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

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 IAI 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 IAI 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 activity was higher, 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 IAI. 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, carbapenem

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 re-
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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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 Enterobacteriales, in particular Escherichia coli and Klebsiella species [2,3]. In the 1980s, extended spectrum beta-lactamase (ESBL)-producing Enterobacteriales 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 carbapenem 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 fulfill 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, Hospital 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 IAI or UTI. 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.

Palabras clave: vigilancia epidemiológica de la resistencia, infección intraabdominal, infección urinaria, betalactamasa de espectro extendido, carbapenem
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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

### 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 Enterobacteriales (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 IAI 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.
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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-clavulanic and *K. pneumoniae*, with the third-generation cephalosporins and *P. mirabilis*, C.

(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 beta-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 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.


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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).

| Organism                  | Type of infection | A/C\(^a\) | P/T | CTX | CAZ | FEP | IPM | ETP | AK | CIP |
|---------------------------|-------------------|-----------|-----|-----|-----|-----|-----|-----|----|-----|
| E. coli                   | IAI               | 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| 99.9| 97.9| 99.0| 72.4| 63.0|
| K. pneumoniae             | IAI               | 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|
| K. oxytoca                | UTI               | 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| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 97.1| 89.4|
| Proteus mirabilis         | IAI               | 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| 100.0| 100.0| 100.0| 100.0| 100.0| 60.8| 54.1|
| Enterobacter cloacae      | UTI               | 70.9      | 78.6| 58.8| 73.3| 52.9| 72.0| 58.8| 84.9| 82.3| 96.0| 94.1| 85.3| 94.1| 97.3| 100.0| 90.6| 70.5|
| Citrobacter freundii      | UTI               | 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       | IAI               | 100.0      | 95.2| 51.8| 71.4| 74.0| 66.6| 93.6| 95.2| 70.3| 90.4| 100.0| 100.0| 100.0| 100.0| 100.0| 70.3| 66.6|
| Serratia marcescens      | UTI               | 88.0      | 100.0| 72.0| 100.0| 96.0| 100.0| 92.0| 100.0| 920.0| 100.0| 920.0| 100.0| 100.0| 100.0| 100.0| 100.0| 96.0| 85.7|
| Other Enterobacteriales   | UTI               | 72.8      | 60.0| 73.8| 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| 81.0| 91.2| 87.8|
| Pseudomonas aeruginosa    | UTI               | 72.8      | 60.0| 81.8| 66.6| 66.6| 72.8| 77.5| 72.0| 74.1| 76.7| 81.0| 66.6| 96.9| 91.3| 70.5| 57.0| 62.7|

\(^a\)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.

**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 has 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 interminently since 2002 and has had the participation of a significant number of Microbiology Departments of Spanish University Hospitals. Previous
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 IAI 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.

### Table 4

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

| Organism              | Type of infection | A/C<sup>a</sup> | P/T | CTX | CAZ | FEP | IPM | ETP | AK | CIP |
|-----------------------|-------------------|-----------------|-----|-----|-----|-----|-----|-----|----|-----|
|                       | 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| 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| 100.0| 100.0| 100.0| 100.0| 96.6|
| Proteus mirabilis     | 62.5              | 78.2            | 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 100.0| 97.4| 96.6|
| Enterobacter cloacae  |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Citrobacter freundii  |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Morganella morganii   |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Serratia marcescens   |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Pseudomonas aeruginosa|                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

<sup>a</sup>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: ceftepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

<sup>b</sup>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              | Type of infection | A/C<sup>a</sup> | P/T | CTX | CAZ | FEP | IPM | ETP | AK | CIP |
|-----------------------|-------------------|-----------------|-----|-----|-----|-----|-----|-----|----|-----|
|                       | 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| 98.3| 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| 100.0| 100.0| 100.0| 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| 100.0| 100.0| 100.0| 51.6| 56.6|
| Enterobacter cloacae  |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Citrobacter freundii  |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Morganella morganii   |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Serratia marcescens   |                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Pseudomonas aeruginosa|                  |                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

<sup>a</sup>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: ceftepime; IPM: imipenem; ETP: ertapenem; AK: amikacin; CIP: ciprofloxacin

