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Antimicrobial susceptibility among important pathogens collected as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) in Spain, 2004–2014

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ABSTRACT

Here we report in vitro activity data from the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) for tigecycline and comparators against Gram-positive and Gram-negative organisms collected from 27 medical centres in Spain between 2004 and 2014. Minimum inhibitory concentrations (MICs) were determined according to the broth microdilution methodology of the Clinical and Laboratory Standards Institute (CLSI) and susceptibility were determined according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria. Susceptibility was >97% for all antimicrobials tested against *Enterococcus faecalis*, and >98% of *Enterococcus faecium* tested were susceptible to tigecycline, linezolid and vancomycin. A total of 34.1% (1071/3143) of *Staphylococcus aureus* were meticillin-resistant *S. aureus* (MRSA), and all MRSA were susceptible to tigecycline and vancomycin. Among the *Streptococcus pneumoniae*, 5.2% (74/1430) were penicillin-resistant and all isolates were susceptible to linezolid and vancomycin. Among the Enterobacteriaceae, 17.1% (542/3167) of *Escherichia coli*, 2.8% (19/682) of *Klebsiella oxytoca* and 19.0% (441/2327) of *Klebsiella pneumoniae* isolates produced extend-spectrum β-lactamases (ESBLs). Against ESBL-producing *E. coli* and *K. pneumoniae*, susceptibility was highest for meropenem, amikacin and tigecycline with rates of >92% and >80%, respectively. Among the *Acinetobacter baumannii*, susceptibility ranged between 23.5% for levofloxacin and 51.4% for amikacin, and an MIC_{90} of 2 mg/L was observed for tigecycline. In conclusion, monitoring of antimicrobial susceptibility among organisms such as *S. aureus*, Enterobacteriaceae and *A. baumannii* is of continuing importance as a guide to clinicians. Depending on the organism to be treated, carbapenems, linezolid, vancomycin and tigecycline continue to be active in Spain.

1. Introduction

Antimicrobial resistance among bacterial pathogens is increasingly threatening our ability to treat common infections, and this lack of treatment options may result in treatment complications and increased healthcare costs [1–4]. Spain is reported to have an antibiotic consumption rate [20.9 defined daily doses (DDD) per 1000 inhabitants per day] that is similar to the European average of 21.5 DDD per 1000 inhabitants per day, although this count does not include consumption without a prescription [5]. A recent report has suggested a variable picture of antimicrobial resistance among common Gram-positive and Gram-negative pathogens in Spain between 2010 and 2013, with increasing resistance to fluoroquinolones, aminoglycosides and carbapenems among *Escherichia coli* and *Klebsiella pneumoniae* but more stable rates among *Pseudomonas aeruginosa*, *Staphylococcus aureus*, enterococci and *Streptococcus pneumoniae* [6].

The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is a global in vitro antimicrobial surveillance study that began in 2004. In this report we examine the in vitro activity of tigecycline and comparators against Gram-positive and Gram-negative organisms collected from medical centres in Spain between 2004 and 2014. Previous publications that have included isolates contained in this report are Rodloff et al. [7], which presented data on antimicrobial susceptibility across France, Germany, Italy, Spain and the UK between 2004 and 2006, and Aznar et al. [8], which

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presented data on antimicrobial susceptibility among *Enterococcus faecalis* and *Enterococcus faecium* from France, Germany, Italy, Spain and the UK between 2004 and 2009. Data from Spanish isolates have also been included in European analyses of the T.E.S.T. programme: Nørskov-Lauritsen et al. presented isolates collected between 2004 and 2007 [9], and Denis et al. presented isolates collected between 2004 and 2010 [10].

2. Materials and methods

This study reports on a subset of data from the T.E.S.T. global study. Detailed materials and methods for the T.E.S.T. study have been previously published elsewhere (e.g. [11]). In total there were 27 centres in Spain over the study period; all centres did not participate in all years.

The maximum number of years that any one centre participated for was 9 years (one centre). Three centres participated for 8 years and seven centres participated for 7 years. The remaining 16 centres participated for between 1 year and 4 years. Minimum inhibitory concentrations (MICs) were determined according to the broth microdilution methodology of the Clinical and Laboratory Standards Institute (CLSI) [12] and antimicrobial susceptibility was determined according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria [13].

In this report, multidrug resistance was defined as resistance to three or more classes of antimicrobial agents. The classes used to define multidrug-resistant (MDR) *Acinetobacter baumannii* were aminoglycosides (amikacin), carbapenems (imipenem/meropenem) and fluoroquinolones (levofloxacin), and the classes used to define MDR *P. aeruginosa* were aminoglycosides (amikacin), β-lactams (cefepime, ceftazidime or piperacillin/tazobactam), carbapenems (imipenem/meropenem) and fluoroquinolones (levofloxacin).

3. Results

Patient demographics and isolate source data for the isolates in this study are presented in Table 1.

