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Global Assessment of Antimicrobial Susceptibility among Gram-Negative Organisms Collected from Pediatric Patients between 2004 and 2012: Results from the Tigecycline Evaluation and Surveillance Trial

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The Tigecycline Evaluation and Surveillance Trial (TEST) was designed to monitor susceptibility to commonly used antimicrobial agents among important pathogens. We report here on susceptibility among Gram-negative pathogens collected globally from pediatric patients between 2004 and 2012. Antimicrobial susceptibility was determined using guidelines published by the Clinical and Laboratory Standards Institute (CLSI). Most *Enterobacteriaceae* showed high rates of susceptibility (>95%) to amikacin, tigecycline, and the carbapenems (imipenem and meropenem); 90.8% of *Acinetobacter baumannii* isolates were susceptible to minocycline, and susceptibility rates were highest in North America, Europe, and Asia/Pacific Rim. Amikacin was the most active agent against *Pseudomonas aeruginosa* (90.4% susceptibility), with susceptibility rates being highest in North America. Extended-spectrum β-lactamases (ESBLs) were reported for 11.0% of *Escherichia coli* isolates and 24.2% of *Klebsiella pneumoniae* isolates globally, with rates reaching as high as 25.7% in the Middle East and >43% in Africa and Latin America, respectively. Statistically significant ($P < 0.01$) differences in susceptibility rates were noted between pediatric age groups (1 to 5 years, 6 to 12 years, or 13 to 17 years of age), globally and in some regions, for all pathogens except *Haemophilus influenzae*. Significant ($P < 0.01$) differences were reported for all pathogens globally and in most regions, considerably more frequently, when pediatric and adult susceptibility results were compared. Amikacin, tigecycline, and the carbapenems were active *in vitro* against most Gram-negative pathogens collected from pediatric patients; *A. baumannii* and *P. aeruginosa* were susceptible to fewer antimicrobial agents. Susceptibility rates among isolates from pediatric patients were frequently different from those among isolates collected from adults.

Bacterial infections in pediatric patients may behave differently than their corresponding infections in adults. Lob et al. showed that *Escherichia coli* isolates from adults with appendicitis were significantly ($P < 0.05$) less susceptible to a number of antimicrobial agents than were those from pediatric patients (1). Pediatric patients have rates of bacteremia up to 2-fold higher than those for adult patients and 7-fold higher than those for neonates (2). Unfortunately, results for pediatric and adult patients are often grouped together in population-based study reports (3).

Key factors in the spread of serious Gram-negative bacilli include the development and spread of numerous resistance mechanisms, decreased research into the development of new antimicrobial agents, and widespread overuse of broad-spectrum antimicrobial agents in the treatment of infections, among other factors (4). Gram-negative pathogens are commonly associated with serious infections and high morbidity and mortality rates. Infections caused by Gram-negative pathogens are common causes of death among patients less than 14 years of age in the United Kingdom (5), and Gram-negative infections represent one of the main risk factors associated with death among pediatric patients with sepsis in Colombia (6).

The Tigecycline Evaluation and Surveillance Trial (TEST) is a global surveillance study monitoring the activity of tigecycline (TIG), a broad-spectrum glycylcycline antimicrobial agent, and a panel of comparator agents against an array of clinically important Gram-positive and Gram-negative pathogens. The TEST commenced in 2004 and is currently ongoing. In this study, we examine the activity of tigecycline and comparators against Gram-negative pathogens collected globally from pediatric patients, 1 to 17 years of age, between 2004 and 2012.

MATERIALS AND METHODS

Isolate collection. Gram-negative isolates from pediatric patients were contributed by 570 centers in 65 countries globally between 2004 and 2012 (see Table S1 in the supplemental material). All participating centers were required to submit at least 135 Gram-negative and 65 Gram-positive isolates that were interpreted by each collecting center to be clinically significant. Among Gram-negative isolates, centers were expected to contribute at least 15 isolates of *Acinetobacter* spp., 15 of *Haemophilus influenzae*, 25 of *Escherichia coli*, 25 of *Enterobacter* spp., 25 of *Klebsiella* spp., 20 of *Pseudomonas aeruginosa*, and 10 of *Serratia* spp. Isolate identification was carried out using center-specific methodology.

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All isolates were collected consecutively from inpatients or outpatients with documented infections of nosocomial or community origin. Only a single isolate per patient was allowed in the study, and inclusion was independent of patient age or sex, previous antimicrobial use, or previous medical history. All body sites were acceptable sources for isolate collection (including bodily fluids, the central nervous system, the cardiovascular system, the gastrointestinal tract, the genitourinary system, the head, ears, eyes, nose, and throat, medical instruments [including catheters, surgical instruments, and prostheses], the integumentary system, the lymphatic system, the muscular system, the reproductive system, the respiratory system, and the skeletal system), but no more than 25% of isolates from any center could originate from urine cultures.

The study was managed by International Health Management Associates, Inc. (IHMA) (Schaumburg, IL); this laboratory produced and maintained a centralized database of all isolates contributed to the TEST. Following collection and antimicrobial susceptibility testing, all organisms were shipped to IHMA. Prior to shipping, organisms that required storage for longer than 5 days were maintained between −70°C and −20°C in tryptic soy broth with glycerol. Organisms could be stored at −70°C or lower for a period of 6 months. Organisms stored between −70°C and −20°C were subcultured every 8 weeks to ensure viability. Organisms that were cultured from a frozen state were subcultured twice before refreezing.

Antimicrobial susceptibility testing. MICs were determined locally using broth microdilution methodology (described by the Clinical and Laboratory Standards Institute [CLSI]) (7) with Sensititre plates (Trek Diagnostic Systems, East Grinstead, England) or MicroScan panels (Siemens, Sacramento, CA). The test panel for this study included the following antimicrobial agents: amikacin (AMK), amoxicillin-clavulanate (AMC), ampicillin (AMP), cefepime (FEP), ceftazidime (CAZ), ceftriaxone (CRO), imipenem (IPM), levofloxacin (LVX), meropenem (MEM), minocycline (MIN), piperacillin-tazobactam (TZP), and tigecycline (TIG). Stability issues were encountered with some imipenem samples, so imipenem was replaced by meropenem in 2006; in the same year, MicroScan panels were replaced by Sensititre plates. Cation-adjusted Mueller-Hinton broth was used to determine MICs. Most panels were incubated in open air at 35°C for 16 to 20 h; *H. influenzae* panels were incubated for 20 to 24 h.

Quality control (QC) testing was carried out daily, using the following QC strains: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, and *H. influenzae* ATCC 49766. Interpretation of antimicrobial susceptibility results was performed using CLSI criteria (8); *Enterobacter* breakpoints for carbapenems have recently been revised (9). FDA-approved breakpoints, provided in the tigecycline package insert, were used for tigecycline (10).

