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Antimicrobial activity against a global collection of skin and skin structure pathogens: results from the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.), 2010–2014

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SUMMARY

Background: As part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) we report antimicrobial resistance among Gram-positive and Gram-negative isolates collected globally from integumentary sources between 2010 and 2014.

Methods: Minimum inhibitory concentrations and antimicrobial resistance were determined according to Clinical and Laboratory Standards Institute guidelines (US Food and Drug Administration breakpoints against tigecycline). The Cochran–Armitage trend test was used to identify statistically significant changes in resistance.

Results: Global rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Acinetobacter baumannii* were 38% and 43%, respectively. No *S. aureus* isolates were resistant to linezolid or vancomycin; all isolates were susceptible to tigecycline. Two percent of *Enterococcus faecalis* and 28% of *Enterococcus faecium* were vancomycin-resistant. Extended-spectrum β-lactamase (ESBL) producers accounted for 22% of *Klebsiella pneumoniae* and 16% of *Escherichia coli*. Resistance to minocycline among *E. faecalis*, *E. faecium*, *K. pneumoniae*, and *E. coli* decreased significantly ($p < 0.0001$). There were significant increases ($p < 0.0001$) in *A. baumannii* resistance to cefepime, ceftazidime, ceftriaxone, levofloxacin, meropenem, and piperacillin–tazobactam.

Conclusions: Among isolates from integumentary sources, rates of MRSA and ESBL-producing Enterobacteriaceae are stabilizing. Carbapenems and tigecycline have retained their *in vitro* activity against Gram-positive and Gram-negative organisms. Few agents were active against *A. baumannii*; its increasing resistance is cause for concern.

1. Introduction

Skin and skin structure infections (SSSIs) are mostly uncomplicated (for example, impetigo and furuncles) and involve invasion of the dermis or epidermis by Gram-positive bacteria, most frequently *Staphylococcus aureus* and *Streptococcus pyogenes*.[1–3] Complicated SSSIs (cSSSIs) arise when bacterial infection involves deeper soft tissues (for example, fascia and muscle), and surgical intervention is often required.[3] These cSSSIs include secondary skin infections that arise from pre-existing nosocomial infections, predisposing risk factors, or comorbidities such as chronic skin conditions, vascular insufficiency, peripheral neuropathy, immunodeficiency, diabetes mellitus, cellulitis, or obesity.[2,4] Causative pathogens associated with cSSSIs include Gram-positive and Gram-negative organisms, as well as their resistant phenotypes, such as methicillin-resistant *S. aureus* (MRSA).[5,6] Gram-negative organisms associated with cSSSIs include *Enterobacter spp.*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[7] Complicated SSSIs pose diagnostic and therapeutic challenges and usually require intravenous antibiotic therapy, surgical intervention, and hospitalization, which contribute to increasing morbidity and mortality rates, as well as being an economic and healthcare burden.[5,8,9]

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Tigecycline is a broad-spectrum antimicrobial agent that has activity against Gram-positive and Gram-negative organisms, as well as multidrug-resistant (MDR) pathogens. It is licensed for the treatment of cSSSIs, complicated intra-abdominal infections (cIAIs), and community-acquired bacterial pneumonia in the USA, and for cSSSIs and cIAIs in Europe.[10,11]

The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is a global multicentre antimicrobial surveillance study that commenced in 2004. The study monitors the *in vitro* activity of tigecycline and comparator agents against a range of clinically important Gram-positive and Gram-negative organisms. This paper reports the antimicrobial resistance rates among isolates collected globally from integumentary sources between 2010 and 2014, and serves as an update of the previous publication by Namdari et al., which covered the period 2004–2009.[12] Also presented is an analysis of rates of antimicrobial resistance among isolates collected between 2004 and 2014.

2. Materials and methods

Between 2010 and 2014, global centres participating in T.E.S.T. submitted a minimum of 65 Gram-positive and 135 Gram-negative isolates. A range of culture sources were acceptable, including integumentary sources such as abscesses, burns, cellulitis, skin ulcers, and wounds. Isolates from both inpatients and outpatients with documented hospital- or community-acquired infections were included in the study. Only a single isolate per patient was allowed in the study, and patient age, sex, medical history, and previous antimicrobial use were not considered relevant. International Health Management Associates (IMHA, Schaumburg, IL, USA) were responsible for isolate collection, identification, and transportation, and for management of a centralized database. Quality control checks were carried out on approximately 10% of isolates annually.

Broth microdilution methodology according to the Clinical and Laboratory Standards Institute (CLSI) guidelines[13] was used to determine minimum inhibitory concentrations (MICs); detailed methodology has been described elsewhere.[14] The antimicrobial panel included amoxicillin–clavulanate, ampicillin, ceftriaxone, levofloxacin, meropenem, minocycline, piperacillin–tazobactam, and tigecycline. In addition, Gram-negative organisms were tested against amikacin, cefepime, and ceftazidime, and Gram-positive organisms were tested against linezolid, penicillin, and vancomycin. Antimicrobial susceptibility was determined using CLSI interpretive criteria,[15] except for tigecycline for which the US Food and Drugs Administration-approved breakpoints were used.[16]

Methicillin resistance in *S. aureus* and extended-spectrum β-lactamase (ESBL) production among *E. coli* and *Klebsiella spp.* was determined by IHMA according to CLSI guidelines.[15]

Multidrug resistance in this study was defined as resistance to three or more classes of antimicrobial agents. The classes used to define MDR *Acinetobacter baumannii* were aminoglycosides (amikacin), β-lactams (cefepime, ceftazidime, ceftriaxone, or piperacillin–tazobactam), carbapenems (imipenem/meropenem), fluoroquinolones (levofloxacin), and tetracyclines (minocycline); the classes used to define MDR *P. aeruginosa* were aminoglycosides (amikacin), β-lactams (cefepime, ceftazidime, or piperacillin–tazobactam), carbapenems (imipenem/meropenem), and fluoroquinolones (levofloxacin).