<sup>b</sup>This antimicrobial is not considered adequate against the microorganism tested.
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 IAI (>97%), and UTIs (>99%) [21] and there is no evidence of loss of activity in 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 Enterobacteriales 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 Enterobacteriales [22] despite the existence of communications that alert of the increase in resistance [6]. Another recent study, unrelated to SMART,
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

### 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 | No. (%) | IAI | Ertapenem | UTI | Ertapenem |
|--------------------|------|--------------|---------|-----|-----------|-----|-----------|
|                    |      |              | (of resistant isolates) |    | No. (%) |    | No. (%) |
|                    |      |              |         |     | Susceptible | Intermediate | Resistant |
|                    |      |              |         |     | No. (%) | No. (%) | No. (%) |
|                    |      |              |         |     | No. (%) | No. (%) | No. (%) |
| *Escherichia coli* |      |              |         |     |           |           |           |
| Negative           | 65   | (15.8)       | 64 (98.4) | 1 (1.6) | 26 (20.8) | 26 (100) |
| A/C                |      |              |         |     |           |           |           |
| Positive           | 16   | (45.7)       | 16 (100)  | 4 (40)  | 4 (100)   |      |           |
| Negative           | 46   | (7.2)        | 43 (93.4) | 1 (2.2) | 2 (4.4)   | 18 (3.8) | 17 (94.4) | 1 (5.6) |
| P/T                |      |              |         |     |           |           |           |
| Positive           | 10   | (18.8)       | 10 (100)  | 9 (21.9) | 8 (88.9)  | 1 (11.1) |
| Negative           | 126  | (19.7)       | 123 (97.7)| 3 (2.3) | 137 (29.4)| 136 (99.3)| 1 (0.7) |
| CIP                |      |              |         |     |           |           |           |
| Positive           | 42   | (79.2)       | 42 (100)  | 39 (95.1)| 38 (97.4) | 1 (2.6) |
| *Klebsiella pneumoniae* |  |              |         |     |           |           |           |
| Negative           | 17   | (22)         | 14 (82.4)| 3 (17.6)| 1 (3.4)   | 1 (100)  |
| A/C                |      |              |         |     |           |           |           |
| Positive           | 28   | (87.5)       | 8 (28.6) | 20 (71.4)| 1 (20)   | 1 (100)  |
| Negative           | 14   | (33.3)       | 11 (78.6)| 3 (21.4)| 11 (7.9)  | 6 (54.5) | 5 (45.5) |
| P/T                |      |              |         |     |           |           |           |
| Positive           | 38   | (30.6)       | 16 (42.1)| 22 (57.9)| 36 (53.7)| 14 (38.9)| 2 (5.5) | 20 (55.6)|
| Negative           | 15   | (35.7)       | 13 (86.2)| 2 (13.3)| 16 (11.5)| 12 (75)  | 4 (25) |
| CIP                |      |              |         |     |           |           |           |
| 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
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, carbapenemases 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 Enterobacteriales 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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REFERENCES

1. Prestinaci F, Pizzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015; 109:309-18. PMID: 26343252.
2. Sartelli M, Chichom-Mefiere A, Labricciosa FM, Hardcastle T, Abu-
Zidan FM, Adesunkanmi AK et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017; 12:29. PMID: 28702076.

3. Jean SS, Coombs G, Ling T, Balaji V, Rodrigues C, Mikamo H, et al. Epidemiology and antimicrobial susceptibility profiles of pathogens causing urinary tract infections in the Asia-Pacific region: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2010–2013. Int J Antimicrob Agents. 2016; 47:328-34. PMID: 27005459.

4. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis. 2008; 8:159-66. PMID: 18291338.

5. Rawat D, Nair D. Extended-spectrum β-lactamases in Gram negative bacteria. J Glob Infect Dis. 2010; 2:263-74. PMID: 20927288.

6. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis. 2017. 215 (Suppl 1):S28-36. PMID: 28375512.