E. coli and *Klebsiella* spp. were tested for the production of extended-spectrum β-lactamases (ESBLs) at the central laboratory (IHMA), using cefotaxime (30 μg), cefotaxime-clavulanic acid (30 μg/10 μg), ceftazidime (30 μg), and ceftazidime-clavulanic acid (30 μg/10 μg) discs (8). The discs were manufactured by Oxoid, Inc. (Ogdensburg, NY), while Mueller-Hinton agar was produced by Remel, Inc. (Lenexa, KS). QC strains used for ESBL testing were *Klebsiella pneumoniae* ATCC 700603 (ESBL positive) and *E. coli* ATCC 25922 (ESBL negative), as well as *P. aeruginosa* (ATCC 27853) for QC of ceftazidime and cefotaxime discs. *H. influenzae* isolates were tested for β-lactamase production by using locally preferred methodologies. Multidrug resistance (MDR) is defined in this study as resistance to three or more classes of antimicrobial agents routinely used to treat the organism; antimicrobial classes are defined here as aminoglycosides (AMK), β-lactams and β-lactam inhibitor combinations (AMP, AMC, FEP, CAZ, CRO, and TZP), carbapenems (IPM and MEM), fluoroquinolones (LVX), tetracyclines (MIN), and glycylcyclines (TIG).

Statistical analysis. The Cochran-Armitage trend test was used to determine statistically significant changes in antimicrobial susceptibility over time. Due to the large number of trend tests performed, only *P* values of <0.01 were regarded as significant. Imipenem and meropenem were excluded from this analysis because data were not available for these antimicrobials for each year of analysis. Pairwise statistical comparisons between patient age groups were carried out using the Cochran-Mantel-Haenszel test.

RESULTS

Patient groups and isolate totals. A total of 18,614 pediatric Gram-negative isolates were submitted to the TEST between 2004 and 2012. Europe and North America were the largest contributors of isolates for all pathogens in this study (Tables 1 and 2). Isolates from both inpatients and outpatients were permitted in the study; globally, the majority of isolates were from inpatients (72.8% [13,551/18,614 isolates]). The same pattern was seen for the majority of organisms and regions (data not shown). An exception to this was isolates of *H. influenzae*, with only 55.4% of isolates (2,307/4,166 isolates) being from inpatients.

Enterobacteriaceae. **(i) *E. coli.*** The highest global rates of susceptibility noted among *E. coli* ($n = 3{,}041$) (Table 1) were for tigecycline (>99.9%), imipenem (99.5%), meropenem (99.1%), and amikacin (97.4%). Rates of susceptibility to several antimicrobial agents varied widely between regions; ceftriaxone susceptibility rates ranged from 61.4% in Asia/Pacific Rim to 94.2% in North America, while ampicillin susceptibility rates were 13.4% in Africa and 44.4% in North America. Large (>27%) regional variations in susceptibility rates were also observed for amoxicillin-clavulanate, levofloxacin, and minocycline (Table 1). Globally, 11.0% of *E. coli* isolates were ESBL producers (Table 2). In North America, ESBLs were reported for only 2.1% of isolates, while rates of ESBL production reached as high as 24.5% in Latin America and 25.7% in the Middle East.

Globally, significant ($P < 0.01$) decreases in susceptibility rates between 2004 and 2012 were noted for ampicillin, cefepime, ceftriaxone, levofloxacin, and minocycline. The rate of susceptibility to ampicillin decreased from 38.3% (92/240 isolates) in 2004 to 30.4% (78/257 isolates) in 2012. For cefepime, the susceptibility rate decreased from 98.3% ($n = 236$) to 91.1% ($n = 234$). The susceptibility rate for ceftriaxone decreased from 93.3% ($n = 224$) to 83.3% ($n = 214$) and that for levofloxacin from 87.1% ($n = 209$) to 83.3% ($n = 214$). For minocycline, the susceptibility rate decreased from 85.0% in 2004 ($n = 204$) to 71.0% (373/525 isolates) in 2009 and then increased to 84.4% ($n = 217$) in 2012.

For the global collection of *E. coli* isolates, no clear pattern in susceptibility rates for the pediatric and adult age groups was observed (see Table S2 in the supplemental material). Statistically significant ($P < 0.01$) differences in pathogen susceptibility rates were observed between pediatric patient groups 1 to 5 years and 13 to 17 years of age in Latin America (for levofloxacin), in North America (for ampicillin), and globally (for ampicillin) and for patients 6 to 12 years and 13 to 17 years of age in Latin America (for meropenem) and globally (for ampicillin and meropenem); however, no clear trends were visible (see Table S3 in the supplemental material). Significant ($P < 0.01$) differences in susceptibility rates between pediatric and adult patients were also observed in Africa, Europe, Latin America, the Middle East, and North America and globally; susceptibility rates were higher among 1- to 5-year-old and ≥18-year-old patients (see Table S4 in the supplemental material).

(ii) *K. pneumoniae.* A total of 2,392 *K. pneumoniae* isolates were contributed to this study. Global susceptibility rates were

TABLE 1 Susceptibility rates among *Enterobacteriaceae* isolates collected from pediatric patients (<18 years of age) during TEST in 2004 to 2012

