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Original

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Monitoring the antimicrobial susceptibility of Gram-negative organisms involved in intraabdominal and urinary tract infections recovered during the SMART study (Spain, 2016 and 2017)

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ABSTRACT

Introduction. Continuous antimicrobial resistance surveillance is recommended by Public Health authorities. We updated data from the SMART (Study for Monitoring Antimicrobial Resistance Trends) surveillance study in Spain.

Material and methods. The antimicrobial susceptibility data and extended-spectrum beta-lactamase (ESBL) production in isolates recovered from intra-abdominal (IAI) (n=1,429) and urinary tract (UTI) (n=937) infections during the 2016-2017 SMART study in 10 Spanish hospitals were analysed.

Results. *Escherichia coli* was the most frequently microorganism isolated (48.3% and 53.7%) followed by *Klebsiella* spp. (11.5% and 21.9%) in IAIs and UTIs, respectively. Figures for *Pseudomonas aeruginosa* were 9.0% and 6.1%, being more frequently recovered from patients with nosocomial infections. Overall, 9.9% (IAI) and 14.0% (UTI) of *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* isolates were ESBL-producers, being *Klebsiella pneumoniae* (34.5%) from UTI of nosocomial origin the most frequent. ESBL-producers were higher in patients >60 years in both IAIs and UTIs. As in previous years, amikacin (96.3%-100% susceptibility), ertapenem (84.2%-100%) and imipenem (70.3%-100%) were the most active antimicrobials tested among Enterobacterales species. The activity of amoxicillin-clavulanic, piperacillin-tazobactam, and ciprofloxacin susceptibility was lower, particularly among ESBL-producers. Ertapenem susceptibility (88.9%-100%) was retained in ESBL-*E. coli* isolates that were resistant to these antimicrobials but decreased (28.6%-100%) in similar isolates of *K. pneumoniae*.

Conclusions. Continuous antimicrobial resistance surveillance from the SMART study reveals overall maintenance of ESBL-producers in Spain, although with higher presence in isolates from UTIs than from IAIs. Moreover, ertapenem activity was high in *E. coli* irrespective of ESBL production but decreased in *K. pneumoniae*, particularly among ESBL-producers.

Key words: antimicrobial resistance surveillance, intra-abdominal infection, urinary tract infection, extended-spectrum-beta-lactamases, carbapenems

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Seguimiento de la sensibilidad antimicrobiana de microorganismos gramnegativos procedentes de infecciones intraabdominales y urinarias del estudio SMART (España, 2016 y 2017)

RESUMEN

Introducción. Las autoridades de Salud Pública recomiendan la vigilancia continua de la resistencia a los antimicrobianos. Se actualizan los datos del estudio SMART (*Study for Monitoring Antimicrobial Resistance Trends*) en España.

Material y métodos. Se analizaron los datos de sensibilidad antimicrobiana y la producción de betalactamasas de espectro extendido (BLEE) en aislamientos obtenidos en el estudio SMART de infecciones intraabdominales (IIA) (n=1.429) y del tracto urinario (ITU) (n=937) durante 2016-2017 en 10 hospitales españoles.

Resultados. *Escherichia coli* fue el microorganismo más frecuente (54,5% y 57,5%, respectivamente), seguido de *Klebsiella* spp. (18,4% y 25,4%) en IIA y en ITU. En *Pseudomonas aeruginosa* estas cifras fueron 9% y 6%, siendo más frecuente en la infección nosocomial. El 9,9% (IIA) y el 14% (ITU) del total de los aislados de *E. coli*, *Klebsiella* spp. y *Proteus mirabilis* producían BLEE, obteniéndose la tasa más alta en *Klebsiella pneumoniae* (34.5%) en ITU nosocomial. El mayor porcentaje de aislados con BLEE se observó en pacientes >60 años, tanto en IIA como en ITU. Como en años anteriores, amikacina (sensibilidad 96,3%-100%), ertapenem (84,2%-100%) e imipenem (70,3%-100%) fueron los antimicrobianos más activos en Enterobacterales. La sensibilidad a amoxicilina-ácido clavulánico, piperacilina-tazobactam y ciprofloxacino fue menor, en particular en los productores de BLEE. La sensibilidad a ertapenem (88,9%-100%) se mantuvo en *E. coli* con BLEE resistente a estos antimicrobianos, pero disminuyó (28,6%-100%) en aislados similares de *K. pneumoniae*.

Conclusiones. La vigilancia continua de la resistencia a los antimicrobianos en el estudio SMART revela el mantenimiento de la frecuencia de aislados productores de BLEE en España, pero con mayor presencia en las ITUs que en las IIAs. Además, la sensibilidad a ertapenem fue alta en *E. coli* con independencia de la producción de BLEE, pero disminuyó en *K. pneumoniae*, sobre todo en los productores de BLEE.