7. Cantón R, Loza E, Aznar J, Barrón-Adúriz R, Calvo J, Castillo FJ, et al. Antimicrobial susceptibility trends and evolution of isolates with extended spectrum β-lactamases among Gram-negative organisms recovered during the SMART study in Spain (2011–2015). Rev Esp Quimioter. 2018; 31:136-45. PMID: 29532655.

8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health-care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008; 36:309-32. PMID: 18538699.

9. International Organization for Standardization (ISO). 2006 Clinical laboratory testing and in vitro diagnostic test systems – Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices – Part 1: Reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases. International Standard 20776-1, ISO, Geneva.

10. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Document M100-S27. Wayne, PA: CLSI, 2017.

11. Sartelli M, Catena F, Abu-Zidan FM, Ansaloni L, Biffl WL, Boermeester MA, et al. Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference. World J Emerg Surg. 2017; 12:22. PMID: 28484510.

12. Rodríguez-Ábañez J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev. 2018; 31(2). pii: e00079-17. PMID:29444952.

13. Lob SH, Kazmierzczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahn DF. Trends in susceptibility of Escherichia coli from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART program, 2009 to 2013. Antimicrob Agents Chemother. 2015; 59:3606-10. PMID: 25801558.

14. Biedenbach D, Bouchillon S, Hackel M, Hoban D, Kazmierzczak K, Hawser S, et al. Dissemination of NDM metallo-β-lactamases genes among clinical isolates of Enterobacteriaceae collected during the SMART Global Surveillance Study from 2008 to 2012. Antimicrob Agents Chemother 2015; 59:826-30. PMID:27216054

15. Morrissey I, Hackel M, Badal R, Bouchillon S, Hawser S, Biedenbach D. A Review of Ten Years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. Pharmaceuticals (Basel). 2013; 6:1335-46. PMID: 24287460.

16. Guembe M, Cercenado E, Alcalá L, Marin M, Insa R, Bouza E. Evolution of antimicrobial susceptibility patterns of aerobic and facultative gram-negative bacilli causing intra-abdominal infections: results from the SMART studies 2003-2007. Rev Esp Quimioter. 2008; 21:166-73. PMID: 18792817.

17. Cantón R, Loza E, Aznar J, Calvo J, Cercenado E, Cisterna R, et al. Antimicrobial susceptibility of Gram-negative organisms from intra-abdominal infections and evolution of isolates with extended spectrum β-lactamases in the SMART study in Spain (2002-2010). Rev Esp Quimioter. 2011; 24:223-32. PMID: 22173194.

18. Babinckach T, Badal R, Hoban D, Hackel M, Hawser S, Lob S et al. Trends in susceptibility of selected gram-negative bacilli isolated from intra-abdominal infections in North America: SMART 2005-2010. Diagn Microbiol Infect Dis. 2013; 76:379-81. PMID: 23541118.

19. Hawser S, Hoban DJ, Badal RE, Bouchillon SK, Biedenbach D, Hackel M, et al. Epidemiology and antimicrobial susceptibility of Gram-negative aerobic bacteria causing intra-abdominal infections during 2010-2011. J Chemother. 2015; 27:67-73. PMID: 24548089.

20. Bouchillon SK, Badal RE, Hoban DJ, Hawser SP. Antimicrobial susceptibility of inpatient urinary tract isolates of Gram-negative bacilli in the United States: results from the study for monitoring antimicrobial resistance trends (SMART) program: 2009-2011. Clin Ther. 2013; 35:872-7. PMID: 23623624.

21. Ponce-de-Leon A, Rodriguez-Noriega E, Morfin-Otero R, Cornejo-Juárez DP, Tinoco JC, Martinez-Gamboa A, et al. Antimicrobial susceptibility of gram-negative bacilli isolated from intra-abdominal and urinary-tract infections in Mexico from 2009 to 2015: Results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). PLoS One. 2018; 13(6):e0198621. PMID:29927958.

22. Lob SH, Hackel MA, Hoban DJ, Young K, Motyl MR, Sahn DF. Activity of ertapenem against Enterobacteriaceae in seven global regions-SMART 2012-2016. Eur J Clin Microbiol Infect Dis. 2018; 37:1481-9. PMID: 29754209.