Species and location	No. of isolates	% of susceptible isolates (no. tested) or no. of susceptible isolates/total no. of isolates[a]										
		AMK	AMC	AMP	FEP	CRO	IPM	LVX	MEM	MIN	TZP	TIG
Escherichia coli												
Africa	82	100	46.3	13.4	92.7	85.4	96.6 (29)	81.7	100 (53)	63.4	86.6	100
Asia/Pacific Rim	153	94.1	53.6	19.0	75.8	61.4	100 (46)	60.1	98.1 (107)	72.5	85.6	100
Europe	1,106	96.8	69.3	33.5	90.1	81.0	99.4 (160)	82.2	99.7 (946)	77.2	91.7	100
Latin America	384	92.4	51.0	19.8	81.3	66.1	100 (34)	68.5	96.9 (350)	60.9	84.4	99.7
Middle East	101	100	63.4	17.8	81.2	65.3	6/6	76.2	98.9 (95)	69.3	93.1	100
North America	1,215	99.5	76.1	44.4	97.9	94.2	99.6 (487)	89.2	99.5 (728)	88.1	97.5	100
Globally	3,041	97.4	68.1	34.3	91.2	83.0	99.5 (762)	81.9	99.1 (2,279)	78.6	92.7	>99.9
Klebsiella pneumoniae												
Africa	60	95.0	40.0	1.7	53.3	38.3	17/17	83.3	93.0 (43)	68.3	75.0	100
Asia/Pacific Rim	136	76.5	40.4	0.7	55.9	42.6	100 (38)	74.3	89.8 (98)	59.6	67.6	96.3
Europe	901	95.3	59.6	1.8 (900)	80.2	62.8	99.1 (109)	88.1	96.8 (792)	67.5	78.2	97.0
Latin America	436	73.4	44.3	0.9 (435)	68.8	42.4	89.7 (29)	78.7	92.1 (407)	63.1	62.4	96.1
Middle East	133	95.5	53.4	1.5	75.2	57.9	18/18	89.5	95.7 (115)	68.4	72.9	95.5
North America	726	98.9	88.4	1.4 (725)	98.2	91.3	99.7 (291)	96.6	97.9 (435)	81.1	94.1	96.1
Globally	2,392	91.3	63.6	1.4 (2,389)	81.3	65.7	99.0 (502)	88.1	95.6 (1,890)	70.4	79.2	96.5
Klebsiella oxytoca												
Africa	9	9/9	8/9	0/9	9/9	7/9	2/2	9/9	7/7	9/9	9/9	9/9
Asia/Pacific Rim	20	90.0	65.0	5.0	85.0	65.0	4/4	80.0	16	75.0	85.0	100
Europe	334	97.9	82.6	3.0	96.4	84.4	100 (54)	97.0	100 (280)	90.1	88.3	99.1
Latin America	54	96.3	83.3	5.6	92.6	75.9	9/9	92.6	97.8 (45)	83.3	88.9	100
Middle East	11	10/11	6/11	0/11	9/11	6/11	1/1	10/11	9/10	10/11	7/11	11/11
North America	287	99.0	88.9	3.8 (286)	99.0	90.9	100 (101)	99.0	98.4 (186)	89.9	95.5	99.7
Globally	715	97.9	84.3	3.5 (714)	96.6	85.3	100 (171)	96.9	99.1 (544)	89.2	90.9	99.4
Enterobacter spp.												
Africa	72	100	9.7	7.0 (71)	83.3	61.1	16/16	91.7	94.6 (56)	75.0	79.2	95.8
Asia/Pacific Rim	167	90.4	4.2	3.7 (164)	80.8	48.5	100 (41)	85.6	94.4 (126)	68.3	70.1	97.6
Europe	1,173	97.2	4.8	4.8 (1,167)	93.3	59.8	90.1 (151)	94.5	97.7 (1,022)	71.7	73.5	97.1
Latin America	431	91.0	10.2	6.5	84.2	50.3	94.5 (55)	87.7	93.6 (376)	56.6	71.5	96.8
Middle East	130	100	3.8	3.8	90.0	60.0	10/12	96.9	99.2 (118)	63.8	73.1	96.9
North America	1,204	99.3	6.2	3.7 (1,194)	97.0	73.2	97.2 (457)	97.4	98.3 (747)	86.5	83.8	97.9
Globally	3,177	96.9	6.1	4.6 (3,157)	92.4	63.0	95.5 (732)	94.2	97.1 (2,445)	74.9	77.1	97.4
Serratia marcescens												
Africa	26	100	11.5	0.0 (25)	96.2	80.8	4/4	100	100 (22)	92.3	100	100
Asia/Pacific Rim	71	90.1	0.0	0.0	84.5	66.2	18/19	87.3	90.4 (52)	73.2	80.3	91.5
Europe	423	97.9	2.6	3.8 (421)	95.5	82.0	91.4 (70)	98.3	99.2 (353)	66.2	92.9	96.0
Latin America	149	77.9	7.4	3.4	82.6	60.4	15/17	85.2	91.7 (132)	51.7	81.2	94.0
Middle East	50	98.0	2.0	2.0	82.0	70.0	2/8	100	97.6 (42)	72.0	82.0	100
North America	531	99.1	2.1	0.9 (530)	97.4	82.7	91.0 (233)	97.6	97.7 (298)	83.4	95.5	97.0
Globally	1,250	95.6	3.0	2.2 (1,246)	93.6	78.3	89.7 (351)	95.9	97.0 (899)	73.0	91.6	96.2

[a] Percentages are presented only for groups with *n* values of ≥20. When *n* values were <20, numbers of susceptible isolates and total numbers of isolates are presented as fractions. Numbers in parentheses represent the number of isolates tested against an antimicrobial agent when the number tested was less than the total.

highest for imipenem (99.0%), tigecycline (96.5%), meropenem (95.6%), and amikacin (91.3%) (Table 1). Regional susceptibility rates were usually lowest in the African, Asian/Pacific Rim, and/or Latin American regions. *K. pneumoniae* susceptibility rates varied widely between regions, with ceftriaxone susceptibility rates varying by as much as 53.0% (ranging from 38.3% in Africa to 91.3% in North America). Ampicillin was notably less effective against *K. pneumoniae* than the other TEST antimicrobial agents, with a susceptibility rate of only 1.4% being observed worldwide (Table 1). The rates of ESBL production among *K. pneumoniae* isolates were low in North America (4.1%) but exceeded 40% in Africa and Latin America; the global average between 2004 and 2012 was 24.2% (Table 2).

Significant ($P < 0.001$) decreases in susceptibility rates over the course of the study were noted for amoxicillin-clavulanate, cefepime, ceftriaxone, levofloxacin, minocycline, and piperacillin-tazobactam. The rate of susceptibility to amoxicillin-clavulanate decreased from 78.2% (122/156 isolates) in 2004 to 65.5% (116/177 isolates) in 2012. The change for cefepime was from 90.4% ($n = 141$) in 2004 to 78.5% ($n = 139$) in 2012, that for ceftriaxone was from 76.3% ($n = 119$) to 68.4% ($n = 121$), that for levofloxacin was from 94.2% ($n = 147$) to 85.9% ($n = 152$), and

TABLE 2 Rates of resistant phenotypes collected from pediatric patients in TEST in 2004 to 2012

Location	Resistant phenotype (% [no. of isolates])				
	ESBL-positive *Escherichia coli*	ESBL-positive *Klebsiella pneumoniae*	ESBL-positive *Klebsiella oxytoca*	MDR *Acinetobacter baumannii*	β-Lactamase-positive *Haemophilus influenzae*
Africa	6.1 (5)	45.0 (27)	11.1 (1)	39.0 (16)	9.2 (8)
Asia/Pacific Rim	16.3 (25)	29.4 (40)	5.0 (1)	39.7 (31)	34.9 (59)
Europe	14.5 (160)	27.1 (244)	5.7 (19)	12.4 (54)	15.7 (315)
Latin America	24.5 (94)	43.6 (190)	11.1 (6)	51.1 (93)	23.9 (84)
Middle East	25.7 (26)	36.1 (48)	9.1 (1)	52.5 (32)	15.6 (31)
North America	2.1 (26)	4.1 (30)	1.7 (5)	5.6 (28)	31.4 (425)
Globally	11.0 (336)	24.2 (579)	4.6 (33)	19.5 (254)	22.1 (922)

that for piperacillin-tazobactam was from 89.1% ($n = 139$) to 79.1% ($n = 140$). The rate of susceptibility to minocycline decreased from 80.8% ($n = 126$) in 2004 to 58.9% (172/292 isolates) in 2010 and then increased to 80.2% ($n = 142$) in 2012.