Palabras clave: vigilancia epidemiológica de la resistencia, infección intraabdominal, infección urinaria, betalactamasas de espectro extendido, carbapenems

INTRODUCTION

The increase in antimicrobial resistance is a worldwide reality that threatens the prevention and effective treatment of an increasing number of infections, challenging clinical microbiologists and infectious disease specialists [1]. Two of the most common infections are urinary tract (UTI) and intra-abdominal (IAI) infections caused mainly by Enterobacterales, in particular *Escherichia coli* and *Klebsiella* species [2,3]. In the 1980s, extended spectrum beta-lactamase (ESBL)-producing Enterobacterales were considered one of the leading causes of nosocomial infections and later also of those acquired in the community [4]. These enzymes have the ability to hydrolyze beta-lactam antibiotics, including penicillins, cephalosporins and the monobactam aztreonam but not carbapenems [5]. As a consequence, carbapenems were considered the antimicrobials of choice for the treatment of infections caused by ESBL producers, however the prevalence of carbapenemases, enzymes that inactivate them, continue to increase worldwide [6]. In addition, the production of ESBL combined with mutations affecting permeability can also contribute to the carbapenems resistance. This situation warns the need for surveillance of susceptibility to antimicrobials, especially to carbapenems. Global surveillance programs such as SMART (Study for Monitoring Antimicrobial Resistance Trends) that evaluates antimicrobial susceptibility to beta-lactam antibiotics, including carbapenems, and also aminoglycosides and quinolones, against a large number of Gram-negative bacilli species collected from IAI and UTI fulfills this function.

In this study, we analysed the antimicrobial susceptibility data from isolates recovered in 2016 and 2017 in Spain from abdominal samples in patients with diagnosis of IAI and urinary samples from patients with UTI included in the SMART database. The ESBL production of these isolates is also presented.

MATERIAL AND METHODS

Microorganisms and participating sites. All isolates studied were obtained from abdominal samples from patients with diagnosis of IAI and from urinary samples from patients with UTI. Details on sampling and criteria for the inclusion of microorganisms were previously described [7]. During the 2 years of the study (2016 and 2017) a total of 10 Spanish hospitals participated (H. Universitario Gregorio Marañón, Madrid, H. Clínico San Carlos, Madrid, H. Universitario Virgen Macarena, Sevilla, H. Universitario Virgen del Rocío, Sevilla, H. Universitario Marqués de Valdecilla, Santander, H. Universitario Son Espases, Palma de Mallorca, H. Clínico Universitario Lozano Blesa, Zaragoza, H. Universitario Bellvitge, Hospitalet de Llobregat, Barcelona, H. Universitario y Politécnico La Fe, Valencia, and H. Universitario Ramón y Cajal, Madrid).

A total of 1,429 intra-abdominal isolates were collected; the most frequent were recovered from peritoneal fluid (41%), intra-abdominal abscesses (31%) and gall bladder (18%), and to a lesser extent and in decreasing order, from the liver, appendix, pancreas, colon, rectum, and other sources. Most of the isolates were obtained during surgery procedures and others from paracentesis and percutaneous aspiration of intra-abdominal abscesses. Regarding UTI, a total of 937 isolates were obtained, being virtually all urine samples (98%). Isolates from other locations (i.e. blood, abdominal drainages, superficial wounds or perirectal abscesses) were excluded.

The identification of the isolates was performed at each hospital and sent to a central laboratory (International Health Management Associates, SA. Schaumburg, IL, US) to confirm the identification and to establish the susceptibility to different antimicrobials of choice for the treatment of IAIs or UTIs. All results were included in a centralized database. In addition to the source of the sample, patient's age was considered. Following the standard criteria of the *Centers for Disease Control and Prevention* (CDC) the organisms were also rated as isolates obtained within 48 h after hospitalization (community-acquired infection) and isolates obtained after 48 h of hospital stay (nosocomial infection) [8].

Antimicrobial susceptibility and ESBL production. Antimicrobial susceptibility testing results were obtained at a central laboratory (International Health Management Associates) using the standard ISO broth microdilution method [9]. MIC results were interpreted each year according to the most recent EUCAST guidelines (http://www.eucast.org/clinical_breakpoints/). Dried MicroScan (Beckman, West Sacramento, CA, US) microdilution panels were used. The antimicrobials analyzed in this study were: piperacillin-tazobactam, cefotaxime, ceftazidime, cefepime, imipenem, ertapenem, amikacin and ciprofloxacin. In addition, susceptibility to amoxicillinclavulanate was measured with a MIC gradient test (Etest®, bioMérieux, Lyon, France). The quality controls strains used were *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control) and *P. aeruginosa* ATCC 27853. *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* isolates were classified as ESBL following CLSI criteria [10].

Statistical analysis. The frequency comparison (incidence between hospital and community isolates) was performed using the chi-squared test (χ^2) taking $P<0.05$ as statistically significant.

RESULTS

During 2016 and 2017, a total of 1,429 isolates from IAI and 937 isolates from UTI recovered in the 10 Spanish hospitals were included (tables 1 and 2). In IAI, the Enterobacterales (1,265) constituted 85.5% of the total isolates. This figure was 876 isolates (93.4%) in UTI. Overall, *E. coli* was the most frequently isolated microorganism (48.3% and 53.7%), followed by *Klebsiella* spp. (11.5% and 21.8%) in IAIs and UTIs, respectively. Figures for *Pseudomonas aeruginosa* were 9.0% and 6.1%, being more frequently recovered in patients with nosocomial infections. When the origin of the isolates was considered (tables 1 and 2), 43.2% of IAI isolates were considered to be acquired in the community compared to 56.8% that had their origin in the nosocomial setting. In UTI, there was also a lower number of isolates from community (47.8%) than from nosocomial origin (52.2%). In 1.5% of IAI isolates, their origin was not specified in the data collection sheets.

Table 1 Distribution of the most common Gram-negative organisms collected in intra-abdominal infections in Spain in the SMART Study (2016-2017).