Statistically significant changes in resistance between 2010–2014 and 2004–2014 were analyzed using the Cochran–Armitage trend test. Due to the large volume of trend tests undertaken, *p*-values of $p < 0.01$ were regarded as statistically significant.

3. Results

Data are presented for a total of 13 856 isolates: 6752 Gram-positive and 7104 Gram-negative strains collected from integumentary sources between 2010 and 2014. In total, 274 global T.E.S.T. study centres submitted isolates between 2010 and 2014: six centres in Africa, 153 in Europe, 31 in Latin America, 11 in the Middle East, and 73 centres in North America. The Asia-Pacific Rim did not submit isolates between 2010 and 2014. Not every centre submitted isolates every year.

3.1. Gram-positive organisms

3.1.1. Staphylococcus aureus

Between 2010 and 2014, a total of 5118 isolates of *S. aureus* sourced globally from integumentary sources were submitted to T.E.S.T., of which 38% were MRSA (Table 1). MRSA rates varied from 26%–30% in Africa, Europe, and the Middle East, to 50% in North America and 55% in Latin America (Table 2).

Among *S. aureus*, global rates of resistance were highest to levofloxacin (32%); 70% of MRSA isolates were resistant to levofloxacin. No *S. aureus* isolates were resistant to linezolid or vancomycin; all isolates were susceptible to tigecycline (Table 3).

Overall, global rates of MRSA significantly decreased between 2004 and 2014 ($p < 0.0001$) (Table 1). Resistance among MRSA to levofloxacin, linezolid, tigecycline, and vancomycin for the period 2004–2014 were comparable to resistance rates reported between 2010 and 2014 (Table 3).

Table 1
Global rates of resistant phenotypes of Gram-positive and Gram-negative organisms collected from integumentary sources as part of T.E.S.T. between 2010 and 2014 (pooled data, 2010–2014 and 2004–2014)

	Staphylococcus aureus		*Enterococcus faecalis*		*Enterococcus faecium*		*Klebsiella pneumoniae*		*Escherichia coli*		*Acinetobacter baumannii*		*Pseudomonas aeruginosa*	
	MRSA		Vancomycin-resistant		Vancomycin-resistant		ESBL-producing		ESBL-producing		Multidrug-resistant		Multidrug-resistant	
	n/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%
2010	416/1151	36.1	5/279	1.8	16/83	19.3	96/340	28.2	75/459	16.3	163/385	42.3	86/584	14.7
2011	345/872	39.6	3/246	1.2	28/78	35.9	35/216	16.2	69/384	18.0	88/305	28.9	30/461	6.5
2012	512/1268	40.4	6/231	2.6	27/94	28.7	60/290	20.7	67/380	17.6	109/210	51.9	41/516	7.9
2013	379/1127	33.6	4/291	1.4	21/88	23.9	77/313	24.6	76/471	16.1	115/231	49.8	51/612	8.3
2014	274/700	39.1	4/170	2.4	23/74	31.1	33/184	17.9	40/297	13.5	58/104	55.8	20/362	5.5
2010–2014	1926/5118	37.6[a]	22/1217	1.8[a]	115/417	27.6[a]	301/1343	22.4[a]	327/1991	16.4[a]	533/1235	43.2[c]	228/2535	9.0[b]
2004–2014	5065/12 363	41.0[b]	75/3151	2.4[a]	332/945	35.1[b]	674/3173	21.2[a]	623/4537	13.7[c]	1190/3429	34.7[c]	580/6038	9.6[a]

T.E.S.T., Tigecycline Evaluation and Surveillance Trial; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase.
[a] Indicates non-significant change in resistance; a cut-off of $p < 0.01$ was used for statistical significance testing.
[b] Indicates a significant decrease in resistance; a cut-off of $p < 0.01$ was used for statistical significance testing.
[c] Indicates a significant increase in resistance; a cut-off of $p < 0.01$ was used for statistical significance testing.

Table 2
Regional rates of resistant phenotypes of Gram-positive and Gram-negative organisms from integumentary sources as part of T.E.S.T. between 2010 and 2014 (pooled data, 2010–2014 and 2004–2014)[a]