The *K. pneumoniae* susceptibility rate was generally highest among ≥18-year-old patients in Asia/Pacific Rim, while the rate of susceptibility of *K. pneumoniae* isolates in the Middle East was highest in 1- to 5-year-old or 6- to 12-year-old patients (see Table S2 in the supplemental material). Statistically significant ($P < 0.01$) differences in susceptibility rates were observed between pediatric patient groups 1 to 5 years and 6 to 12 years of age in Latin America (for minocycline) and the Middle East (for cefepime), 1 to 5 years and 13 to 17 years of age in North America (for levofloxacin) and globally (for amikacin), and 6 to 12 years and 13 to 17 years of age globally (for amikacin). However, no trends were observed (see Table S3 in the supplemental material). Furthermore, statistically significant ($P < 0.01$) differences in antimicrobial susceptibility rates between adult and pediatric patient groups were observed in Asia/Pacific Rim, Europe, Latin America, the Middle East, and North America and globally; susceptibility rates were higher among adults in Asia/Pacific Rim, 1- to 5-year-old and 6- to 12-year-old patients in the Middle East, and 1- to 5-year-old patients in North America (see Table S4 in the supplemental material).

(iii) *Klebsiella oxytoca*. *K. oxytoca* was represented by 715 isolates globally between 2004 and 2012. The lowest rates of susceptibility were reported in Asia/Pacific Rim for most antimicrobial agents; data are incomplete for imipenem and meropenem (Table 1). All isolates were susceptible to imipenem, while high susceptibility rates were noted for tigecycline (99.4%), meropenem (99.1%), amikacin (97.9%), levofloxacin (96.9%), and cefepime (96.6%). ESBL production rates were low among *K. oxytoca* isolates, reaching a maximum of 11.1% in Africa and Latin America (Table 2).

A significant ($P < 0.01$) decrease in the susceptibility rate over the course of the study was noted only for minocycline. The susceptibility rate decreased from 94.4% (67/71 isolates) in 2004 to 80.3% (57/71 isolates) in 2010 and then increased to 90.9% (70/77 isolates) in 2012.

Compared with susceptibility rates among isolates from patients ≥18 years of age, susceptibility rates were often higher in the pediatric age groups (see Table S2 in the supplemental material). Statistically significant ($P < 0.01$) differences in susceptibility rates were observed between pediatric patient groups 1 to 5 years and 13 to 17 years of age in Europe (for amoxicillin-clavulanate and levofloxacin) and globally (for levofloxacin) (see Table S3 in the supplemental material). Statistically significant ($P < 0.01$) differences in susceptibility rates were also observed between pediatric (1 to 5 years of age) and adult patients in Europe (for amoxicillin-clavulanate and levofloxacin), in North America (for ampicillin), and globally (for amoxicillin-clavulanate, levofloxacin, and piperacillin-tazobactam) (see Table S4 in the supplemental material). In all cases in which significant differences in susceptibility rates occurred, the highest susceptibility rate was seen among 1- to 5-year-old patients.

(iv) *Enterobacter* spp. A total of 3,177 isolates of *Enterobacter* spp. were collected as part of the TEST between 2004 and 2012 (Table 2). The most active agent against *Enterobacter* spp. was tigecycline, with a susceptibility rate of ≥97.4% being observed globally (Table 1). High rates of susceptibility were also noted for meropenem (97.1%), amikacin (96.9%), and imipenem (95.5%). The rates of susceptibility to cephalosporins varied widely between regions, with variations of 80.8% (Asia/Pacific Rim) to 97.0% (North America) for cefepime and 48.5% (Asia/Pacific Rim) to 73.2% (North America) for ceftriaxone.

The only agent for which a significant decrease in the susceptibility rate over the course of the study was recorded was minocycline. The rate of susceptibility to minocycline decreased from 89.6% (199/222 isolates) in 2004 to 56.7% (229/404 isolates) in 2010 and then increased, reaching 84.8% (251/296 isolates) in 2012 ($P < 0.0001$).

No clear pattern in susceptibility rates between the age groups was seen either regionally or globally (see Table S2 in the supplemental material). Statistically significant ($P < 0.01$) differences in ceftriaxone susceptibility rates were observed globally between pediatric patients 1 to 5 years and 13 to 17 years of age, as well as 6 to 12 years and 13 to 17 years of age; susceptibility rates were highest among 13- to 17-year-old patients (see Table S3 in the supplemental material). Significant ($P < 0.01$) differences in susceptibility rates between adult and pediatric patients were observed in Europe, Latin America, and North America and globally (see Table S4 in the supplemental material). When statistically significant differences in antimicrobial susceptibility rates were noted, isolates from ≥18-year-old patients showed lower rates of susceptibility to all antibiotics (see Table S4 in the supplemental material).

(v) *Serratia marcescens*. *S. marcescens* ($n = 1,250$) showed high rates of susceptibility to meropenem (97.0%), tigecycline (96.2%), levofloxacin (95.6%), and amikacin (95.6%) (Table 1). Cephalosporin susceptibility rates varied widely between regions, with variations of 82.0% (Middle East) to 97.4% (North America) for cefepime and 60.4% (Latin America) to 82.7% (North America) for ceftriaxone. The rates of susceptibility to many agents were

TABLE 3 Susceptibility rates among non-*Enterobacteriaceae* isolates collected from pediatric patients (<18 years of age) during TEST in 2004 to 2012