		Community associated		Nosocomial associated	
Organisms	No. isolates	No.	%	No.	%
Escherichia coli	690	337	54.6	353	43.4
Klebsiella pneumoniae	165	54	8.7	111	13.6
Klebsiella oxytoca	69	39	6.3	30	3.6
Proteus mirabilis	46	17	2.7	29	3.5
Enterobacter cloacae	75	30	4.8	45	5.5
Citrobacter freundii	31	19	3.0	12	1.4
Morganella morganii	27	6	0.9	21	2.5
Serratia marcescens	25	9	1.4	16	1.9
Other Enterobacterales	137	44	7.1	93	11.4
Pseudomonas aeruginosa	129	54	8.7	75	9.2
Other Gram-negative bacilli	35	8	1.2	27	3.3
TOTAL	1,429	617	43.2	812	56.8

Table 2 Distribution of the most common Gram-negative organisms collected in urinary tract infections in Spain in the SMART Study (2016-2017).

		Community associataed		Nosocomial associated	
Organisms	No. isolates	No.	%	No.	%
Escherichia coli	504	284	63.3	220	44.9
Klebsiella pneumoniae	205	66	14.7	139	28.4
Klebsiella oxytoca	18	9	2.0	9	1.8
Proteus mirabilis	61	31	6.9	30	6.1
Enterobacter cloacae	16	5	1.1	11	2.2
Citrobacter freundii	11	6	1.3	5	1.0
Morganella morganii	21	8	1.7	13	2.6
Serratia marcescens	7	3	0.6	4	0.8
Other Enterobacterales	33	13	2.9	20	4.0
Pseudomonas aeruginosa	57	22	4.9	35	7.1
Other Gram-negative bacilli	4	1	0.2	3	0.6
TOTAL	937	448	47.8	489	52.2

Tables 1 and 2 also show the distribution of the most frequent microorganisms according with their origin. The percentage of *E. coli* of isolates in IAI (table 1) acquired in the community (54.6%) was higher than in those of nosocomial origin (43.4%) ($P<0.01$). On the contrary, the percentage in *P. aeruginosa* was higher in infections acquired in the hospital (9.2% vs. 8.7%) but without statistical significance ($P=0.751$). The same situation occurs, even to a greater extent, in the UTIs

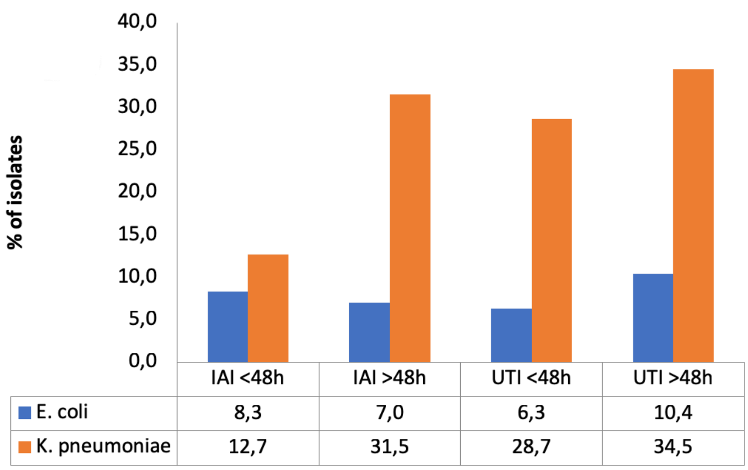

Figure 1 **Percentage of *Escherichia coli* and *Klebsiella pneumoniae* isolates with extended spectrum β-lactamases by origin of acquisition of infection in the SMART study in Spain comparing intra-abdominal (IAI) and urinary tract infections (UTI) infections.**

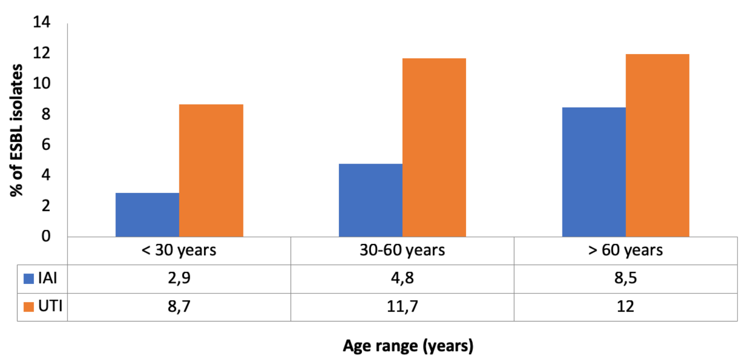

Figure 2 **Frequency of Enterobacterales (*Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca* and *Proteus mirabilis*) with extended spectrum β-lactamases according to age of the patients in the SMART study in Spain comparing intra-abdominal (IAI) and urinary tract infections (UTI) infections.**

(Table 2). In *E. coli*, the corresponding numbers are 63.3% in the community and 44.9% in nosocomial infection (p<0.01). In *P. aeruginosa* these percentages were 4.9 and 7.1, respectively (P=0.150).

Overall, the Enterobacterales with AmpC-type inducible chromosomal β-lactamases, such as *Enterobacter cloacae*, *Morganella morganii* and *Serratia marcescens*, were mainly recovered in infections of hospital origin, both in IAI and in UTI (tables 1 and 2).

