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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.