urinary pathogens to ertapenem and 12 other antibiotics. J Antimicrob Chemother 2004;53:1090–4.

Bader MS, Hawboldt J, Brooks A. Management of complicated urinary tract infections in the era of antimicrobial resistance. Postgrad Med 2010;122:7–15.

Bogaerts P, Hujer AM, Nass T, Rezende de Castro R, Endimiani A, Nordmann P, et al. Multicenter evaluation of a new DNA microarray for rapid detection of clinically relevant bla genes from beta-lactam-resistant Gram-negative bacteria. Antimicrob Agents Chemother 2011;55:4457–60.

Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing: 21st informational supplement (M100–S22). Wayne, PA: CLSI; 2012.

Gordon KA, Jones RN. Susceptibility patterns of orally administered antimicrobials among urinary tract infection pathogens from hospitalized patients in North America: comparison report to Europe, Latin America. Results from the SENTRY Antimicrobial Surveillance Program (2000). Diagn Microbiol Infect Dis 2003;45:295–301.

Hawser SP, BouchillonSK Hoban DJ, Badal RE, Cantón R, Baquero F. Incidence and antimicrobial susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* and extended-spectrum ß-lactamases in community- and hospital-associated intra-abdominal infections in Europe: results of the 2008 Study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrob Agents Chemother 2010;54:3043–6.

Hoban DJ, Bouchillon S, Hawser SP, Badal RE, LaBombardi VJ, DiPersio J. Susceptibility of Gram-negative pathogens isolated from complicated intra-abdominal infections in the United States 2007–2008: results of the SMART study. Antimicrob Agents Chemother 2010a;54:3031–4.

Hoban DJ, BouchillonSK Hawser SP, Badal RE. Trends in the frequency of multiple drug-resistant Enterobacteriaceae and their susceptibility to ertapenem, imipenem, and other antimicrobial agents: data from the Study for Monitoring Antimicrobial Resistance Trends 2002 to 2007. Diagn Microbiol Infect Dis 2010b;66:78–86.

Hoban DJ, Nicolle LE, Hawser S, Bouchillon S, Badal R. Antimicrobial susceptibility of global inpatient urinary tract isolates of *Escherichia coli*: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program: 2009–2010. Diagn Microbiol Infect Dis 2011;70:507–11.

Hsueh P-R, Hoban DJ, Carmeli Y, Chen S-Y, Desikan S, Alenjandria M, et al. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. J Infect 2011;63:114–23.

Lascols C, Hackel M, Marshall SH, Hujer AM, Bouchillon S, Badal R, et al. Increasing prevalence and dissemination of NDM-1 metallo-beta-lactamase in India: data from the SMART study (2009). J Antimicrob Chemother 2011;66:1992–7.

Mathai D, Jones RN, Pfaller MA, The SENTRY Participant Group North America. Epidemiology and frequency of resistance among pathogens causing urinary tract infections in 1,510 hospitalized patients: a report from the SENTRY Antimicrobial Surveillance Program (North America). Diagn Microbiol Infect Dis 2001;40:129–36.

Meier S, Weber R, Zbinden R, Ruef C, Hasse B. Extended-spectrum ß-lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. Infection 2011;39:333–40.

Mena A, Plasencia V, Garcia L, Hidalgo GO, Ayestaran JI, Alberti S, et al. Characterization of a large outbreak of CTX-M-1-producing *Klebsiella pneumoniae* and mechanisms leading to in vivo carbapenem resistance development. J Clin Microbial 2006;44:2831–7.

Mulvey MR, Bryce E, Boyd D, Ofner-Agostini M, Christianson S, Simor AE, et al. Ambler class A extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* spp. in Canadian hospitals. Antimicrob Agents Chemother 2004;48:1204–14.

Nuesch-Inderbinen MT, Hachler H, Kayser FH. Detection of genes coding for extended-spectrum SHV beta-lactamases in clinical isolates by a molecular genetic method, and comparison with the E test. Eur J Clin Microbiol Infect Dis 1996;15:398–402.

Paterson DL. Resistance in Gram-negative bacteria: Enterobacteriaceae. Am J Med 2006;119:S20–8.

Perez F, Endimiani A, Hujer KM, Bonomo RA. The continuing challenge of ESBLs. Curr Opin Pharmacol 2007;7:459–69.

Speldooren V, Heym B, Labia R, Nicolas-Chanoine MH. Discriminatory detection of inhibitor-resistant beta-lactamases in *Escherichia coli* by single-strand conformation polymorphism-PCR. Antimicrob Agents Chemother 1998;42:879–84.

Wagenlehner FME, Niemetz AH, Weidner W, Naber KG. Spectrum and antibiotic resistance of uropathogens from hospitalized patients with urinary tract infections: 1994–2005. Int J Antimicrob Agents 2008;31S:S25–34.

Wagenlehner FME, Cek M, Naber KG, Kiyota H, Bjerklund-Johansen TE. Epidemiology, treatment and prevention of healthcare-associated urinary tract infections. World J Urol 2012;30:59–67.

Woodford N, Fagan EJ, Ellington MJ. Multiplex PCR for rapid detection of genes encoding CTX-M extended-spectrum (beta)-lactamases. J Antimcirob Chemother 2006;57:154–5.

Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2001;45: 1151–61.

Zhanel GG, DeCorby M, Adam H, Mulvey MR, McCracken M, Lagacé-Wiens P, et al. Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: results of the Canadian Ward Surveillance Study (CANWARD 2008). Antimicrob Agents Chemother 2010;54:4684–93.