The presence of ESBL in Enterobacterales such as *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* was specifically studied in IAI and in UTI. In IAI a total of 96 (9.9%) were ESBL producers. The highest frequency was found in *K. pneumoniae* (25.4%), followed by *E. coli* (7.6%) and *K. oxytoca* (1.4%). In *P. mirabilis* none was found. In UTI the same pattern was followed with higher percentages: *K. pneumoniae* had a higher percentage of ESBL (32.6%) followed by *E. coli* (8.1%), *K. oxytoca* (5.5%) and *P. mirabilis* (1.6%). In all microorganisms with ESBL, the frequency of these enzymes was higher in nosocomially acquired than in community infections (figure 1), with the exception of *E. coli* and *P. mirabilis* in IAI. Likewise, an increase of the ESBL isolates was observed in parallel with the increase of the age of the patients, reaching a frequency higher than 8% in those over 60 years in both types of infection (figure 2).

The susceptibility profile for the antibiotics studied of the most common microorganisms is detailed in table 3. In IAI, the most active antibiotics in Enterobacterales were amikacin (susceptibility rates range: 96.3%-100%), ertapenem (84.2%-100%) and imipenem (70.3%-100%). Ciprofloxacin demonstrated less activity with a percentage of resistance in *E. coli* greater than 25% and close to 40% in *K. pneumoniae*. Regarding the associations of penicillins with beta-lactamase inhibitors, piperacillin-tazobactam susceptibility ranged from 66.6% to 100% and amoxicillin-clavulanic acid from 58.3% to 81.5% (table 3). In *P. aeruginosa*, amikacin, imipenem and ceftazidime, were the most active compounds (96.9%, 76.7% and 72.8% susceptible, respectively).

In UTI the most active antibiotics against Enterobacterales were the same as in IAI, with similar figures for amikacin (97%-100% susceptibility) and higher ones for ertapenem (94.7%-100%) and imipenem (90.4%-100%). Regarding ciprofloxacin, the loss of activity against isolates from urine is noteworthy: only 63% of *E. coli*, 57% of *K. pneumoniae* and 54.1% of *P. mirabilis* were susceptible to this fluoroquinolone.

On the other hand, considering the most frequent microorganisms recovered from IAI (n=1,429), 43.2% were of community origin compared to 56.8% of hospital origin. Of those responsible for the UTIs (n=937), 47.8% were community acquired and 52.2% were of hospital origin. Tables 4 and 5 comparatively analyze the activity of the different antibiotics against community and hospital isolates. Systematically, in the isolates with higher numbers (*E. coli* and *K. pneumoniae*), the activity of all antimicrobials was higher in those originated in the community. However, in the remaining species, there were some exceptions. In those from IAI (table 4), the opposite occurs in *C. freundii* with piperacillin-tazobactam and the third-generation cephalosporins and in *M. morganii* with ciprofloxacin. In UTI (table 5), exceptions occurred with amoxicillin-clavulanate and *K. pneumoniae*, with the third-generation cephalosporins and *P. mirabilis*, *C.*

Table 3 **Activity of different antimicrobial used in intra-abdominal (IAI) and urinary tract infections (UTI) against the most common microorganisms collected in Spain in the SMART study (2016-2017).**

	Percentage of susceptible isolates[a]																	
Organism	A/C[a]		P/T		CTX		CAZ		FEP		IPM		ETP		AK		CIP	
Type of infection	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI	IAI	UTI
Escherichia coli	81.5	77.7	90.0	90.9	90.5	90.1	89.8	89.1	92.0	90.9	99.7	99.8	99.4	99.4	97.9	99.0	72.4	63.0
Klebsiella pneumoniae	58.3	94.1	66.6	69.7	72.7	64.3	67.8	64.8	72.7	65.3	95.1	97.0	84.2	86.8	98.7	97.0	62.4	57.0
Klebsiella oxytoca	76.3	100.0	85.5	84.2	97.1	94.7	97.1	94.7	100.0	94.7	100.0	100.0	100.0	94.7	100.0	100.0	97.1	89.4
Proteus mirabilis	74.1	100.0	100.0	100.0	100,0	96.7	100.0	93.4	100.0	100.0	91.3	100.0	100.0	100.0	100.0	100.0	60.8	54.1
Enterobacter cloacae	_[b]	_[b]	78.6	58.8	73.3	52.9	72.0	58.8	84.0	82.3	96.0	94.1	85.3	94.1	97.3	100.0	90.6	70.5
Citrobacter freundii	_[b]	_[b]	70.9	90.9	70.9	72.7	54.8	63.6	87.1	90.9	93.5	90.9	96.7	90.9	100.0	100.0	93.5	81.8
Morganella morganii	_[b]	_[b]	100,0	95.2	51.8	71.4	74.0	66.6	96.3	95.2	70.3	90.4	100.0	100.0	96.3	100.0	70.3	66.6
Serratia marcescens	_[b]	_[b]	88,0	100,0	72.0	100.0	96.0	100.0	92.0	100.0	92.0	100.0	92.0	100.0	100.0	100.0	96.0	85.7
Other Enterobacterales	36.3	60.0	79.8	74.1	82.4	84.8	72.8	78.7	98.2	93.9	99.1	100.0	96.4	100.0	98.2	100.0	91.2	87.8
Pseudomonas aeruginosa	_[b]	_[b]	66.6	81.8	_[b]	_[b]	72.8	77.5	72.0	74.1	76.7	81.0	_[b]	_[b]	96.9	91.3	70.5	67.2

[a]**EUCAST criteria except A/C in which CLSI criteria were considered. A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin**

[b]**This antimicrobial is not considered adequate against the microorganism tested.**

freundii and *M. morganii*, with ciprofloxacin in *P. mirabilis* and *M. morganii* and with imipenem in *S. marcescens*. Moreover, in *P. aeruginosa* recovered from IAI, all the antibiotics tested were more active when this pathogen was originated in the community, but in the UTI this premise was not observed with piperacillin-tazobactam, ceftazidime and cefepime.