Species and location	No. of isolates	% of susceptible isolates (no. tested) or no. of susceptible isolates/total no. of isolates[a]											
		AMK	AMC	AMP	FEP	CAZ	CRO	IPM	LVX	MEM	MIN	TZP	TIG
Acinetobacter baumannii													
Africa	41	43.9			34.1	31.7	19.5	12/18	48.8	43.5 (23)	70.7	41.5	
Asia/Pacific Rim	78	55.1			46.2	51.3	21.8	70.0 (20)	53.8	53.4 (58)	92.3	47.4	
Europe	437	82.8			75.1	72.5	41.4	89.4 (66)	80.5	85.7 (371)	92.7	71.4	
Latin America	182	42.9			44.0	33.0	19.2	9/11	40.7	55.0 (171)	84.6	36.8	
Middle East	61	44.3			42.6	34.4	24.6	1/2	54.1	40.7	82.0	31.1	
North America	503	94.2			81.5	81.7	50.9	96.5 (202)	89.1	95.0 (3.1)	93.8	88.5	
Globally	1,302	77.0			68.7	66.2	39.3	90.9 (319)	74.4	77.6 (983)	90.8	68.9	
Haemophilus influenzae													
Africa	87		100	90.8	100		100	18/18	100	100 (69)	100	100	98.9
Asia/Pacific Rim	169		98.2	60.4	99.4		100	100 (46)	100	100 (123)	99.4	100	98.8
Europe	2,008		99.8	82.8	99.5		99.9	100 (310)	100	99.9 (1,698)	98.3	99.9	99.2
Latin America	351		99.4	74.9	99.4		99.7	100 (50)	100	100 (301)	98.0	98.6	99.1
Middle East	199		100	82.9	100		100	13/13	100	100 (186)	98.0	99.5	99.0
North America	1,352		99.8	67.5	99.0		100	100 (599)	100	99.5 (753)	99.4	99.9	99.3
Globally	4,166		99.7	76.4	99.4		99.9	100 (1,036)	100	99.8 (3,130)	98.7	99.8	99.2
Pseudomonas aeruginosa													
Africa	71	88.7			70.4	80.3		14/18	77.5	71.7 (53)		73.2	
Asia/Pacific Rim	124	79.0			68.5	62.9		71.4 (35)	73.4	70.8 (89)		68.5	
Europe	963	91.2			82.8	79.9		79.9 (154)	81.3	79.7 (809)		82.1	
Latin America	340	76.8			71.8	59.4		69.0 (42)	70.0	61.1 (298)		65.9	
Middle East	99	89.9			75.8	69.7		3/4	77.8	81.1 (95)		73.7	
North America	974	95.9			87.2	87.7		89.1 (404)	84.2	86.5 (570)		88.6	
Globally	2,571	90.4			81.7	78.9		84.3 (657)	80.3	78.3 (1,914)		81.2	

[a] Percentages are presented only for groups with *n* values of ≥20. When *n* values were <20, numbers of susceptible isolates and total numbers of isolates are presented as fractions. Numbers in parentheses represent the number of isolates tested against an antimicrobial agent when the number tested was less than the total.

lower in Asia/Pacific Rim, Latin America, and/or the Middle East than in North America, as well as the global average (Table 1).

As seen with other organisms in this study, the only agent for which a significant decrease in the susceptibility rate was recorded was minocycline. The rate of susceptibility was 92.0% (104/113 isolates) in 2004 and decreased to 40.6% (52/128 isolates) in 2010 before increasing to 83.5% (91/109 isolates) in 2012.

In the global collection of *S. marcescens* isolates, no clear pattern in susceptibility rates among the age groups was observed (see Table S2 in the supplemental material). Statistically significant ($P < 0.01$) differences in ampicillin susceptibility rates were observed globally between pediatric patients 1 to 5 years and 13 to 17 years of age (see Table S3 in the supplemental material). Significant ($P < 0.01$) differences in susceptibility rates were also observed between pediatric and adult patients in Asia/Pacific Rim, Europe, Latin America, the Middle East, and North America and globally. When significant differences existed between age groups, susceptibility rates were generally higher among adult patients (see Table S4 in the supplemental material).

Non-*Enterobacteriaceae*. (i) *Acinetobacter baumannii*. A total of 1,302 isolates of *A. baumannii* were collected globally for the TEST between 2004 and 2012. The lowest MIC_{90}s for *A. baumannii* were reported for tigecycline, with values of 1 mg/liter in all regions except the Middle East (2 mg/liter) (see Table S5 in the supplemental material). Imipenem and minocycline exhibited the highest susceptibility rates with *A. baumannii*, i.e., 90.9% and 90.8%, respectively, globally (Table 3). Susceptibility rates for all agents were consistently higher in Europe and North America than in the other collection regions (Table 3). In contrast, 77.6% of *A. baumannii* isolates were susceptible to meropenem. Globally, 19.5% of all *A. baumannii* isolates were multidrug resistant (Table 2). Only 5.6% of isolates were MDR in North America, compared with >50% in Latin America and the Middle East. No statistically significant changes in susceptibility were recorded over time for any antimicrobial agents with *A. baumannii*.

Statistically significant ($P < 0.01$) differences in susceptibility rates were observed between pediatric patient groups 1 to 5 years and 6 to 12 years of age in Europe (for amikacin, cefepime, ceftazidime, ceftriaxone, levofloxacin, and piperacillin-tazobactam), in Latin America (for amikacin), and globally (for amikacin, ceftazidime, and imipenem) and between groups 1 to 5 years and 13 to 17 years of age for isolates from Europe (for amikacin, cefepime, ceftazidime, levofloxacin, and piperacillin-tazobactam) and globally (for amikacin, cefepime, ceftazidime, ceftriaxone, levofloxacin, and piperacillin-tazobactam). When statistically significant differences in susceptibility rates were observed between patient age groups, susceptibility rates were highest among 1- to 5-year-old patients (see Table S3 in the supplemental material). Additionally, significant ($P < 0.01$) differences in susceptibility rates between pediatric and adult patients were evident in Africa, Europe, Latin America, and North America and globally (see Table S4 in the supplemental material). Global susceptibility rates were higher among pediatric patients than adult patients for all antimicrobial agents (see Table S6 in the supplemental material).

(ii) *H. influenzae*. *H. influenzae* ($n = 4,166$) showed high levels

of susceptibility, with low MIC_{90}s, for most agents in the TEST antimicrobial panel; the most notable exception was ampicillin, for which susceptibility rates ranged from 60.4% (Asia/Pacific Rim) to 90.8% (Africa) (Table 3). The global rate of β-lactamase production was 22.1% (Table 2).

No statistically significant differences in susceptibility rates between the different patient age groups or between pediatric and adult patients (data not shown) during the study period were observed. Ampicillin susceptibility rates were reduced in Asia/Pacific Rim, particularly among juvenile patients (see Table S6 in the supplemental material).

(iii) *P. aeruginosa*. Globally, 2,571 isolates of *P. aeruginosa* were collected as a part of the TEST in 2004 to 2012. The most active antimicrobial agent against this pathogen was amikacin (susceptibility rate of 90.4% globally), with relatively high susceptibility rates also being observed for imipenem (84.3%), cefepime (81.7%), piperacillin-tazobactam (81.2%), and levofloxacin (80.3%). Tigecycline was not active against *P. aeruginosa*. Regional susceptibility rates were highest in North America (Table 3).

The rates of susceptibility to ceftazidime and piperacillin-tazobactam for *P. aeruginosa* decreased significantly ($P < 0.01$) between 2004 and 2012. For both agents, the rates of susceptibility were lowest in 2009 and then increased. The rates of susceptibility to ceftazidime were 86.9% (172/198 isolates) in 2004, 68.0% (270/397 isolates) in 2009, and 86.7% (241/278 isolates) in 2012. For piperacillin-tazobactam, susceptibility rates were 92.4% (183/198 isolates) in 2004, 70.5% (280/397 isolates) in 2009, and 86.0% (239/278 isolates) in 2012.

