International Journal of Antimicrobial Agents 41 (2013) 224–228

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Monitoring the global in vitro activity of ertapenem against *Escherichia coli* from intra-abdominal infections: SMART 2002–2010

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ARTICLE INFO

Article history:
Received 22 August 2012
Accepted 16 October 2012

Keywords:
Ertapenem
Susceptibility
Trends
Escherichia coli
SMART
Intra-abdominal

ABSTRACT

During 2002–2010, a total of 30 840 *Escherichia coli* clinical isolates from intra-abdominal infections were collected globally in the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance programme. The incidence of extended-spectrum β-lactamase (ESBL)-producing isolates ranged from 9.2% in 2002 to 21.2% in 2010. The highest rates were observed in Asia (38.3%) and Latin America (22.9%) and the lowest rates in Africa (6.3%), North America (6%) and South Pacific (5.8%). Global susceptibility trends showed that there were only minor fluctuations in susceptibility to ertapenem and imipenem, with no significant decrease over time. Against ESBL-positive isolates, ertapenem susceptibility significantly increased during 2002–2010 globally. Moreover, susceptibility to ertapenem in the different geographical regions studied was also high, with only minor fluctuations generally observed. Notably, in Asia where the highest ESBL-positives rates (38.3%) were observed, susceptibility to ertapenem had actually significantly increased in this population during the 9-year study period. By contrast, susceptibility to amikacin, cephalosporins, fluoroquinolones and β-lactam/β-lactamase inhibitor combinations generally decreased over time. Further monitoring of the susceptibility to ertapenem and other antibiotics through SMART is warranted.

1. Introduction

Escherichia coli plays a key role as the causative pathogen in various clinical indications. One of these is intra-abdominal infections (IAIs), a frequently encountered infection in the healthcare setting of which the majority of pathogens are Gram-negative bacilli. The species most commonly isolated in IAIs are *E. coli* and *Klebsiella* spp., including extended-spectrum β-lactamase (ESBL)-producing isolates, *Proteus* spp., *Enterobacter* spp., *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [1,2]. However, *E. coli* is the most commonly isolated pathogen from IAIs, constituting ≥50% of the total, and by virtue of its frequency merits particular attention with respect to susceptibility trends.

A variety of antimicrobial agents are recommended for use for the treatment of IAIs but the utility of many of these has become restricted, over time, owing to increasing resistance rates. Recommended agents include the carbapenems (ertapenem, imipenem and meropenem) and piperacillin/tazobactam. Cephalosporins and fluoroquinolones are also recommended although their utility is evident only when used in combination with other drugs [3]. Ertapenem has been shown to be active against ESBL-producing Enterobacteriaceae, including *E. coli*, with positive clinical outcomes associated with empirical ertapenem therapy against these difficult-to-treat pathogens [4–6].

The Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance programme monitors the susceptibility of Gram-negative bacilli from IAIs to ertapenem and comparators and has been ongoing since 2002, with nearly 200 hospitals participating worldwide in 2010. Data from the study have demonstrated generally high worldwide ertapenem susceptibility with *E. coli*, and this agent will be focused upon in this investigation in comparison with imipenem and non-carbapenem agents [7–10]. We recently reported that susceptibility to ertapenem, unlike several comparator antimicrobials, has remained consistently high in North America. However, North American isolates consisted of low numbers of ESBL-positive isolates [11]. It is noteworthy to mention, therefore, that since the emergence of metallo-β-lactamases

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http://dx.doi.org/10.1016/j.ijantimicag.2012.10.014

and carbapenemases, the effectiveness of carbapenem therapy is speculated to become more limited [12–15]. The current report describes data from SMART 2002–2010 and highlights susceptibility trends for ertapenem, imipenem and several comparators in *E. coli* isolates collected globally from IAIs.

2. Materials and methods

2.1. Clinical isolates

All isolates were derived from IAIs and were collected from a cumulative total of 833 hospitals in 47 countries from 2002–2010. Of these, 21, 188, 286, 129, 27, 136 and 46 centres were from Africa, Asia, Europe, Latin America, Middle East, North America and the South Pacific, respectively. There were 605 unique sites; 512 (84.6%) participated in 1 year and 93 (15%) participated in ≥2 years [including 45 (7%) that participated in ≥4 years]. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of patient antimicrobial use, age or sex. Only one isolate per species per patient was accepted into the study. Up to 100 consecutive, non-selected Gram-negative aerobic and facultative bacilli from each participating hospital were cultured from specimens from intra-abdominal body sites (e.g. appendix, peritoneum, colon, bile, pelvis and pancreas). The majority of intra-abdominal specimens were obtained during surgery, although some paracentesis specimens were also accepted. Isolates from blood, urine and perirectal abscesses were excluded. No identifiable patient-specific information, including symptoms, diagnosis or accession numbers, was recorded.

2.2. Susceptibility testing

From 2002–2007, isolates were identified to species level and were tested for antimicrobial susceptibility at each site using custom MicroScan® dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA); however, beginning in 2008 all isolates were sent to a central laboratory (Laboratories International for Microbiology Studies, a subsidiary of International Health Management Associates, Inc., Schaumburg, IL) for confirmation of identification and antimicrobial susceptibility testing using the same MicroScan panels. Development and maintenance of a combined database of study results was managed by the central laboratory.