When ESBL producers were considered and compared with non-ESBL producers in IAI (figure 3), the activity of imipenem (99.6% non-ESBL, 100% ESBL) and ertapenem (99.3% non-ESBL, 100% ESBL) remained about at the same level in *E. coli* whereas amikacin was slightly affected (98.9% non ESBL, 86.7% ESBL). On the contrary, the associations of penicillins with the beta-lactamase inhibitors, as well as third generation cephalosporins and ciprofloxacin importantly decreased their activity. In *K. pneumoniae*, amikacin susceptibility (100% non-ESBL, 95.2% ESBL) was little affected compared with that of imipenem (97.5% non-ESBL, 88.1% ESBL) and especially with ertapenem (97.5% non ESBL, 45.2% ESBL) and decreases drastically in the rest of antibiotics as described in *E. coli*. In UTI, *E. coli* isolates showed similar results than those described for IAI. In *K. pneumoniae,* the activity of ertapenem was affected (96.3% non ESBL, 67.1% ESBL), although to a lesser extent than in the IAI isolates.

Finally, when analyzing the activity of carbapenems both in ESBL and in non-ESBL producing *E. coli* and *K. pneumoniae* that were resistant to amoxicillin-clavulate, piperacillin-tazobactam or ciprofloxacin from IAI and UTI (table 6), it was observed that in *E. coli* both the activity of imipenem (data not shown) and that of ertapenem was scarcely modified with susceptibility values higher than 88%. However, in *K. pneumoniae*, ertapenem activity was retained to a lesser extent. In IAI, 28.6% of ESBL producers that were also resistant to amoxicillin-clavulanate were susceptible to ertapenem and in UTI 38.9% of ESBL producers that were resistant to piperacillin-tazobactam were susceptible to ertapenem.

DISCUSSION

Antimicrobial resistance is a global increased problem and poses challenges for the effective treatment of many types of infections, including IAI and UTI. This situation, mainly due to its wide dispersion, is especially alarming in relation to microorganisms that produce ESBL. As a consequence, carbapenems are generally considered the treatment of choice for these infections [11,12], although a decrease in the susceptibility to these compounds have been observed due to the production of carbapenemases or alterations in the porins combined with the production of ESBL or AmpC cephalosporinases [13,14]. Epidemiological surveillance studies analyze trends in resistance but also allow data to progressively adapt treatment guidelines over time, providing valuable information for the selection of initial antibiotic treatment, often empirical. The SMART study (Study for Antimicrobial Resistance Trends), initiated in 2002, is a worldwide program designed to longitudinally monitor the involvement of aerobic and facultative Gram-negative bacilli in IAI, both from community and nosocomial acquisition, as well as their patterns of resistance [15-18]. As of 2009, microorganisms isolated from UTI were also included. The program has been developed in Spain uninterruptedly since 2002 and has had the participation of a significant number of Microbiology Departments of Spanish University Hospitals. Previous

Table 4 **Susceptibility of community-associated (CA) and hospital-associated (HA) microorganisms collected of IAI in Spain in the SMART study (2016-2017).**

Organism	Percentage of susceptible isolates[a]																	
	A/C[a]		P/T		CTX		CAZ		FEP		IPM		ETP		AK		CIP	
Type of infection	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA
Escherichia coli	88.7	75.9	93.4	86.6	91.3	89.8	91.0	88.6	91.6	92.3	100,0	99.3	99.4	99.4	98.5	97.4	75.3	69.9
Klebsiella pneumoniae	83.8	48.7	85.4	57.6	87.2	65.7	85.4	59.4	87.2	65.7	100.0	92.7	96.3	78.3	100.0	98.2	74.5	55.8
Klebsiella oxytoca	84.2	68.4	92.3	76.6	97.4	96.6	97.4	96.6	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	97.4	96.6
Proteus mirabilis	62.5	78.2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	94.1	89.6	100.0	100.0	100.0	100.0	64.7	58.6
Enterobacter cloacae	_[b]	_[b]	93.3	68.8	83.3	66.6	80.0	66.6	90.0	80.0	100.0	93.3	93.3	80.0	100.0	95.5	96.6	86.6
Citrobacter freundii	_[b]	_[b]	68.4	75.0	68.4	75.0	57.8	50.0	89.4	83.3	94.7	91.6	100.0	91.6	100.0	100.0	94.7	91.6
Morganella morganii	_[b]	_[b]	100.0	100.0	66.6	47.6	66.6	76.1	100.0	95.2	83.3	66.6	100.0	100.0	100.0	95.2	50.0	76.1
Serratia marcescens	_[b]	_[b]	88.8	87.5	66.6	75.0	100.0	93.7	100.0	87.5	100.0	87.5	100.0	87.5	100.0	100.0	100.0	93.7
Pseudomonas aeruginosa	_[b]	_[b]	79.6	57.3	_[b]	_[b]	85.1	64.0	88.8	60.0	88.8	68.0	_[b]	_[b]	98.1	96.0	79.6	64.0

[a]EUCAST criteria except A/C in which CLSI criteria were considered. A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

[b]This antimicrobial is not considered adequate against the microorganism tested.