Antimicrobial susceptibility among *P. aeruginosa* was generally lower among isolates from Asia/Pacific Rim, Latin America, and the Middle East, compared with other regions, across all patient age groups. The rates of susceptibility to cephalosporins and piperacillin-tazobactam were lower among 6- to 12-year-old patients than other age groups from Africa, although isolate numbers were low ($n = 26$) (see Table S6 in the supplemental material). Statistically significant ($P < 0.01$) differences in susceptibility rates were observed between isolates from pediatric patient groups 1 to 5 years and 6 to 12 years of age in Europe (for levofloxacin), in North America (for amikacin), and globally (for levofloxacin), between groups 1 to 5 years and 13 to 17 years of age in Europe (for amikacin and levofloxacin), in North America (for amikacin, cefepime, and levofloxacin), and globally (for amikacin, cefepime, and levofloxacin), and between groups 6 to 12 years and 13 to 17 years of age for isolates from Europe and globally (both for amikacin). When statistically significant differences between pediatric age groups were observed, susceptibility rates were higher among 1- to 5-year-old patients in most cases (see Table S3 in the supplemental material). Some statistically significant ($P < 0.01$) differences in antimicrobial susceptibility rates between adult and pediatric patients were observed in Europe, Latin America, and North America and globally. When significant differences between pediatric and adult patients were observed, higher susceptibility rates were observed among pediatric patients for all antibiotics except amikacin (see Table S4 in the supplemental material).

DISCUSSION

The relative prevalence rates of Gram-negative pathogens among pediatric patients vary widely in relation to numerous factors, such as region, infection type, or ward type. Henderson et al. showed that Gram-positive pathogens were considerably more common among pediatric patients with bacteremia in England and Wales, with the most common Gram-negative pathogens being *E. coli* and *Neisseria meningitidis*, which accounted for only 5% of infections each (11). In a pediatric intensive care unit (ICU) in Brazil, however, Gram-negative pathogens accounted for the largest proportion of infections (47%) among cases of sepsis, pneumonia, and urinary tract infections, with *E. coli* and *Enterococcus faecalis* being the most common pathogens encountered (18% each) (12). An even more dramatic difference was observed among nosocomial infections (NIs) in a general pediatric hospital in Turkey, where Gram-negative pathogens accounted for 79.8% of cultured pathogens among 229 NIs; the most common pathogens identified were *Klebsiella* spp. (28.7%), *P. aeruginosa* (19.1%), and *E. coli* (9.6%) (13).

In the current study, ESBL-positive *K. pneumoniae*, *K. oxytoca*, and *E. coli* isolates were less common in North America (4.1%, 1.7%, and 2.1%, respectively) than in other regions. A recent study in Texas supports these low pediatric rates in North America, with an ESBL rate of 6.6% being seen among 1,430 *Enterobacteriaceae* isolates from patients in a pediatric tertiary care facility (14). Hawser et al., reporting on the Study for Monitoring Antimicrobial Resistance Trends (SMART), also reported a low rate (6%) of ESBL production among *E. coli* isolates from North America, although the isolates were collected from intra-abdominal infections (IAIs) and not specifically from pediatric patients (15). The ESBL-positive *E. coli* rates reported by Hawser et al. (15) closely mirrored those seen in the current study for Latin America (22.9%, compared with 24.5% in the current study) and Africa (6.3%, compared with 6.1% in the current study), although the rate reported by Hawser et al. (15) for Asia (38.3%) was more than double the rate seen in this study (16.3%). This dramatic difference is likely due in part to differences in the geographical zonation used in the two studies and the fact that Hawser et al. (15) examined only IAI isolates and not specifically pediatric isolates.

Another recent report from the SMART examined Gram-negative bacteria from IAIs among general pediatric patients and pediatric ICU patients globally between 2008 and 2010 (16). The authors reported ESBL production among 11.0% of *E. coli* isolates, identical to the global rate shown for pediatric patients in the current study. The SMART also showed 38.9% ESBL prevalence among *K. pneumoniae* isolates, considerably higher than the 24.2% recorded by the TEST between 2004 and 2012. This difference could be due in part to the SMART report sampling a considerably shorter period of time (only 3 years, compared to 9 years) and focusing only on IAIs.

Tigecycline is not currently indicated for the treatment of infections in patients <18 years of age, and it should be used for pediatric patients only when no alternative antimicrobial agents are available (10). Purdy et al. recently reported on a phase II trial designed to assess the pharmacokinetic properties, safety profile, and efficacy of tigecycline in pediatric patients 8 to 11 years of age with community-acquired pneumonia, complicated intra-abdominal infections, or complicated skin and skin structure infections (17). Because of possible effects on tooth development, use among patients under 8 years of age is not recommended.

Published reports of tigecycline use among children are uncommon, but successful treatments have been described, usually against MDR isolates when tigecycline was used as a salvage treatment. De Luca et al. reported a case of successful treatment of

sepsis due to MDR *A. baumannii* with tigecycline plus colistin in a patient with neurotoxoplasmosis (18). Ozdemir et al. successfully treated a MDR *E. coli* bacteremic infection in a young girl with acute myeloid leukemia (19). Six of nine patients 0 to 14 years of age with carbapenem-resistant *K. pneumoniae* infections showed complete resolution of the infections after treatment with 1 mg/kg tigecycline every 12 h, with no adverse events reported (20).

Although tigecycline is not indicated for the treatment of infections caused by *A. baumannii*, increases in the prevalence of infections caused by carbapenem-resistant *A. baumannii* often leave clinicians with few practical treatment options. Tigecycline has been shown to possess good *in vitro* activity against *A. baumannii*, including carbapenem-resistant or MDR isolates (21–23). Tigecycline performed well against *A. baumannii* in the current study, with MIC_{90} values of 1 mg/liter reported globally and in most regions (a MIC_{90} of 2 mg/liter was observed in the Middle East).

Clinical results for tigecycline treatment of infections caused by *A. baumannii* have been inconsistent. Tsioutis et al. reported complete resolution of infections and shorter hospital stays among patients in Greece who were infected with pan-drug-resistant Gram-negative pathogens and treated with tigecycline (24). This was a relatively small study, however, due to the scarcity of pan-drug-resistant pathogens, with only 21 patients involved. In a retrospective study of 34 patients with MDR *A. baumannii* infections in the United Kingdom, Gordon and Wareham reported positive clinical outcomes for 23 (68%) of 34 patients (25). The correlation between clinical results and microbiological eradication was poor, with eradication being observed for only 10 patients (29%). The clinical efficacy of tigecycline against infections caused by *A. baumannii* thus remains unclear.