	2010		2011		2012		2013		2014		2010–2014		2004–2014	
	n/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%
Staphylococcus aureus: MRSA														
Africa	0/0	-	9/28	32.1	12/42	28.6	4/28	14.3	0/0	-	25/98	25.5	68/210	32.4
Europe	174/619	28.1	118/467	25.3	248/690	35.9	165/633	26.1	127/423	30.0	832/2832	29.4	1481/5231	28.3
Latin America	53/94	56.4	15/22	68.2	15/32	46.9	11/26	42.3	20/34	58.8	114/208	54.8	338/685	49.3
Middle East	11/52	21.2	7/12	58.3	14/43	32.6	8/26	30.8	0/0	-	40/133	30.1	85/334	25.4
North America	161/322	50.0	196/343	57.1	223/461	48.4	191/414	46.1	127/243	52.3	898/1783	50.4	2910/5437	53.5
Enterococcus faecalis: vancomycin-resistant														
Africa	0/0	-	0/9	-	0/16	0.0	0/8	-	0/0	-	0/33	0.0	0/54	0.0
Europe	1/149	0.7	1/132	0.8	2/106	1.9	2/153	1.3	1/98	1.0	7/638	1.1	10/1228	0.8
Latin America	0/25	0.0	0/4	-	0/8	-	0/12	0.0	0/10	0.0	0/59	0.0	0/251	0.0
Middle East	0/9	-	0/1	-	0/9	-	0/8	-	0/0	-	0/27	0.0	0/79	0.0
North America	4/92	4.3	2/100	2.0	4/92	4.3	2/110	1.8	3/62	4.8	15/456	3.3	64/1453	4.4
Enterococcus faecium: vancomycin-resistant														
Africa	0/0	-	0/0	-	0/1	-	0/3	-	0/0	-	0/4	-	0/10	0.0
Europe	1/48	2.1	7/50	14.0	2/57	3.5	6/64	9.4	10/58	17.2	26/277	9.4	46/462	10.0
Latin America	1/5	-	0/0	-	0/1	-	0/0	-	1/2	-	2/8	-	13/63	20.6
Middle East	1/4	-	0/0	-	3/4	-	0/2	-	0/0	-	4/10	40.0	7/18	38.9
North America	13/21	61.9	21/28	75.0	22/31	71.0	15/19	78.9	12/14	85.7	83/113	73.5	261/365	71.5
Klebsiella pneumoniae: ESBL-producing														
Africa	0/0	-	3/7	-	10/19	52.6	6/12	50.0	0/0	-	19/38	50.0	37/85	43.5
Europe	60/187	32.1	20/111	18.0	24/144	16.7	43/178	24.2	26/119	21.8	173/739	23.4	306/1344	22.8
Latin America	16/39	41.0	0/5	-	3/5	-	6/11	54.5	4/10	40.0	29/70	41.4	128/306	41.8
Middle East	11/31	35.5	5/6	-	8/21	38.1	11/20	55.0	0/0	-	35/78	44.9	54/147	36.7
North America	1/69	1.4	7/87	8.0	15/101	14.9	11/92	12.0	3/55	5.5	37/404	9.2	121/1196	10.1
Escherichia coli: ESBL-producing														
Africa	0/0	-	3/11	27.3	5/16	31.3	4/20	20.0	0/0	-	12/47	25.5	15/87	17.2
Europe	40/261	15.3	50/217	23.0	37/203	18.2	47/269	17.5	29/205	14.1	203/1155	17.6	344/2059	16.7
Latin America	20/65	30.8	11/23	47.8	3/10	30.0	4/18	22.2	6/17	35.3	44/133	33.1	121/411	29.4
Middle East	7/30	23.3	2/11	18.2	12/32	37.5	7/24	29.2	0/0	-	28/97	28.9	43/183	23.5
North America	5/92	5.4	3/122	2.5	10/119	8.4	14/140	10.0	5/75	6.7	37/548	6.8	75/1689	4.4
Acinetobacter baumannii: MDR														
Africa	0/0	-	4/10	40.0	3/5	-	7/10	70.0	0/0	-	14/25	56.0	32/58	55.2
Europe	89/210	42.4	50/176	28.4	64/108	59.3	63/126	50.0	32/55	58.2	298/675	44.1	516/1499	34.4
Latin America	23/39	59.0	0/0	-	5/6	-	4/8	-	6/7	-	38/60	63.3	125/203	61.6
Middle East	12/23	52.2	8/13	61.5	11/17	64.7	7/8	-	0/0	-	38/61	62.3	75/115	65.2
North America	26/94	27.7	26/106	24.5	26/74	35.1	34/79	43.0	20/42	47.6	132/395	33.4	378/1404	26.9
Pseudomonas aeruginosa: MDR														
Africa	0/0	-	5/12	41.7	2/20	10.0	4/18	22.2	0/0	-	11/50	22.0	16/144	11.1
Europe	53/339	15.6	18/304	5.9	21/285	7.4	26/375	6.9	12/222	5.4	130/1525	8.5	256/2750	9.3
Latin America	21/63	33.3	4/9	-	6/16	37.5	3/14	21.4	2/14	14.3	36/116	31.0	122/430	28.4
Middle East	3/23	13.0	1/14	7.1	5/33	15.2	10/30	33.3	0/0	-	19/100	19.0	33/209	15.8
North America	5/134	3.7	2/122	1.6	7/162	4.3	8/175	4.6	6/126	4.8	28/719	3.9	110/2264	4.9

T.E.S.T., Tigecycline Evaluation and Surveillance Trial; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant.
[a] Data for the Asia-Pacific region are not presented as centres in this region stopped participation in T.E.S.T. in 2010. '-' % resistance not calculated when $N < 10$ isolates.

3.1.2. *Enterococcus faecalis*

Of the 1217 *E. faecalis* isolates submitted globally between 2010 and 2014, 2% were vancomycin-resistant (Table 1). No vancomycin-resistant isolates were collected from Africa, Latin America, or the Middle East; seven vancomycin-resistant isolates were collected from Europe and 15 isolates from North America (Table 2).

Among *E. faecalis*, global resistance was highest to levofloxacin (31%). Resistance to minocycline was highest in 2010 (50%), decreased by 38% in 2011, and then remained below 9% for the subsequent years of collection ($p < 0.0001$). Between 2010 and 2014 resistance to ampicillin and penicillin was low (1%). Among *E. faecalis*, 99.8% of isolates were susceptible to tigecycline. No resistance to linezolid was seen among *E. faecalis* isolates (Table 3).

3.1.3. *Enterococcus faecium*

Of the 417 *E. faecium* isolates collected globally (2010–2014), 28% were vancomycin-resistant (Table 1). Between 2010 and 2014 global resistance to vancomycin fluctuated between 19% and 36% (Table 3). The highest rates of vancomycin resistance were seen in North America (74%). In Europe, 9% of isolates were vancomycin-resistant. Fewer than five resistant isolates were submitted from Africa, Latin America, and the Middle East between 2010 and 2014 (Table 2).

High percentages (>80%) of *E. faecium* isolates were resistant to ampicillin, penicillin, and levofloxacin. Among *E. faecium*, global resistance to minocycline was highest in 2010 (22%), and decreased to 4% in 2014 ($p < 0.0001$). A single *E. faecium* isolate submitted from Europe in 2010 showed resistance to linezolid; no other isolates were linezolid-resistant. All *E. faecium* isolates were susceptible to tigecycline (Table 3).

Between 2004 and 2014 there was a significant decrease in the global rate of vancomycin-resistant *E. faecium* ($p < 0.0001$) (Table 1). The MICs of three *E. faecium* isolates submitted between 2004 and 2014 were above the susceptibility breakpoint for tigecycline (Table 3).

3.2. Gram-negative organisms

3.2.1. *Klebsiella pneumoniae*

Of the 1343 *K. pneumoniae* isolates collected globally between 2010 and 2014, 22% were ESBL-producers (Table 1). Rates of ESBL production ranged from 9% in North America to 50% in Africa (Table 2).