Table 5 **Susceptibility of community-associated (CA) and hospital-associated (HA) microorganisms collected of UTI in Spain in the SMART study (2016-2017).**

Organism	Percentage of susceptible isolates[a]																	
	A/C[a]		P/T		CTX		CAZ		FEP		IPM		ETP		AK		CIP	
Type of infection	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA	CA	HA
Escherichia coli	77.6	78.2	91.5	90.0	92.6	86.8	91.5	85.9	92.6	88.6	100.0	99.5	99.6	99.0	99.3	98.6	64.0	61.3
Klebsiella pneumoniae	90.0	100.0	71.2	69.0	66.6	63.3	69.7	62.5	69.7	63.3	100.0	95.6	92.4	84.1	98.4	96.4	59.0	56.1
Klebsiella oxytoca	100.0	0.0	88.8	77.7	100.0	88.8	100.0	88.8	100.0	88.8	100.0	100.0	100.0	88.8	100.0	100.0	100.0	77.7
Proteus mirabilis	100.0	100.0	100.0	100.0	93.5	100.0	90.3	96.6	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	51.6	56.6
Enterobacter cloacae	_[b]	_[b]	100.0	36.3	80.0	36.3	100.0	36.3	100.0	72.7	100.0	90.9	100.0	90.9	100.0	100.0	100.0	54.5
Citrobacter freundii	_[b]	_[b]	100.0	80.0	66.6	80.0	50.0	80.0	100.0	80.0	100.0	80.0	100.0	80.0	100.0	100.0	83.3	80.0
Morganella morganii	_[b]	_[b]	100.0	92.3	50.0	84.6	37.5	84.6	100.0	92.3	87.5	92.3	100.0	100.0	100.0	100.0	62.5	69.2
Serratia marcescens	_[b]	_[b]	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	66.6	100.0	100.0	100.0	100.0	100.0	100.0	75.0
Pseudomonas aeruginosa	_[b]	_[b]	72.7	77.1	_[b]	_[b]	77.2	80.0	72.7	77.1	81.8	80.0	_[b]	_[b]	95.4	88.5	68.1	68.5

[a]EUCAST criteria except A/C in which CLSI criteria were considered. A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

[b]This antimicrobial is not considered adequate against the microorganism tested.

articles represent the general picture of antimicrobial susceptibility in our country; the last one (7) updates up to 2015 the evolution of ESBL producing isolates in IAIs in Spain. In the present study, the following two years (2016 and 2017) were analyzed but also including information from UTI pathogens. In general, the results are in line with those obtained in the 2011-2015 period and with others from different regions of the world [13,19-21].

We confirm the relevance of *E. coli* in IAI and UTI and in both cases it is isolated in greater proportion in community-acquired infections than in nosocomial infections, in line with other recent publications [20-22]. *K. pneumoniae* is the second microorganism in order of frequency in both types of infections and unlike the previous period (2011-2015) a greater proportion of isolates was found in nosocomial compared to community infections, both in IAI and in UTI.