Tigecycline is effective in the treatment of patients with complicated skin and soft tissue infections and complicated IAIs caused by MDR pathogens (26), although tigecycline resistance has been shown to develop during clinical therapy. For example, New Delhi metallo-β-lactamase-1-producing *E. coli* developed resistance to tigecycline after long-term (53-day) tigecycline treatment of a patient with calciphylaxis, with the tigecycline MIC increasing from <0.25 mg/liter to 8 mg/liter over the course of treatment (27). High-dose tigecycline therapy may be effective for the treatment of highly resistant pathogens. Cunha showed that high-dose tigecycline therapy (a loading dose of 200 mg in 400 ml of solution, followed by 100 mg in 200 ml of solution daily) was effective for the treatment of urosepsis caused by MDR *K. pneumoniae* and MDR *A. baumannii*, with no adverse events reported (due to the large volume of intravenous solution used) (28); tigecycline is not indicated for the treatment of urosepsis. This use of high-dose tigecycline therapy may help to reduce or even circumvent the development of tigecycline resistance during antimicrobial treatment of highly resistant pathogens.

Dramatic differences in antimicrobial susceptibility between isolates derived from pediatric patients versus adult patients have been demonstrated in this study. Similar results have been shown previously for Gram-negative pathogens. After investigating susceptibility among *E. coli* isolates from pediatric (≤12 years of age) and adult patients from emergency room, hospital, and outpatient settings in a single hospital in the United States, Boggan et al. reported that rates of resistance to amoxicillin, amikacin, and cotrimoxazole were higher among isolates from pediatric patients (29); conversely, pediatric *E. coli* isolates showed reduced levels of resistance to amoxicillin-clavulanate and ciprofloxacin. Pediatric *E. coli* urinary isolates were shown to be significantly more resistant to ampicillin and ticarcillin but more susceptible to quinolones than were isolates from adults in a general tertiary care hospital in Greece between 2003 and 2008 (30). In a report of Gram-negative isolates collected from pediatric and adult patients with appendicitis, Lob et al. showed that 17.7% of isolates from adult patients were ESBL positive, compared to only 11.4% from pediatric patients; furthermore, *E. coli* isolates from adult patients were significantly ($P < 0.05$) less susceptible to most antimicrobial agents tested than were isolates from pediatric patients (1). In this study, 11.0% of *E. coli* isolates and 24.2% of *K. pneumoniae* isolates were ESBL positive.

While ≤10% of the *Enterobacteriaceae* isolates in this study were resistant to amikacin, carbapenems, or tigecycline, multidrug resistance is becoming more common among key pathogens, including *E. coli* and *K. pneumoniae* (31). Tigecycline retains activity against many pathogens that are resistant to other widely used antimicrobial agents, including the carbapenems, and so may provide an important therapeutic alternative for the treatment of drug-resistant infections (32).

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REFERENCES

1. **Lob SH, Badal RE, Bouchillon SK, Hawser SP, Hackel MA, Hoban DJ.** 2013. Epidemiology and susceptibility of Gram-negative appendicitis pathogens: SMART 2008–2010. Surg Infect (Larchmt) **14:**203–208. http://dx.doi.org/10.1089/sur.2012.034.
2. **Japoni A, Farshad S, Alborzi A, Kalani M, Rafaatpour N, Oboodi B, Pourabbas B.** 2008. Epidemiology and antibacterial susceptibility patterns of bloodstream infections, 2001–2004: an experience with BACTEC 9240 in southern Iran. Pak J Biol Sci **11:**422–427. http://dx.doi.org/10.3923/pjbs.2008.422.427.
3. **Calitri C, Virano S, Scolfaro C, Raffaldi I, De Intinis G, Gregori G, Bianciotto M, Tovo PA.** 2012. Community-acquired bloodstream infections among paediatric patients admitted to an Italian tertiary referral centre: a prospective survey. Infez Med **20:**176–181.
4. **Kunz AN, Brook I.** 2010. Emerging resistant Gram-negative aerobic bacilli in hospital-acquired infections. Chemotherapy **56:**492–500. http://dx.doi.org/10.1159/000321018.
5. **Ladhani S, Pebody RG, Ramsay ME, Lamagni TL, Johnson AP, Sharland M.** 2010. Continuing impact of infectious diseases on childhood deaths in England and Wales, 2003–2005. Pediatr Infect Dis J **29:**310–313. http://dx.doi.org/10.1097/INF.0b013e3181d73322.
6. **Jaramillo-Bustamante JC, Marín-Agudelo A, Fernández-Laverde M, Bareño-Silva J.** 2012. Epidemiology of sepsis in pediatric intensive care units: first Colombian multicenter study. Pediatr Crit Care Med **13:**501–508. http://dx.doi.org/10.1097/PCC.0b013e31823c980f.
7. **Clinical and Laboratory Standards Institute.** 2009. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—8th ed. Document M7-A8. Clinical and Laboratory Standards Institute, Wayne, PA.
8. **Clinical and Laboratory Standards Institute.** 2010. Performance standards for antimicrobial susceptibility testing—20th ed. Document M100-S20. Clinical and Laboratory Standards Institute, Wayne, PA.
9. **Clinical and Laboratory Standards Institute.** 2010. Performance standards for antimicrobial susceptibility testing—20th ed (June 2010 up-