Table 3
Global MIC_{90} values (mg/L) and *in vitro* resistance rates of Gram-positive organisms collected from integumentary sources as part of T.E.S.T. between 2010 and 2014 (pooled data, 2010–2014 and 2004–2014)

	2010		2011		2012		2013		2014		2010–2014			2004–2014		
	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	*p*-Value	MIC_{90}	% R	*p*-Value
S. aureus[a,b]	*N* = 1151		*N* = 872		*N* = 1268		*N* = 1127		*N* = 700		*N* = 5118			*N* = 12 363		
Levofloxacin	16	29.9	32	34.3	16	33.4	16	28.9	16	33.4	16	31.8	NS	16	32.3	NS
Linezolid	4	0.0	2	0.0	2	0.0	2	0.0	2	0.0	2	0.0	-	2	0.0	-
Minocycline	1	1.8	0.5	0.2	≤0.25	0.0	≤0.25	0.0	≤0.25	0.0	0.5	0.4	<0.0001[d]	0.5	0.6	NS
Tigecycline[c]	0.25	(0)	0.25	(0)	0.12	(0)	0.12	(0)	0.12	(0)	0.25	(0)	-	0.25	(0)	-
Vancomycin	1	0.0	1	0.0	1	0.0	1	0.0	1	0.0	1	0.0	-	1	0.0	-
MRSA[a]	*N* = 416		*N* = 345		*N* = 512		*N* = 379		*N* = 274		*N* = 1926			*N* = 5065		
Levofloxacin	32	69.7	32	70.7	32	68.6	32	70.2	32	69.3	32	69.6	NS	32	68.1	<0.01
Linezolid	2	0.0	2	0.0	2	0.0	2	0.0	2	0.0	2	0.0	-	2	0.0	-
Minocycline	4	2.6	0.5	0.3	≤0.25	0.0	0.5	0.0	≤0.25	0.0	0.5	0.6	<0.0001[d]	0.5	0.9	NS
Tigecycline[c]	0.25	(0)	0.25	(0)	0.12	(0)	0.25	(0)	0.25	(0)	0.25	(0)	-	0.25	(0)	-
Vancomycin	1	0.0	1	0.0	1	0.0	1	0.0	1	0.0	1	0.0	-	1	0.0	-
E. faecalis	*N* = 279		*N* = 246		*N* = 231		*N* = 291		*N* = 170		*N* = 1217			*N* = 3151		
Amox/clav	1	-	1	-	0.5	-	1	-	1	-	1	-	-	1	-	-
Ampicillin	2	0.4	1	1.6	1	1.7	1	1.0	1	0.0	2	1.0	NS	2	0.4	<0.01
Ceftriaxone	≥128	-	≥128	-	≥128	-	≥128	-	≥128	-	≥128	-	-	≥128	-	-
Levofloxacin	≥64	33.3	≥64	30.1	≥64	34.2	≥64	30.6	≥64	25.9	≥64	31.1	NS	≥64	33.1	<0.01[d]
Linezolid	2	0.0	2	0.0	2	0.0	2	0.0	2	0.0	2	0.0	-	2	0.1	NS
Meropenem	8	-	8	-	8	-	8	-	8	-	8	-	-	8	-	-
Minocycline	≥16	49.5	≥16	11.4	8	7.4	8	6.2	8	8.8	≥16	17.7	<0.0001[d]	≥16	22.9	NS
Penicillin	4	0.4	4	2.4	4	1.7	4	1.0	4	0.0	4	1.2	NS	4	0.6	<0.01
Pip/taz	8	-	4	-	4	-	4	-	4	-	4	-	-	4	-	-
Tigecycline[c]	0.25	(0)	0.12	(1)	0.12	(0)	0.12	(0)	0.12	(1)	0.25	(2)	-	0.25	(9)	-
Vancomycin	2	1.8	2	1.2	2	2.6	2	1.4	2	2.4	2	1.8	NS	2	2.4	NS
E. faecium	*N* = 83		*N* = 78		*N* = 94		*N* = 88		*N* = 74		*N* = 417			*N* = 945		
Amox/clav	≥16	-	≥16	-	≥16	-	≥16	-	≥16	-	≥16	-	-	≥16	-	-
Ampicillin	≥32	85.5	≥32	84.6	≥32	77.7	≥32	89.8	≥32	85.1	≥32	84.4	NS	≥32	81.7	NS
Ceftriaxone	≥128	-	≥128	-	≥128	-	≥128	-	≥128	-	≥128	-	-	≥128	-	-
Levofloxacin	≥64	84.3	≥64	85.9	≥64	75.5	≥64	88.6	≥64	86.5	≥64	83.9	NS	≥64	82.4	NS
Linezolid	2	1.2	2	0.0	2	0.0	2	0.0	2	0.0	2	0.2	NS	2	0.3	NS
Meropenem	≥32	-	≥32	-	≥32	-	≥32	-	≥32	-	≥32	-	-	≥32	-	-
Minocycline	≥16	21.7	≥16	11.5	8	9.6	8	4.5	8	4.1	≥16	10.3	<0.0001[d]	≥16	13.0	NS
Penicillin	≥16	85.5	≥16	82.1	≥16	76.6	≥16	85.2	≥16	79.7	≥16	81.8	NS	≥16	81.3	NS
Pip/taz	≥32	-	≥32	-	≥32	-	≥32	-	≥32	-	≥32	-	-	≥32	-	-
Tigecycline[c]	0.25	(0)	0.12	(0)	0.12	(0)	0.12	(0)	0.12	(0)	0.12	(0)	-	0.12	(3)	-
Vancomycin	≥64	19.3	≥64	35.9	≥64	28.7	≥64	23.9	≥64	31.1	≥64	27.6	NS	≥64	35.1	<0.0001[d]

T.E.S.T., Tigecycline Evaluation and Surveillance Trial; MIC_{90}, minimum inhibitory concentration required to inhibit growth of 90% of isolates (mg/l); R, resistance; *S. aureus*, *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; *E. faecalis*, *Enterococcus faecalis*; *E. faecium*, *Enterococcus faecium*; Amox/clav, amoxicillin–clavulanate; Pip/taz, piperacillin–tazobactam; NS, not significant; '-', no CLSI breakpoints available.