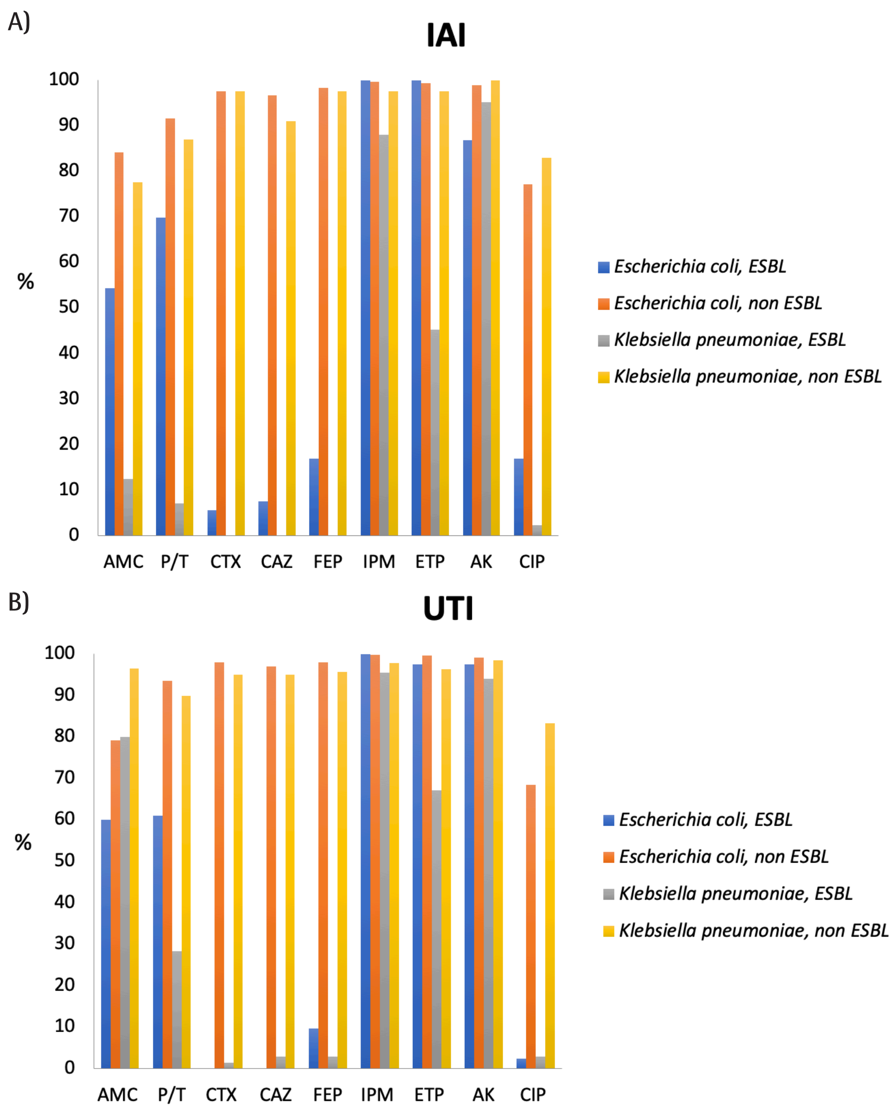

Figure 3 **Percentage of susceptibility of different antimicrobials used in intra-abdominal (A) and urinary tract infections (B) against ESBL producing and non-ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in the SMART study in Spain (2016-2017).**

A/C: amoxicillin-clavulanic acid, P/T: piperacillin/tazobactam; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

Given its epidemiological importance, knowledge of the antimicrobial susceptibility of *E. coli* is crucial regarding empirical therapy, as well as for attempts to control the spread of ESBL and, more recently, of carbapenemases. As in other studies [3,13,19,21], imipenem, ertapenem and amikacin were the most active antimicrobials tested against *E. coli* in both IAIs (>97%), and UTIs (>99%) (21) and there is no evidence of loss of activity in 2016 and 2017 compared to 2011-2015 [7]. On the contrary, in *K. pneumoniae* a decrease in the activity of ertapenem in IAI is verified by comparing the two time periods (95.5% in 2011-2015 *versus* 84.2% in 2016-2017) [7]. In UTI, the percentage of susceptibility is 86.8%, slightly lower to that published in studies from other countries [3,21].

In a recent publication, small decreases, although statistically significant, of ertapenem susceptibility in Enterobacterales isolated from IAI and UTI were observed in most regions of the world. Nevertheless, the susceptibility remains above 90% in all regions, except in Asia [22]. In community infections, the activity was >92% in all regions against Enterobacterales [22] despite the existence of communications that alert of the increase in resistance [6]. Another recent study, unrelated to SMART,

Table 6 **Activity of ertapenem in ESBL producing *Escherichia coli* and *Klebsiella pneumoniae* isolates resistant to amoxicillin-clavulanate, piperacillin-tazobactam and ciprofloxacin in intra-abdominal (IAI) and urinary tract infections (UTI) of the SMART study (2016-2017) in Spain.**

Microorganisms	ESBL	Antimicrobial	IAI				UTI			
			No. (% of resistant isolates)	Ertapenem Susceptible No. (%)	Ertapenem Intermediate No. (%)	Ertapenem Resistant No. (%)	No. (% of resistant isolates)	Ertapenem Susceptible No. (%)	Ertapenem Intermediate No. (%)	Ertapenem Resistant No. (%)
Escherichia coli	Negative	A/C	65 (15.8)	64 (98.4)		1 (1.6)	26 (20.8)	26 (100)		
	Positive		16 (45.7)	16 (100)			4 (40)	4 (100)		
	Negative	P/T	46 (7.2)	43 (93.4)	1 (2.2)	2 (4.4)	18 (3.8)	17 (94.4)	1 (5.6)	
	Positive		10 (18.8)	10 (100)			9 (21.9)	8 (88.9)	1 (11.1)	
	Negative	CIP	126 (19.7)	123 (97.7)		3 (2.3)	137 (29.4)	136 (99.3)	1 (0.7)	
	Positive		42 (79.2)	42 (100)			39 (95.1)	38 (97.4)	1 (2.6)	
Klebsiella pneumoniae	Negative	A/C	17 (22)	14 (82.4)		3 (17.6)	1 (3.4)	1 (100)		
	Positive		28 (87.5)	8 (28.6)		20 (71.4)	1 (20)	1 (100)		
	Negative	P/T	14 (33.3)	11 (78.6)		3 (21.4)	11 (7.9)	6 (54.5)		5 (45.5)
	Positive		38 (30.6)	16 (42.1)		22 (57.9)	36 (53.7)	14 (38.9)	2 (5.5)	20 (55.6)
	Negative	CIP	15 (35.7)	13 (86.7)		2 (13.3)	16 (11.5)	12 (75)		4 (25)
	Positive		40 (32.2)	17 (42.5)	1 (2.5)	22 (55)	61 (91)	40 (65.6)	2 (3.3)	19 (31.1)

A/C: amoxicillin-clavulanate; P/T: piperacillin/tazobactam; CIP: ciprofloxacin

reported a percentage of susceptibility to ertapenem in the Enterobacterales group of 94.5% (98.7% in *E. coli* and 87.4% in *K. pneumoniae*) [23]. In the study of Lob et al. [22], susceptibility to ertapenem significantly decreased in *K. pneumoniae* between 2012 and 2016 in Africa (6%), Europe (8%) and US/Canada (2.5%). Despite this fact, in 2016 the susceptibility of *K. pneumoniae* to ertapenem remains above 90% in the US/Canada and in the South Pacific area, being greater than 80% in the rest of the world.