date). Document M100-S20U. Clinical and Laboratory Standards Institute, Wayne, PA.
10. **Wyeth Pharmaceuticals.** 2013. Tygacil package insert. Pfizer Inc., Philadelphia, PA. http://www.pfizerpro.com/hcp/tygacil.
11. **Henderson KL, Johnson AP, Muller-Pebody B, Charlett A, Gilbert R, Sharland M.** 2010. The changing aetiology of paediatric bacteraemia in England and Wales, 1998–2007. J Med Microbiol **59:**213–219. http://dx.doi.org/10.1099/jmm.0.015271-0.
12. **Porto JP, Mantese OC, Arantes A, Freitas C, Gontijo Filho PP, Ribas RM.** 2012. Nosocomial infections in a pediatric intensive care unit of a developing country: NHSN surveillance. Rev Soc Bras Med Trop **45:**475–479. http://dx.doi.org/10.1590/S0037-86822012005000003.
13. **Balaban I, Tanır G, Metin Timur O, Oz FN, Aydın Teke T, Bayhan GI, Sözak N, Göl N.** 2012. Nosocomial infections in the general pediatric wards of a hospital in Turkey. Jpn J Infect Dis **65:**318–321. http://dx.doi.org/10.7883/yoken.65.318.
14. **Chandramohan L, Revell PA.** 2012. Prevalence and molecular characterization of extended-spectrum-β-lactamase-producing *Enterobacteriaceae* in a pediatric patient population. Antimicrob Agents Chemother **56:**4765–4770. http://dx.doi.org/10.1128/AAC.00666-12.
15. **Hawser SP, Badal RE, Bouchillon SK, Hoban DJ, Biedenbach DJ, Cantón R, Paterson DL.** 2013. Monitoring the global *in vitro* activity of ertapenem against *Escherichia coli* from intra-abdominal infections: SMART 2002–2010. Int J Antimicrob Agents **41:**224–228. http://dx.doi.org/10.1016/j.ijantimicag.2012.10.014.
16. **Badal RE, Bouchillon SK, Lob SH, Hackel MA, Hawser S, Hoban DJ.** 2013. Etiology, extended-spectrum β-lactamase rates, and antimicrobial susceptibility of Gram-negative bacilli causing intra-abdominal infections in patients in general pediatric and pediatric intensive care units: global data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) 2008–2010. Pediatr Infect Dis J **32:**636–640. http://dx.doi.org/10.1097/INF.0b013e3182886377.
17. **Purdy J, Jouve S, Yan JL, Balter I, Dartois N, Cooper CA, Korth-Bradley J.** 2012. Pharmacokinetics and safety profile of tigecycline in children aged 8 to 11 years with selected serious infections: a multicenter, open-label, ascending-dose study. Clin Ther **34:**496–507. http://dx.doi.org/10.1016/j.clinthera.2011.12.010.
18. **De Luca M, Angelino G, Calò Carducci FI, Martino A, Bernardi S, Bernaschi P, Carletti M, D'Argenio P, Palma P.** 2011. Multidrug-resistant *Acinetobacter baumannii* infection in children. BMJ Case Rep **2011:**pii=bcr0220113807. http://dx.doi.org/10.1136/bcr.02.2011.3807.
19. **Ozdemir H, Ciftçi E, Karbuz A, Oktay G, Aysev D, Yavuz G, Ince E.** 2012. Successful treatment of multidrug-resistant *Escherichia coli* bacteremia with tigecycline in an acute myeloid leukemia child. Turk J Pediatr **54:**59–60.
20. **Hurtado IC, Trujillo M, Restrepo A, Garcés C, Tamayo C, Mesa JG.** 2012. Experience with tigecycline compassionate use in pediatric patients infected with carbapenem resistant *Klebsiella pneumoniae*. Rev Chilena Infectol **29:**317–321. http://dx.doi.org/10.4067/S0716-10182012000300011.
21. **Aimsaad L, Diraphat P, Utrarachkij F, Thunyaharn S, Samakoses R, Siripanichgon K.** 2009. Epidemiological characteristics of *Acinetobacter baumannii* infections at Phramongkutklao Hospital. J Med Assoc Thai **92**(Suppl 7)**:**S164–S172.
22. **Schimith Bier KE, Luiz SO, Scheffer MC, Gales AC, Paganini MC, Nascimento AJ, Carignano E, Dalla Costa LM.** 2010. Temporal evolution of carbapenem-resistant *Acinetobacter baumannii* in Curitiba, southern Brazil. Am J Infect Control **38:**308–314. http://dx.doi.org/10.1016/j.ajic.2009.09.012.
23. **Buccoliero G, Morelli E, Lonero G, Romanelli C, Resta F, Pisconti S.** 2012. Rapid spread of multiresistant *Acinetobacter baumannii* isolates in intensive care units (ICUs) and *in vitro* activity of colistin and tigecycline. Infez Med **20:**296–298.
24. **Tsioutis C, Kritsotakis EI, Maraki S, Gikas A.** 2010. Infections by pandrug-resistant Gram-negative bacteria: clinical profile, therapeutic management, and outcome in a series of 21 patients. Eur J Clin Microbiol Infect Dis **29:**301–305. http://dx.doi.org/10.1007/s10096-009-0857-7.
25. **Gordon NC, Wareham DW.** 2009. A review of clinical and microbiological outcomes following treatment of infections involving multidrug-resistant *Acinetobacter baumannii* with tigecycline. J Antimicrob Chemother **63:**775–780. http://dx.doi.org/10.1093/jac/dkn555.
26. **Heizmann WR, Dupont H, Montravers P, Guirao X, Eckmann C, Bassetti M, García MS, Capparella MR, Simoneau D, Bodmann KF.** 2013. Resistance mechanisms and epidemiology of multiresistant pathogens in Europe and efficacy of tigecycline in observational studies. J Antimicrob Chemother **68**(Suppl 2)**:**ii45–ii55. http://dx.doi.org/10.1093/jac/dkt144.
27. **Stone NR, Woodford N, Livermore DM, Howard J, Pike R, Mushtaq S, Perry C, Hopkins S.** 2011. Breakthrough bacteraemia due to tigecycline-resistant *Escherichia coli* with New Delhi metallo-β-lactamase (NDM)-1 successfully treated with colistin in a patient with calciphylaxis. J Antimicrob Chemother **66:**2677–2678. http://dx.doi.org/10.1093/jac/dkr337.
28. **Cunha BA.** 2009. Pharmacokinetic considerations regarding tigecycline for multidrug-resistant (MDR) *Klebsiella pneumoniae* or MDR *Acinetobacter baumannii* urosepsis. J Clin Microbiol **47:**1613. http://dx.doi.org/10.1128/JCM.00404-09.
29. **Boggan JC, Navar-Boggan AM, Jhaveri R.** 2012. Pediatric-specific antimicrobial susceptibility data and empiric antibiotic selection. Pediatrics **130:**e615–e622. http://dx.doi.org/10.1542/peds.2012-0563.
30. **Mantadakis E, Tsalkidis A, Panopoulou M, Pagkalis S, Tripsianis G, Falagas ME, Kartali-Ktenidou S, Chatzimichael A.** 2011. Antimicrobial susceptibility of pediatric uropathogens in Thrace, Greece. Int Urol Nephrol **43:**549–555. http://dx.doi.org/10.1007/s11255-010-9768-x.
31. **Catal F, Bavbek N, Bayrak O, Karabel M, Karabel D, Odemis E, Uz E.** 2009. Antimicrobial resistance patterns of urinary tract pathogens and rationale for empirical therapy in Turkish children for the years 2000–2006. Int Urol Nephrol **41:**953–957. http://dx.doi.org/10.1007/s11255-008-9445-5.
32. **Kresken M, Becker K, Seifert H, Leitner E, Körber-Irrgang B, von Eiff C, Löschmann PA.** 2011. Resistance trends and *in vitro* activity of tigecycline and 17 other antimicrobial agents against Gram-positive and Gram-negative organisms, including multidrug-resistant pathogens, in Germany. Eur J Clin Microbiol Infect Dis **30:**1095–1103. http://dx.doi.org/10.1007/s10096-011-1197-y.