[a] Amoxicillin–clavulanate, ampicillin, ceftriaxone, meropenem, penicillin, and piperacillin–tazobactam are not active against *S. aureus*, therefore their data are not presented.

[b] *S. aureus* data include MRSA data.

[c] No resistance breakpoint is available, number of isolates above the susceptibility breakpoint given in parentheses.

[d] Indicates a significant decrease in resistance; otherwise a significant result indicates an increase in resistance. A cut-off of $p < 0.01$ was used for statistical significance testing.

Between 2010 and 2014, 33% of *K. pneumoniae* isolates were resistant to ceftriaxone, 25% were resistant to cefepime, and 23% of isolates were resistant to each of amoxicillin–clavulanate and levofloxacin. Resistance to piperacillin–tazobactam and meropenem was 17% and 8%, respectively. Resistance to minocycline in 2010 was 32%, decreased by 21% in 2011, and then remained below 16% ($p < 0.0001$). Less than 2% of *K. pneumoniae* isolates were resistant to amikacin and tigecycline (Table 4).

Pooled data for the 2004–2014 time period show significant increases in rates of resistance among *K. pneumoniae* isolates to cefepime and ceftriaxone ($p < 0.0001$), levofloxacin ($p < 0.001$), and amoxicillin–clavulanate, meropenem, piperacillin–tazobactam, and tigecycline ($p < 0.01$) (Table 4).

3.2.2. *Escherichia coli*

Of the 1991 *E. coli* isolates submitted globally between 2010 and 2014, 16% were ESBL-producers (Table 1). Rates of ESBL-producing isolates varied between regions, with the highest rate recorded for Latin America (33%) (Table 2).

Among all *E. coli* isolates, the highest level of resistance was observed for ampicillin (66%) (Table 4). Thirty-four percent of isolates were resistant to levofloxacin and 22% were resistant to ceftriaxone. There were moderate levels of resistance to amoxicillin–clavulanate (15%) and cefepime (13%). Resistance to minocycline decreased from 19% in 2010 to 9% in 2011 and thereafter remained below 8% ($p < 0.0001$). Overall resistance to piperacillin–tazobactam was low (6%). Less than 1% of *E. coli* isolates were resistant to amikacin and meropenem, with no isolates resistant to tigecycline (Table 4).

Pooled data for the period 2004–2014 showed a significant increase in rates of ESBL-producing *E. coli* ($p < 0.0001$) (Table 1). During this period there were significant increases in resistance among *E. coli* isolates to cefepime and ceftriaxone ($p < 0.0001$), ampicillin and levofloxacin ($p < 0.01$) (Table 4).

3.2.3. *Acinetobacter baumannii*

Overall, 1235 isolates of *A. baumannii* were submitted globally between 2010 and 2014. Forty-three percent of these were MDR strains, with resistance rates increasing from 29% in 2011 to 56% in 2014. There was a significant increase in rates of MDR *A. baumannii* between 2010 and 2014 (Table 1). By region, Latin America and the Middle East had the highest levels of multidrug resistance (63% and

Table 4
Global MIC_{90} values (mg/L) and *in vitro* resistance of Gram-negative Enterobacteriaceae organisms collected from integumentary sources as part of T.E.S.T. between 2010 and 2014 (pooled data, 2010–2014 and 2004–2014)

	2010		2011		2012		2013		2014		2010–2014			2004–2014		
	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	*p*-Value	MIC_{90}	% R	*p*-Value
K. pneumoniae	*N* = 340		*N* = 216		*N* = 290		*N* = 313		*N* = 184		*N* = 1343			*N* = 3173		
Amikacin	16	1.2	4	1.4	16	2.1	16	2.6	4	0.0	16	1.6	NS	16	2.9	NS
Amox/clav	≥64	29.4	32	1.5	≥64	23.1	≥64	22.7	≥64	21.7	≥64	22.7	NS	≥64	21.1	<0.01
Cefepime	≥64	27.4	≥64	16.7	≥64	26.9	≥64	29.1	≥64	19.0	≥64	24.8	NS	≥64	20.3	<0.0001
Ceftriaxone	≥128	40.3	64	23.6	64	31.7	64	37.1	64	28.8	64	33.4	NS	≥128	30.5	<0.0001
Levofloxacin	≥16	30.0	≥16	15.3	≥16	20.7	≥16	25.6	≥16	18.5	≥16	23.0	NS	≥16	21.1	<0.001
Meropenem	0.5	6.2	0.12	4.6	4	10.7	4	10.2	0.25	6.5	1	7.9	NS	0.5	6.7	<0.01
Minocycline	≥32	31.8	16	11.1	16	12.4	16	15.7	16	14.7	16	18.2	<0.0001[a]	16	17.1	NS
Pip/taz	≥256	19.4	32	8.8	≥256	18.3	≥256	18.5	≥256	14.7	≥256	16.6	NS	≥256	15.4	<0.01
Tigecycline	2	0.9	1	0.5	2	2.4	2	1.3	2	0.5	2	1.2	NS	2	0.7	<0.01
E. coli	*N* = 459		*N* = 384		*N* = 380		*N* = 471		*N* = 297		*N* = 1991			*N* = 4537		
Amikacin	8	0.4	8	0.0	8	0.3	8	0.6	8	0.0	8	0.3	NS	8	0.8	NS
Amox/clav	32	18.1	32	16.7	32	14.7	32	10.2	32	18.9	32	15.4	NS	32	16.1	NS
Ampicillin	≥64	68.8	≥64	65.4	≥64	63.9	≥64	63.1	≥64	69.7	≥64	66.0	NS	≥64	64.7	<0.01
Cefepime	32	13.5	32	14.1	32	13.7	16	13.2	16	11.1	32	13.2	NS	16	11.3	<0.0001
Ceftriaxone	≥128	25.7	64	22.4	64	23.2	64	19.5	64	20.5	64	22.4	NS	64	20.0	<0.0001
Levofloxacin	≥16	35.7	≥16	35.7	≥16	31.6	≥16	31.6	≥16	35.7	≥16	34.0	NS	≥16	33.1	<0.01
Meropenem	≤0.06	0.2	≤0.06	0.0	0.12	0.5	≤0.06	0.8	≤0.06	0.0	≤0.06	0.4	NS	≤0.06	0.5	NS
Minocycline	16	19.0	8	9.4	8	7.6	8	6.4	8	7.1	16	10.2	<0.0001[a]	16	12.0	NS
Pip/taz	32	6.5	32	8.1	16	4.5	16	3.6	16	5.1	16	5.5	NS	16	4.7	NS
Tigecycline	0.5	0.0	0.25	0.0	0.25	0.0	0.5	0.0	0.25	0.0	0.5	0.0	-	0.5	0.0	-