In recent years, there is a continuous increase in the rates of Enterobacterales with ESBL around the world, especially in Asia [24]. In a recent review of the global epidemiology, the prevalence of CTX-M ESBLs increased over time in all geographic regions, especially in community isolates [25]. In our study, in IAI the percentage of ESBL in *E. coli* is overall 7.6% (8.3% in community and 7% in nosocomial infection), keeping the total figures in line with the period 2011-2015 [7]. It is noteworthy that the rate is somewhat higher in community-acquired infections, a fact not communicated in most of the published surveillance studies [13,21], although the reports on the spread of ESBL in the community are worrisome [26,27]. In *K. pneumoniae*, the ESBL rate increased with respect to previous years, from 18.6% in 2015 to 25.4% in 2016-2017, especially at the expense of infections of nosocomial origin (12.7% community and 31.5% nosocomial). In UTI, the figures in ESBL producing *E. coli* are slightly higher (overall 8.1%; 6.3% community and 10.4% nosocomial) and much higher in *K. pneumoniae* (overall 32.6%; 28.7% community and 34.5% nosocomial). Our rates of ESBL in *K. pneumoniae* are difficult to compare with those published in other regions where there are large variations, although it can be summarized that they are lower than those of most countries in Asia, especially China and Thailand [3], and higher than those of the US/Canada [28]. Our study also shows that the highest percentage of ESBL isolates occurs in IAI of hospital origin and in patients of advanced ages. Both circumstances have already been indicated as risk factors for the acquisition of infections due to ESBL producers [29]. In this line, in a recent study in UTI in the US when data are stratified by sex, age and time of hospital stay, there is a higher percentage of ESBL isolations in men, patients ≥65 years and in nosocomial infections [28].

In IAI, the activity of imipenem, ertapenem and amikacin in ESBL-producing *E. coli* isolates remains practically at the same level in relation to those that do not produce ESBLs. This fact is also confirmed in other publications [13,21,22]. However, one of these articles [13] found some evidence of increased resistance among isolates from the community, in addition to the known decreasing trends in susceptibility to quinolones and third-generation cephalosporins. In ESBL-producing *K. pneumoniae*, the activity of imipenem decreased by almost 10% and that of ertapenem by more than 50%. This decrease is not reflected so strongly in any other study and follows the trend already mentioned in the study of the years 2010-2016 in Spain [7]. Ertapenem susceptibility figures below 90% (83.6% in Africa and 85.5% in Europe) have already been published, although data came from a joined analysis including *E. coli, K. pneumoniae, K. oxytoca* and *P. mirabilis* ESBL producers from IAI and UTI and not from an individualized analysis [22].

In UTI, the behavior of imipenem, ertapenem and amikacin in *E coli*. and *K. pneumoniae* is similar to that commented for IAI. However, the activity of ertapenem decreased to a lesser extent (somewhat less than 30%) in *K. pneumoniae* being higher than in other publications [3,21]. Regarding the origin of the isolates, *E. coli* slightly decreased their susceptibility to the most active compounds (imipenem, ertapenem and amikacin) when having a hospital origin both in IAI and in UTI, in line with what it is reflected in other studies [3,19,21]. In *K. pneumoniae*, in IAI, the susceptibility decreased to a greater extent, data not sufficiently confirmed in other studies to date [3,19,21].

As in the 2011-2015 study the co-resistance analysis, which is relevant to designing antimicrobial treatment protocols [30], showed that both imipenem (data not shown) and ertapenem have a good activity against ESBL-producing *E. coli* recovered from IAI and UTI that were also resistant to amoxicillin-clavulanic acid, piperacillin-tazobactam or fluoroquinolones. Nevertheless, the same did not occur in the case of ESBL-producing *K. pneumoniae*, although ertapenem retained its activity in 28.6%, 42.1% and 42.5% of amoxicillin-clavulanic acid, piperacillin-tazobactam or ciprofloxacin resistant isolates, respectively. These figures were more favorable in UTI, particularly for ciprofloxacin resistant isolates (65.6% of ertapenem susceptibility). The reason for the increased loss of susceptibility to ertapenem in *K. pneumoniae* was analyzed in a recent study and concluded that it was not only due to production of carbapenemases but to permeability defects [31]. The genes encoding the OmpK35 and OmpK36 porins of the outer membrane were studied and most of the isolates (83.0%) had one or both genes affected. In isolates with higher ertapenem MICs (>4 mg/L), 60.5% of the total isolates, a mutation was found in both porin genes.

Despite the above observations, carbapenems are still considered as empirical therapy of choice in infections suspected to be caused by ESBL producers or AmpC hyperproducers both in IAI and UTI [12,32,33]. Regardless of the spread of ESBL worldwide, a very recent study showed that ertapenem was active against more than 90% of Enterobacterales isolates recovered from IAI and UTI with the ESBL phenotype in Latin America, Middle East, South Pacific, US and Canada. Our study also shows that ertapenem continue to exhibit good activity, despite the emergence of carbapenemases in Spain [34,35], when compared to broad spectrum cephalosporins and associations of penicillins with beta-lactamase inhibitors. This activity is higher in isolates from community origin and may be a viable option to reduce the length of hospitalization of stable patients together with its easy once-a-day dosing, safety and tolerability [36,37]. Continuous surveillance efforts should be performed at local and global levels, since knowledge of the patterns and resistance trends are essential for making decisions about empirical treatment and support infection control efforts.

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CONFLICTS OF INTEREST

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