23. Karlovska YJ, Biedenbach DJ, Kazmierzczak KM, Stone GG, Sahn DF (2016) Activity of ceftazidime-avibactam against extended-Spectrum- and AmpC beta-lactamase-producing Enterobacteriaceae collected in the INFORM global surveillance study from 2012 to 2014. Antimicrob Agents Chemother 60:2849–57. PMID:26926635.

24. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE, Hsueh PR, Paterson DL. Emergence of high levels of extended-spectrum-beta-lactama-seproducing gram-negative bacilli in the Asia-Pacific region: data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, 2007. Antimicrob Agents Chemother. 2009; 53:3280-4. PMID: 19506060.

25. Bevan ER, Jones AM, Hawksey PM. Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype. J An-
timicrob Chemother. 2017; 72:2145-55. PMID: 28541467.

26. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. J Antimicrob Chemother. 2005; 56:52-9. PMID: 15917288.

27. Pitout JD. Enterobacteriaceae that produce extended-spectrum \( \beta \)-lactamases and AmpC \( \beta \)-lactamases in the community: the tip of the iceberg? Curr Pharm Des. 2013; 19:257-63. PMID: 22934977.

28. Lob SH, Nicolle LE, Hoban DJ, Kazmierczak KM, Badal RE, Sahm DF. Susceptibility patterns and ESBL rates of Escherichia coli from urinary tract infections in Canada and the United States, SMART 2010-2014. Diagn Microbiol Infect Dis. 2016; 85:459-65. PMID: 27306116.

29. Ofner-Agostini M, Simor A, Mulvey M, McGee A, Hirji Z, McCracken M, Gravel D, Boyd D, Bryce E. Risk factors for and outcomes associated with clinical isolates of Escherichia coli and Klebsiella species resistant to extended-spectrum cephalosporins among patients admitted to Canadian hospitals. Can J Infect Dis Med Microbiol. 2009; 20(3):e43-8. PMID: 20808455.

30. WHO. Global Antimicrobial Resistance Surveillance System (GLASS) (http://www.who.int/glass/en), last access October 12th, 2018.

31. Wise MG, Horvath E, Young K, Sahm DF, Kazmierczak KM. Global survey of Klebsiella pneumoniae major porins from ertapenem non-susceptible isolates lacking carbapenemases. J Med Microbiol. 2018; 67:289-95. PMID: 29458684.

32. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, Chang PK, O’Neill PJ, Mollen KP, Huston JM, Diaz JJ Jr, Prince JM. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. Surg Infect (Larchmt). 2017; 18:1-76. PMID: 28085573.

33. Bader MS, Loeb M, Brooks AA. An update on the management of urinary tract infections in the era of antimicrobial resistance. Postgrad Med. 2017; 129:242-58. PMID: 27712137.

34. Pérez-Vázquez M, Oteo J, García-Cobos S, Aracil B, Harris SR, Ortega A, et al. Phylogeny, resistome and mobile genetic elements of emergent OXA-48 and OXA-245 Klebsiella pneumoniae clones circulating in Spain. J Antimicrob Chemother. 2016; 71:887-96. PMID: 26769896.

35. Oteo J, Pérez-Vázquez M, Bautista V, Ortega A, Zamarrón P, Saez D, et al. The spread of KPC-producing Enterobacteriaceae in Spain: WGS analysis of the emerging high-risk clones of Klebsiella pneumoniae ST11/KPC-2, ST101/KPC-2 and ST512/KPC-3. J Antimicrob Chemother. 2016; 71:3392-9. PMID: 27530752.

36. Rattanaumpawan P, Werarak P, Jitmuang A, Kiratisin P, Thamlikitkul V. Efficacy and safety of de-escalation therapy to ertapenem for treatment of infections caused by extended-spectrum-\( \beta \)-lactamase-producing Enterobacteriaceae: an open-label randomized controlled trial. BMC Infect Dis. 2017; 17:183. PMID: 28249572.

37. Seo YB, Lee J, Kim YK, Lee SS, Lee JA, Kim HY, et al. Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli. BMC Infect Dis. 2017; 17:404. PMID: 28592240.