T.E.S.T., Tigecycline Evaluation and Surveillance Trial; MIC_{90}, minimum inhibitory concentration required to inhibit growth of 90% of isolates (mg/l); R, resistance; Amox/clav, amoxicillin–clavulanate; Pip/taz, piperacillin–tazobactam; *K. pneumoniae*, *Klebsiella pneumoniae*; *E. coli*, *Escherichia coli*; NS, not significant; '-', no CLSI breakpoints available.
[a] Indicates a significant decrease in resistance; otherwise a significant result indicates an increase in resistance. A cut-off of $p < 0.01$ was used for statistical significance testing.

62%, respectively), while North America had the lowest level (33%) (Table 2).

Between 2010 and 2014, statistically significant increases in global resistance were seen among *A. baumannii* isolates to cefepime, ceftazidime, ceftriaxone, levofloxacin, meropenem, and piperacillin–tazobactam ($p < 0.0001$) (Table 5). By 2014, resistance to these antimicrobials ranged from 57% to 63%. Between 2010 and 2014 the greatest increases in resistance among *A. baumannii* isolates were seen for cefepime and meropenem, rising from 35% to 59%, and 41% to 63%, respectively. There was a greater than 10% increase in resistance to ceftazidime (45% in 2010 to 57% in 2014), levofloxacin (44% to 58%), and piperacillin–tazobactam (49% to 60%). Resistance to ceftriaxone increased by 9% from 2010 to 2014. Thirty-one percent of isolates

Table 5
Global MIC_{90} values (mg/L) and *in vitro* resistance of Gram-negative non-Enterobacteriaceae organisms collected from integumentary sources as part of T.E.S.T. between 2010 and 2014 (pooled data, 2010–2014 and 2004–2014)

	2010		2011		2012		2013		2014		2010–2014			2004–2014		
	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	MIC_{90}	% R	*p*-Value	MIC_{90}	% R	*p*-Value
A. baumannii	*N* = 385		*N* = 305		*N* = 210		*N* = 231		*N* = 104		*N* = 1235			*N* = 3429		
Amikacin	≥128	33.8	≥128	21.6	≥128	35.2	≥128	31.2	≥128	37.5	≥128	30.9	NS	≥128	25.6	<0.0001
Amox/clav	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	-	≥64	-	-
Ampicillin	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	-	≥64	-	-
Cefepime	≥64	34.5	≥64	30.5	≥64	51.0	≥64	55.4	≥64	58.7	≥64	42.3	<0.0001	≥64	36.0	<0.0001
Ceftazidime	≥64	45.2	32	32.8	32	51.9	32	62.3	32	56.7	32	47.4	<0.0001	≥64	43.7	<0.0001
Ceftriaxone	≥128	50.6	64	33.4	64	53.8	64	64.5	64	59.6	64	50.3	<0.0001	≥128	47.0	<0.0001
Levofloxacin	≥16	44.2	≥16	29.5	≥16	51.0	≥16	54.5	≥16	57.7	≥16	44.8	<0.0001	≥16	40.4	<0.0001
Meropenem	≥32	41.3	≥32	32.1	≥32	54.3	≥32	52.4	≥32	62.5	≥32	45.1	<0.0001	≥32	39.1	<0.0001
Minocycline	8	8.8	8	3.3	8	4.8	16	10.8	8	2.9	8	6.6	NS	8	4.7	<0.0001
Pip/taz	≥256	48.6	≥256	34.8	≥256	54.3	≥256	58.9	≥256	59.6	≥256	49.0	<0.0001	≥256	40.1	<0.0001
Tigecycline	2	-	1	-	1	-	2	-	2	-	2	-	-	2	-	-
P. aeruginosa	*N* = 584		*N* = 461		*N* = 516		*N* = 612		*N* = 362		*N* = 2535			*N* = 6038		
Amikacin	32	6.2	8	2.2	16	3.1	8	3.8	8	3.3	16	3.8	NS	16	4.6	NS
Amox/clav	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	-	≥64	-	-
Ampicillin	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	≥64	-	-	≥64	-	-
Cefepime	32	13.5	16	8.9	16	7.6	32	10.5	16	6.4	16	9.7	<0.01[a]	32	10.4	NS
Ceftazidime	32	23.5	16	9.5	16	9.5	32	11.8	16	8.0	32	13.1	<0.0001[a]	32	14.5	NS
Ceftriaxone	≥128	-	64	-	64	-	64	-	64	-	64	-	-	≥128	-	-
Levofloxacin	≥16	30.8	≥16	22.6	≥16	24.4	≥16	24.2	≥16	20.7	≥16	25.0	<0.01[a]	≥16	27.0	<0.01[a]
Meropenem	16	20.9	16	17.4	16	20.9	16	16.3	16	14.9	16	18.3	NS	16	18.0	NS
Minocycline	≥32	-	≥32	-	≥32	-	≥32	-	≥32	-	≥32	-	-	≥32	-	-
Pip/taz	≥256	21.4	64	8.2	64	7.6	128	10.6	32	5.5	128	11.3	<0.0001[a]	128	12.3	NS
Tigecycline	16	-	16	-	16	-	16	-	16	-	16	-	-	16	-	-