3.1. Gram-positive pathogens

Data for antimicrobials with EUCAST breakpoints are shown in Tables 2 and 3. Susceptibility was >97% for all antimicrobials tested against *E. faecalis*, and >98% of *E. faecium* tested were susceptible to tigecycline, linezolid and vancomycin (Table 2). A total of 0.4% (5/1205) of *E. faecalis* and 1.5% (8/535) of *E. faecium* isolates were resistant to vancomycin. All vancomycin-resistant isolates were susceptible to linezolid and tigecycline.

All isolates of meticillin-susceptible *S. aureus* (MSSA) were susceptible to linezolid, tigecycline and vancomycin, whilst 97.1% were susceptible to minocycline (Table 2). More than one-third of the *S. aureus* isolates collected were meticillin-resistant (34.1%; 1071/3143), and all of the meticillin-resistant *S. aureus* (MRSA) isolates were susceptible to tigecycline and vancomycin (Table 3).

Among the streptococci, all *Streptococcus agalactiae* isolates collected were susceptible to linezolid, penicillin and vancomycin, and all *S. pneumoniae* were susceptible to linezolid and vancomycin (Table 2). A total of 5.2% (74/1430) of *S. pneumoniae* were penicillin-resistant and all were susceptible to linezolid and vancomycin (Table 3). Susceptibility to the macrolides was 85% among penicillin-susceptible *S. pneumoniae* and 43–47% among penicillin-resistant *S. pneumoniae* (Tables 2 and 3).

An analysis of susceptibility by culture source and by intensive care unit (ICU) versus non-ICU status was also performed; however, few differences were observed (Supplementary Tables S1 and S2). Differences included lower susceptibility to levofloxacin among MSSA from genital/urinary sources (72.2%) compared with other culture sources (ca. 90%), and variable levofloxacin susceptibility among MRSA ranging from 5.3% among isolate from respiratory sources to 18.2% among isolates from body fluids (Supplementary Table S1). No differences in susceptibility profiles between ICU and non-ICU isolates were observed (Supplementary Table S2).

3.2. Gram-negative pathogens

Data for antimicrobials with EUCAST breakpoints are shown in Tables 4 and 5. More than 90% of *Enterobacter* spp. were susceptible to amikacin, meropenem and tigecycline (Table 4). The antimicrobial agents with the highest rates of susceptibility against the *E. coli* collected were tigecycline, meropenem and amikacin (Table 4). Moreover, 17.1% (542/3167) of all *E. coli* isolates produced extended-spectrum β-lactamases (ESBLs), and among these isolates 99.4% and 98.9% were susceptible to meropenem and tigecycline, respectively (Table 5). Resistance rates were higher among ESBL-positive *E. coli* isolates compared with *E. coli* isolates overall (Tables 4 and 5).

Among the *Klebsiella* spp., susceptibility of ≥95% against *Klebsiella oxytoca* was reported for amikacin, meropenem and tigecycline (Table 4), and 2.8% (19/682) of all *K. oxytoca* isolates were ESBL-producers. More than 96% of *K. pneumoniae* isolates were susceptible to amikacin and meropenem (Table 4). The agents with the highest rates of susceptibility against the ESBL-positive *K. pneumoniae* [19.0% (441/2327) of all isolates] were meropenem, amikacin and tigecycline (Table 5).

Against the *Serratia marcescens* collected, susceptibility to meropenem, amikacin, cefepime, piperacillin/tazobactam, levofloxacin and ceftriaxone was >90% (Table 4).

Susceptibility among isolates of *Haemophilus influenzae* to the antimicrobial panel was >92%, with the exception of ampicillin (Table 4). A total of 15.9% (237/1490) of *H. influenzae* were β-lactamase-producers, and all β-lactamase producers were susceptible to levofloxacin and meropenem (Table 5).

Among the *A. baumannii*, susceptibility ranged between 23.5% for levofloxacin and 51.4% for amikacin (Table 4). An MIC_{90} value (MIC for 90% of the isolates) of 2 mg/L was observed for tigecycline. A total of 30.2% (429/1419) of all *A. baumannii* isolates were MDR. The only agents with low MIC_{50} (MIC for 50% of the isolates) and MIC_{90} values were minocycline (2 mg/L and 8 mg/L, respectively) and tigecycline (1 mg/L and 2 mg/L, respectively).

Table 1
Patient demographics and source data for the isolates collected in Spain, 2004–2014.

Characteristic	*N* (%)
Sex	
Male	13,154 (57.2)
Female	9603 (41.8)
Unknown	243 (1.1)
Age group	
<18 years	1987 (8.6)
18–64 years	8919 (38.8)
≥65 years	10,903 (47.4)
Unknown	1191 (5.2)
Source of isolates[a]	
Cardiovascular system	5916 (25.7)
Respiratory	4604 (20.0)
Body fluids	4373 (19.0)
Integumentary	3334 (14.5)
Genital/urinary	2475 (10.8)
Other	2298 (10.0)

[a] Only culture sources making up ≥5% of the total are presented individually; all other culture sources are pooled into 'other'.