MicroScan minimum inhibitory concentration (MIC) panels were set up following the manufacturer's and Clinical and Laboratory Standards Institute (CLSI) guidelines [16]. The following antimicrobial agents were included on the panels (with their dilution ranges expressed in μg/mL): ertapenem, 0.03–4; imipenem, 0.06–8; cefepime, 0.5–32; ceftazidime, 0.5–128; ceftazidime/clavulanic acid, 0.12/4–16/4; cefoxitin, 2–16; ciprofloxacin, 0.25–2; amikacin, 4–32; levofloxacin, 0.5–4; cefotaxime, 0.5–128; cefotaxime/clavulanic acid, 0.12/4–16/4; piperacillin/tazobactam, 2/4–64/4; ampicillin/sulbactam, 2/2–16/2; and ceftriaxone, 1–32. MIC interpretive criteria from CLSI document M100-S22 were followed and were applied retroactively for all years in this analysis utilising the following breakpoint criteria for third- and fourth-generation cephalosporins: cefotaxime and ceftriaxone, susceptible ≤1 μg/mL and resistant ≥4 μg/mL; ceftazidime, susceptible ≤4 μg/mL and resistant ≥16 μg/mL; and cefepime, susceptible ≤8 μg/mL and resistant ≥32 μg/mL [17].

2.3. Quality control

Using CLSI guidelines, *E. coli* were classified as ESBL-producers if there was at least an eight-fold reduction (i.e. three doubling dilutions) of the MIC for ceftazidime or cefotaxime tested in combination with clavulanic acid versus their MICs when tested alone [17]. Quality control (QC) testing was performed each day of testing using the CLSI-recommended QC strains *E. coli* ATCC 25922, *E. coli* ATCC 35218, *P. aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control). Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines [17].

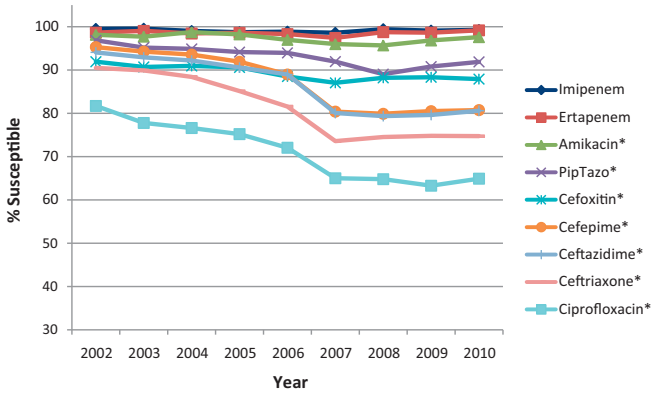

Fig. 1. Percent susceptible of 30 840 global clinical isolates of *Escherichia coli* from intra-abdominal infections, 2002–2010. * Susceptibility significantly reduced ($P < 0.05$) during the 9-year study period. Pip Tazo, piperacillin/tazobactam.

2.4. Statistical analyses

The Cochran–Armitage test for trend was used to analyse linear trends in the proportion of susceptible isolates over the 9-year period. Trends in MIC values over time were assessed using linear regression of the log-transformed MIC values. In all analyses, a *P*-value of <0.05 was considered significant for two-tailed tests. Data were analysed with JMP® Base Version 8.0.2 (SAS Institute Inc., Cary, NC) and XLSTAT (Addinsoft USA, New York, NY).

3. Results

A total of 30 840 *E. coli* isolates were collected during 2002–2010. Of these, 11 533, 7218, 4965, 3693, 1727, 946 and 758 were from Europe, Asia, Latin America, North America, South Pacific, Middle East and Africa, respectively. Global rates of ESBL-positive isolates ranged from 9.2% in 2002 increasing to 21.2% in 2010. At the end of the current study analysis (2010), ESBL rates were 38.3%, 22.9%, 18.5%, 9.4%, 6.3%, 6% and 5.8% in Asia, Latin America, Middle East, Europe, Africa, North America and the South Pacific, respectively.

Figs. 1 and 2 show the percent susceptibility trends for nine selected study drugs tested against the *E. coli* isolates (Fig. 1) and the ESBL-positive *E. coli* isolates (Fig. 2). Of the nine antimicrobial agents presented in the figures, only amikacin, ertapenem and imipenem consistently exhibited percent susceptibilities of ≥90% for all 9 years of the study. Susceptibility trend analysis also showed that there were no statistically significant decreases in susceptibilities to the two carbapenems, whilst susceptibility to amikacin was shown to be significantly reduced ($P < 0.001$) during the 9-year study period (Fig. 1). Percents susceptible to the other antibiotics were also significantly decreased, but to a lesser degree ($P < 0.05$) during the 9-year study period (Fig. 1).

With the exception of imipenem, no antibiotics consistently inhibited ≥90% of the ESBL-positive *E. coli* isolates for all years of the study. Indeed, no statistically significant changes in susceptibility were noted for imipenem. Although ertapenem did not exhibit percent susceptibility of ≥90% for all study years, susceptibility to