T.E.S.T., Tigecycline Evaluation and Surveillance Trial; MIC_{90}, minimum inhibitory concentration required to inhibit growth of 90% of isolates (mg/l); R, resistance; *A. baumannii*, *Acinetobacter baumannii*; *P. aeruginosa*, *Pseudomonas aeruginosa*; Amox/clav, amoxicillin–clavulanate; Pip/taz, piperacillin–tazobactam; NS, not significant; '-', no CLSI breakpoints available.
[a] Indicates a significant decrease in resistance; otherwise a significant result indicates an increase in resistance. A cut-off of $p < 0.01$ was used for statistical significance testing.

collected were resistant to amikacin. *A. baumannii* isolates showed the lowest levels of resistance to minocycline (7%). Tigecycline was active against *A. baumannii* isolates at a MIC_{90} of 2 mg/L (Table 5).

The global rate of MDR *A. baumannii* increased significantly between 2004 and 2014 ($p < 0.0001$) (Table 1). Global rates of resistance to amikacin, cefepime, ceftazidime, ceftriaxone, levofloxacin, meropenem, minocycline, and piperacillin–tazobactam also increased significantly between 2004 and 2014 ($p < 0.0001$) (Table 5).

3.2.4. *Pseudomonas aeruginosa*

Of the 2535 *P. aeruginosa* isolates submitted globally between 2010 and 2014, 9% were MDR (Table 1). Rates of multidrug resistance were lowest in North America and Europe (4% and 9%, respectively), and highest in Latin America (31%) (Table 2). Between 2010 and 2014 there was a significant decrease in MDR *P. aeruginosa* ($p < 0.0001$) (Table 1).

Among *P. aeruginosa* isolates collected between 2010 and 2014 the highest levels of global resistance were observed against levofloxacin (25%), although resistance significantly decreased from 31% in 2010 to 21% in 2014 ($p < 0.01$) (Table 5). Resistance to meropenem was 18%. Significant decreases in resistance were observed for cefepime (14% in 2010 to 6% in 2014; $p < 0.01$), ceftazidime (24% in 2010 to 8% in 2014; $p < 0.0001$), and piperacillin–tazobactam (21% in 2010 to 6% in 2014; $p < 0.0001$). Resistance to amikacin was low among isolates of *P. aeruginosa* (4%). Tigecycline was active at a MIC_{90} of 16 mg/L (Table 5).

Pooled data for the 2004 to 2014 period show no significant change in global rates of MDR *P. aeruginosa.* Among isolates of *P. aeruginosa* there was a significant decrease in resistance to levofloxacin between 2004 and 2014 ($p < 0.01$) (Table 5).

4. Discussion

This report shows that although global rates of antimicrobial resistance among Gram-positive and Gram-negative organisms isolated from integumentary sources remain high, the rates of resistance among resistance phenotypes including MRSA and ESBL-producing Enterobacteriaceae appear to be stabilizing. This report identifies significant increases in rates of MDR *A. baumannii*. Significant increases in rates of resistance among *A. baumannii* to a wide range of antimicrobials including carbapenems, cephalosporins, fluoroquinolones, and β-lactamase inhibitors between 2010 and 2014 (and 2004–2014) were also seen.

As shown by the results in this report, global rates of MRSA remained stable among isolates from integumentary sources (ranging from 34% to 40% between 2010 and 2014), and were unchanged from the overall global rate reported by Namdari et al. (41%).[12] Regionally, rates in Europe, Latin America, and North America were also consistent over the time period, with the highest overall rates of MRSA reported for Latin America (55%) and North America (50%). Rates in Africa and the Middle East were more variable, and this is likely due, in part, to the low numbers of isolates collected in some years. This stabilization of MRSA rates is consistent with previous reports from European countries,[17–19] as well as North America;[20] however supporting data for Latin America are lacking. More information is also needed for the Africa and Middle East regions.

Linezolid, tigecycline, and vancomycin are effective in treating cSSSIs due to *S. aureus*, including MRSA.[21,22] All isolates of *S. aureus* collected in this study were susceptible to these agents, however the activity of these antimicrobials should continue to be monitored. Over recent years there have been reported outbreaks of linezolid-resistant MRSA,[23,24] although data from global surveillance studies have shown low levels of linezolid resistance (<1% of *S. aureus* isolates).[25–27]

Linezolid-resistant enterococci have also been reported by surveillance studies,[26,28] and our report showed the sporadic occurrence of linezolid-resistant enterococci, with one linezolid-resistant *E. faecium* isolate reported from Europe in 2010. Namdari et al. also reported low numbers of linezolid-resistant enterococci (four isolates).[12]

As described above, all isolates of *S. aureus* were susceptible to tigecycline. Among the enterococci, all isolates of *E. faecium* and 99.8% of *E. faecalis* were susceptible to tigecycline at a breakpoint of ≤0.25 mg/L. Among Enterobacteriaceae, 99.9% of *E. coli* and 94% of *K. pneumoniae* were susceptible to tigecycline at a breakpoint of 2 mg/L. Similar activity was reported by Namdari et al. between 2004 and 2009, suggesting that the *in vitro* activity of tigecycline against integumentary isolates is unchanged.[12] Other agents that maintained their activity against Gram-positive organisms in this study included meropenem, linezolid, and vancomycin. Regarding the Enterobacteriaceae, meropenem and amikacin showed high antimicrobial activity, which is also supported by the data presented by Namdari et al.[12] Among the non-Enterobacteriaceae, the MIC_{90} for tigecycline against isolates of *A. baumannii* and *P. aeruginosa* were 2 mg/L and 16 mg/L, respectively. Tigecycline is not active clinically against *P. aeruginosa*.[29] The MIC_{90} against *A. baumannii* was similar to that reported by Namdari et al.[12]

The global rates of ESBL production among *E. coli* and *K. pneumoniae* between 2010 and 2014 reported herein (16% and 22%, respectively) are comparable with those in the earlier report by Namdari et al. (12% and 20%, respectively).[12] Global surveillance reports from the Study for Monitoring Antimicrobial Resistance Trends (SMART) have reported the rates of ESBL-producing *E. coli* (9% in 2002 to 21% in 2010)[30] and ESBL-producing *K. pneumoniae* (2008–2009, 22%) isolated from intra-abdominal infections.[31] In this T.E.S.T. report, higher percentages of ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae* were isolated from Latin America (33% and 41%, respectively) and the lowest from North America (7% and 9%, respectively). These results are comparable with those of Namdari et al.[12] and Hawser et al.[30,31]

Between 2004 and 2014, significant increases in resistance among *K. pneumoniae* to amoxicillin–clavulanate, cefepime, ceftriaxone, levofloxacin, meropenem, piperacillin–tazobactam, and tigecycline were seen. Similarly there were significant increases in resistance among *E. coli* to ampicillin, cefepime, ceftriaxone, and levofloxacin. Namdari et al. reported increasing levels of resistance among *K. pneumoniae* and *E. coli* between 2004 and 2009.[12] Our report shows a further increase in resistance in 2010; however this was followed by a stabilization in resistance rates (<10% change in resistance) between 2011 and 2014. Despite significant increases in carbapenem resistance among *K. pneumoniae* and *E. coli*, these antimicrobial agents remain the most active. Hawser et al. reported similar results, showing that susceptibility among *K. pneumoniae* and *E. coli* to the majority of antimicrobial agents either fluctuated slightly or decreased; however this decrease in susceptibility was less for carbapenems.[30,31] They also reported that susceptibility to amikacin, cephalosporins, fluoroquinolones, and β-lactamase inhibitors decreased over time.[30,31]

Worldwide, *A. baumannii* and *P. aeruginosa*, including MDR strains, are serious nosocomial pathogens and are intrinsically resistant to many antimicrobials.[32,33] Our study showed high rates of MDR *A. baumannii* (43%), with significant increases in MDR strains between 2010–2014 and 2004–2014. In contrast, less than 10% of *P. aeruginosa* isolates were MDR strains. By region, the highest rates of multidrug resistance among MDR *A. baumannii* and MDR *P. aeruginosa* were in Latin America and the lowest in North America. This geographical difference in resistance has been

reported previously by Gales et al.[34] Among *A. baumannii* isolates submitted in this report, resistance to the majority of antimicrobials significantly increased, including resistance to carbapenems, which have previously been reported as the most active agents against non-Enterobacteriaceae.[35] This report also highlighted increasing numbers of MDR *A. baumannii*.[35] These results are comparable with resistance rates reported by Namdari et al., and are reflected by significant increases in resistance among *A. baumannii* between 2004 and 2014 to these antimicrobials.[12] Surveillance data have shown increasing rates of MDR *Acinetobacter spp.* and increasing resistance to meropenem (43.4%) and imipenem (42.5%).[35] More recently, Morfín-Otero et al. reported on *A. baumannii* infections in a tertiary care teaching hospital in Mexico over a 13-year period and showed that the susceptibility of *A. baumannii* to meropenem decreased from 92% in 1999 to 12% in 2011.[36] They reported that *A. baumannii* was one of the most frequently isolated pathogens, overtaking *P. aeruginosa*, and was the second most common Gram-negative pathogen after *E. coli* in 2011.[36]

Among isolates of *E. faecalis*, *E. faecium*, *K. pneumoniae*, and *E. coli*, resistance to minocycline decreased significantly by 12%–41% between 2010 and 2014. Namdari et al. previously reported the opposite; increasing levels of minocycline resistance among these organisms between 2004 and 2009, and concluded that the reason for the initial increase in minocycline was unclear.[12] Among the Gram-negative isolates (*K. pneumoniae* and *E. coli*), resistance to minocycline in 2014 was comparable with that reported by Namdari et al. in 2004.[12] Minocycline resistance among Gram-positive isolates of *E. faecalis* and *E. faecium* in 2014 was lower than that reported by Namdari et al. in 2004 (difference of 5–15%).[12] To the authors' knowledge, such changes in susceptibility to minocycline have not been reported by other studies. Following this increase, the largest decrease in minocycline resistance was seen between 2010 and 2011 and this may be due to the decrease in the number of centres submitting isolates between these two years.

The discussion above highlights one of the limitations of this study; the varying number of participating centres between years. A second limitation of the T.E.S.T. study is the regional distribution of centres. Europe and North America accounted for 82% of participating centres in this study; therefore the results are heavily influenced by these regions. In addition, centres from the Asia-Pacific region were not involved in T.E.S.T. between 2010 and 2014, which impacts the global spread of the study. As an example, a total of 6% of the *S. aureus* reported by Namdari et al. came from the Asia-Pacific region.[12] Some of the CLSI breakpoints applied in this study have been updated since the study by Namdari et al.,[12] specifically, cefepime and the Enterobacteriaceae, the carbapenems and *A. baumannii*, and piperacillin–tazobactam, ceftriaxone, and the carbapenems and *P. aeruginosa*. Such changes should be borne in mind when comparing the studies.

In conclusion, resistance among pathogens involved in integumentary infections remains high, with global rates of MRSA at 38% and MDR *A. baumannii* at 43%. Despite high rates of MRSA resistance and resistance among ESBL-producing Enterobacteriaceae, these rates appear to be stabilizing. Few agents were active *in vitro* against *A. baumannii* and *P. aeruginosa* except for carbapenems, which, unfortunately, show increasing resistance compared to earlier years, giving cause for concern. Tigecycline was also active against *A. baumannii* but not *P. aeruginosa*. Among Gram-positive organisms isolated from integumentary sources, meropenem, linezolid, vancomycin, and tigecycline maintained their *in vitro* activity. Meropenem, amikacin, and tigecycline also continue to be active against Enterobacteriaceae. These trends highlight the importance of global and regional antimicrobial surveillance studies to help monitor resistance rates among clinically important pathogens.

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